
1157:

Final Decision
Analytical Protocol
(DAP) to guide the
assessment of cell
enrichment liquid
based cytology in
routine screening for
the prevention of
cervical cancer

May 2012

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MSAC and PASC

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

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

Purpose of this document

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

The protocol guiding the assessment of the health intervention has been developed using the widely accepted "PICO" approach. The PICO approach involves a clear articulation of the following aspects of the research question that the assessment is intended to answer:

Patients – specification of the characteristics of the patients in whom the intervention is to be considered for use;

Intervention – specification of the proposed intervention

Comparator – specification of the therapy most likely to be replaced by the proposed intervention

Outcomes – specification of the health outcomes and the healthcare resources likely to be affected by the introduction of the proposed intervention

Purpose of application

A proposal for an application requesting Medicare Benefits Schedule (MBS) listing of liquid-based cytology for cervical cancer screening (SurePath™ LBC system) was received from Becton Dickinson Pty Ltd by the Department of Health and Ageing in April 2011.

PASC has finalised this protocol to guide the assessment of the safety, effectiveness and cost-effectiveness of liquid-based cytology for cervical cancer screening in order to inform MSAC's decision-making regarding public funding

Intervention

Description

The National Cervical Screening Program (NCSP) promotes routine screening with Pap smears every two years for women between the ages of 18 (or two years after first sexual intercourse, whichever is later) and 69 years.

In Australia, cervical cytology is routinely undertaken using the conventional Papanicolaou (Pap) smear test (also referred to as conventional cytology in this document). This involves the collection of cells from the uterine cervix. Cells are collected from the cervix using a small cytobrush/broom or spatula and smeared onto a glass slide for examination under the microscope by a cytologist.

Liquid-based cytology (LBC) uses a different method for preparing cervical cells for cytological examination than the conventional Pap smear test. Cells are collected from the cervix using a brush, broom or spatula in the same way as they are collected for a conventional Pap smear, but the head of the brush or spatula is either rinsed into or detached into a vial of preservative fluid to produce a cell suspension which is sent to the laboratory. In the direct-to-vial collection method, instead of smearing the cells directly onto a glass slide, cells collected from the cervical scraping are transferred directly to the LBC preservative fluid.

Under LBC at the laboratory, the cell sample is treated to remove obscuring factors, such as blood, mucus and inflammatory cells, so that a thin layer of cervical cells can be placed on a slide for microscopic examination.

There are currently two marketed LBC preparation systems available in Australia. These systems use different technical methods for storing and preparing the cervical cytology sample, some of which are patented. The SurePath™ LBC system (Beckton Dickinson Pty Ltd) requires that the head of the brush or spatula to be detached into a vial of liquid to produce a cell suspension which undergoes "enrichment" prior to slide preparation via gravity sedimentation. The ThinPrep® Pap system (Hologic [Australia] Pty Ltd) requires that the head of the brush or spatula to be rinsed into a vial of liquid to produce a cell suspension which then undergoes membrane filtration and the cell residue is transferred to the slide.

Automated slide reading may also be used in conjunction with LBC. Automated slide reading assists the cytologist by directing him/her to the areas on the specimen most likely to contain abnormalities. The aim of automated slide reading is to reduce cytology reading time and detection error. Both the SurePath™ LBC system and the ThinPrep® Pap system can be reviewed using *either* manual or automated reading methods.

This protocol refers to the assessment of the SurePath™ LBC system, also referred to in the document as cell enrichment LBC. It encompasses both manual and automated reading methods of the slides.

Administration, dose, frequency of administration, duration of treatment

The National Cervical Screening Programme was established in Australia in 1991 to identify and treat women with precancerous cervical intraepithelial neoplasia (CIN) before it progresses to invasive cancer. Cervical cytology tests are recommended every two years starting at 18 (or two years after first sexual intercourse, whichever occurs first) and ceasing at age 69 years.

Women may need to undergo a repeat test if the sample is unsatisfactory, due to the cells being obscured by blood or inflammation, or if abnormalities are detected. A claim of LBC is that because of the different method in which the cells are collected, stored and processed, the number of unsatisfactory samples is reduced, thereby reducing the need for repeat Pap smear test.

Cell enrichment LBC Pap tests do require sample collection vials and sample collection devices. These are provided by the pathology companies. Training is also required for LBC specimen collection, processing and specimen review. Specimen review training is the most intensive, potentially involving training over four days.

In terms of automated slide reading, individual laboratories currently make the decision whether to review slides using manual or automated methods. If pathology laboratories wish to introduce automation to streamline their processes, instrumentation may be purchased outright or funded over time via the vial price. Generally it is the larger laboratories with highest throughput which are able to generate the efficiencies from automated guided screening to offset the additional outlay on capital expenditure.

Co-administered interventions

Cervical cancer cytology is a stand-alone primary screening test and is commonly administered within the context of a medical consultation (MBS Item 3, 23, 36, 44). It can also be administered by other qualified health professionals (MBS Item 52, 53, 54, 57) or in the context of a specialist appointment (MBS Item 104,105). A colposcopy, and referral to a specialist, may be indicated following any abnormal test result from the initial screen.

LBC can also be used for adjunctive testing for a range of pathogens including human papilloma virus (HPV), *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. This however is not routinely done in Australia.

Background

MSAC has reviewed LBC twice before. The first review concluded that, 'there is currently insufficient evidence pertaining to liquid based cytology for cervical screening' (Medical Services Advisory Committee 2002). The second review in 2009 led MSAC to conclude that 'in comparison to Papanicolaou (Pap) test that LBC is safe, is at least effective, is not cost effective at the price requested' (Medical Services Advisory Committee 2009b).

As mentioned previously there are two principal systems available for LBC. This review will focus on one of these systems: SurePath™ LBC system (cell enrichment).

Current arrangements for public reimbursement

LBC by any method is not listed on the MBS. It is, in fact, explicitly excluded from the MBS (see Table 1). However LBC is currently provided by all private pathology laboratories for a fee additional to the MBS fee for conventional Pap smears, and is collected using the split-sample technique in conjunction with conventional Pap smears. The additional fee is paid by the patient (around \$30 or more). The exception to this is in Queensland (namely Far North Queensland) where thin layer technology (ThinPrep®) is offered as an adjunctive test to conventional Pap smears in women meeting specific criteria (Queensland Cervical Screening Program 2008); this program is funded by the Queensland State Government

Below are listed the current MBS item descriptors for cervical cancer cytology. A review of these items processed shows that Medicare funded 1.7 million Pap smears through the MBS in the 2010 calendar year.

Table 1: Current MBS item descriptor for cervical cancer cytology

Category 6– Pathology Services (Cytology)
<p>MBS 73053</p> <p>Cytology of a smear from cervix where the smear is prepared by direct application of the specimen to a slide, excluding the use of liquid-based slide preparation techniques, and the stained smear is microscopically examined by or on behalf of a pathologist - each examination</p> <p>(a) for the detection of precancerous or cancerous changes in women with no symptoms, signs or recent history suggestive of cervical neoplasia, or</p> <p>(b) if a further specimen is taken due to an unsatisfactory smear taken for the purposes of paragraph (a); or</p> <p>(c) if there is inadequate information provided to use item 73055;</p> <p><i>(See para P16.11 of explanatory notes to this Category)</i></p> <p>Fee: \$19.60 Benefit: 75% = \$14.70 85% = \$16.70</p>

MBS 73055

Cytology of a smear from cervix, not associated with item 73053, where the smear is prepared by direct application of the specimen to a slide, excluding the use of liquid-based slide preparation techniques, and the stained smear is microscopically examined by or on behalf of a pathologist - each test

(a) for the management of previously detected abnormalities including precancerous or cancerous conditions; or

(b) for the investigation of women with symptoms, signs or recent history suggestive of cervical neoplasia;

(see para 16.11 of explanatory notes to this Category)

(See para P16.11 of explanatory notes to this Category)

Fee: \$19.60 Benefit: 75% = \$14.70 85% = \$16.70

MBS 73057

Cytology of smears from vagina, not associated with item 73053 or 73055 and not to monitor hormone replacement therapy, where the smear is prepared by direct application of the specimen to a slide, excluding the use of liquid based slide preparation techniques, and the stained smear is microscopically examined by or on behalf of a pathologist - each test.

(See para P16.11 of explanatory notes to this Category)

Fee: \$19.60 Benefit: 75% = \$14.70 85% = \$16.70

Explanatory notes for above items:

P16.11: Item 73053 applies to the cytological examination of cervical smears collected from women with no symptoms, signs or recent history suggestive of cervical neoplasia as part of routine, biennial examination for the detection of pre-cancerous or cancerous changes. This item also applies to smears repeated due to an unsatisfactory routine smear, or if there is inadequate information provided to use item 73055.

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

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

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

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

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

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

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

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

Related Items: 73053, 73055, 73057

Regulatory status

LBC tests with manual or automated slide reading are *in vitro* diagnostic (IVD) tests that are not of human origin and were, prior to 1 July 2010, exempt from the regulatory requirements of the Therapeutics Goods Act 1989. With the introduction on 1 July 2010 of a revised Regulatory Framework for IVDs, all IVDs supplied prior to 1 July 2010 are provided with a four year transition period (i.e. until 30 June 2014) to be brought into the new Regulatory Framework. Becton Dickinson Pty Ltd has advised that all products supplied in Australia are in accordance with the relevant legislation.

Patient population

The National Cervical Screening Program promotes the routine screening with Pap smears every two years for women between the ages of 18 and 69 years. In Australia each year approximately 2 million women are screened as part of this Program. These figures reflect a participation rate of 61 per cent of women in the target age range, based on consistent figures from 1996 to 2006 (AIHW & AACR 2008)

As previously mentioned there is a small subgroup of women who because of geographical location and a history of unsatisfactory smears, may benefit more from LBC. However the needs of this particular population have been largely addressed through other policy mechanisms.

Proposed MBS listing

It is intended that the SurePath™ LBC Pap test will be an alternative method of preparing a conventional Pap smear and will therefore be listed in category 6 Pathology Services, Group P6 Cytology of the MBS as is the routine Pap smear (MBS item number 73053, 73055 and 73057).

The Explanatory notes should be amended to reflect that on any one occasion only one of the techniques available should be used.

While the proposed descriptor refers to cell enrichment, further details of the methods used in the cell enrichment process may be needed in the below item to ensure that other methods cannot be claimed using the below item. This issue should be considered in the review.

Table 2: Proposed MBS item descriptor for liquid based cytology with cell enrichment

Category 6 – Pathology services (cytology)
<p>MBS 73053,73055,73057</p> <p>Cytology of a smear from cervix or vagina where the smear is prepared by direct application of the specimen to a slide or using cell enrichment liquid based techniques and the smear is microscopically examined by or on behalf of a pathologist using manual or automated methods.</p> <p>Fee: \$19.60 Benefit: 75% = \$14.70 85% = \$16.70</p> <p>Explanatory notes for above items:</p> <p>P16.11: Item 73053 applies to the cytological examination of cervical smears collected from women with no symptoms, signs or recent history suggestive of cervical neoplasia as part of routine, biennial examination for the detection of pre-cancerous or cancerous changes. This item also applies to smears repeated due to an unsatisfactory routine smear, or if there is inadequate information provided to use item 73055.</p> <p>Cytological examinations carried out under item 73053 should be in accordance with the agreed National Policy on Screening for the Prevention of Cervical Cancer. This policy provides for:</p> <ul style="list-style-type: none"> (i) an examination interval of two years for women who have no symptoms or history suggestive of abnormal cervical cytology, commencing between the ages of 18 to 20 years, or one to two years after first sexual intercourse, whichever is later; and (ii) cessation of cervical smears at 70 years for women who have had two normal results within the last five years. Women over 70 who have never been examined, or who request a cervical smear, should be examined. (iii) that on any one occasion only a direct application of the specimen to a slide or a cell enrichment liquid based technique should be used <p>The Health Insurance Act 1973 excludes payment of Medicare benefits for health screening services except where Ministerial directions have been issued to enable benefits to be paid, such as the Papanicolaou test. As there is now an established policy which has the support of the relevant professional bodies, routine screening in accordance with the policy will be regarded as good medical practice.</p> <p>The screening policy will not be used as a basis for determining eligibility for benefits. However, the policy will be used as a guide for reviewing practitioner profiles.</p> <p>Item 73055 applies to cervical cytological examinations where the smear has been collected for the purpose of management, follow up or investigation of a previous abnormal cytology report, or collected from women with symptoms, signs or recent history suggestive of abnormal cervical cytology.</p> <p>Items 73057 applies to all vaginal cytological examinations, whether for a routine examination or for the follow up or management of a previously detected abnormal smear.</p> <p>For cervical smears, treating practitioners are asked to clearly identify on the request form to the pathologist, by item number, if the smear has been taken as a routine examination or for the management of a previously detected abnormality.</p> <p>Related Items: 73053, 73055, 73057</p>

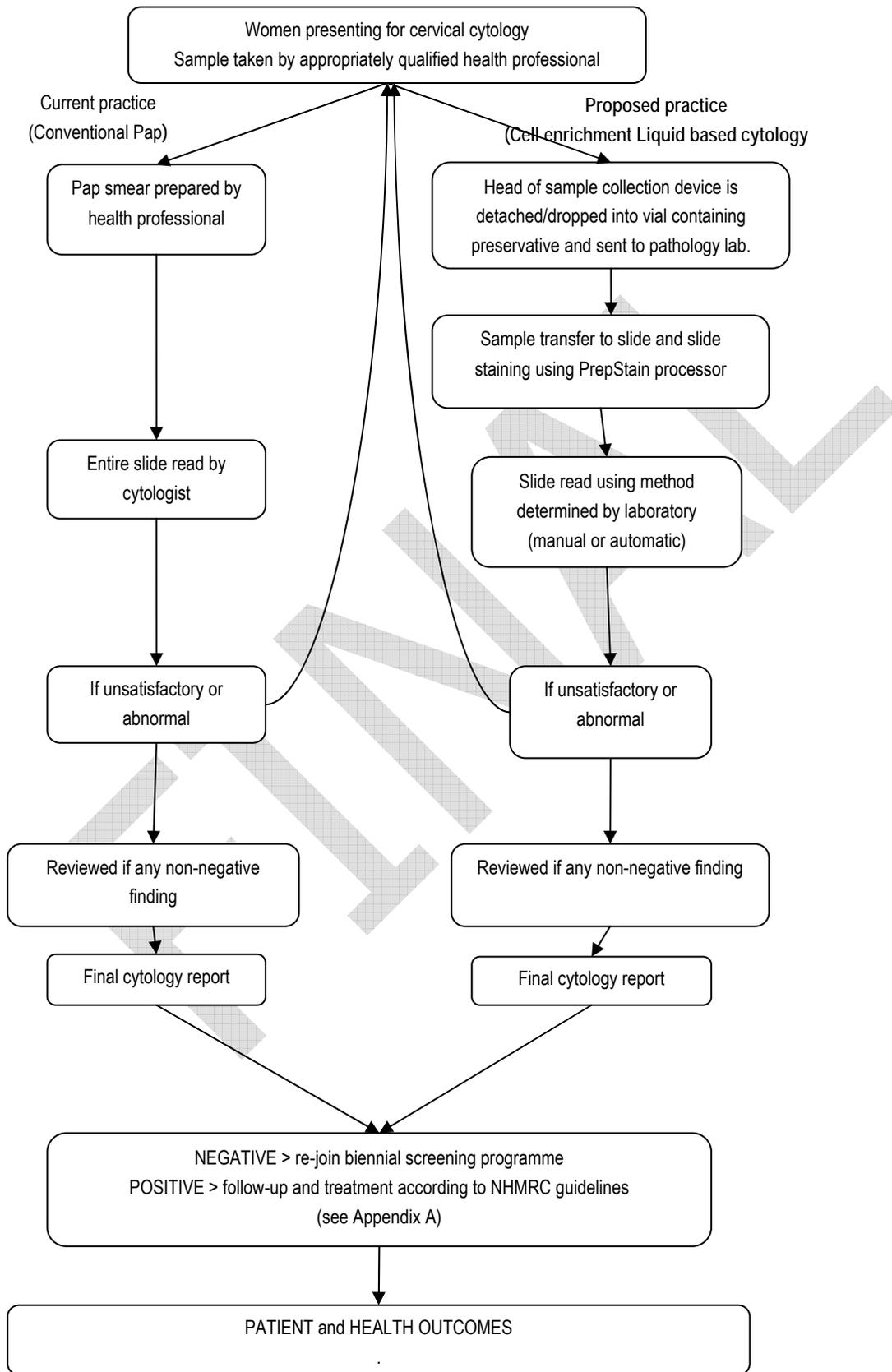
Clinical place for proposed intervention

Cell enrichment LBC is proposed to be a direct substitute for current conventional Pap smear cytology (see Figure 1). It is not proposed that cell enrichment LBC be used in conjunction with conventional cytology. Conventional Pap smear cytology would still be available on the MBS however its utilisation would be expected to decrease with the introduction of LBC.

Appendix A outlines the management of participants testing positive in the screening program.

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Figure 1 Current practice on the MBS compared with proposed practice



Comparator

The comparator for cell enrichment LBC is manual screening of conventional Pap smear cytology.

Secondary comparisons:

As in the 2009 MSAC review of LBC, secondary comparisons will be undertaken to examine the issue of automated versus manual reading of slides.

Cell enrichment LBC will also be compared with cell filtration LBC.

Clinical claim

In March 2009, MSAC published a report on '*Automated-Assisted and Liquid Based Cytology for Cervical Screening* (Medical Services Advisory Committee 2009a)'. The primary research question of the report was to assess the safety, effectiveness and cost-effectiveness of liquid based cytology using automated image analysis systems in comparison to manual reading of conventionally prepared Pap smear cytology samples for the screening and diagnosis of cervical cancer.

In addition the following secondary research questions were addressed:

What is the safety, effectiveness and cost-effectiveness of:

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

No studies were identified that assessed the impact of LBC with manual or automated slide reading on the incidence of invasive cervical cancer or consequent mortality rates compared to conventional cytology. The report therefore relied on evidence about the relative accuracy of manual or automated LBC for detecting precancerous cervical lesions to draw conclusions about its relative effectiveness.

The report concluded that LBC compared to conventional cytology:

- Is safe;
- Provides no statistically significant increase in sensitivity or specificity;
- Provides no statistically significant difference in sensitivity (high-grade squamous intraepithelial lesion [HSIL], low-grade squamous intraepithelial lesion [LSIL] or possible

low-grade squamous intraepithelial lesion [pLSIL] thresholds) or specificity (HSIL or LSIL thresholds) for the detection of CIN 2+;

- Reduces the specificity for the detection of cervical intraepithelial neoplasia [CIN 2+] at a threshold of pLSIL;
- Classifies more slides as positive for low grade lesions;
- Reduces the rate of unsatisfactory smears; and
- Has a high cost-effectiveness ratio which appears to be unfavourable in the current Australian setting.

The Medical Services Advisory Committee Public Summary Document (Medical Services Advisory Committee 2009b) outlines the decision of MSAC in respect to LBC after considering a wide range of information, including the report assessing the evidence, feedback on the report provided by the applicant and/or other relevant parties, as well as drawing on the individual expertise of MSAC members. Following consideration of this evidence MSAC concluded the following:

The MSAC finds that, in comparison to the Papanicolaou (Pap) test, LBC is safe, is at least as effective, but is not cost effective at the price requested. MSAC advises that LBC not be supported for public funding.

With respect to automated (computerised) testing of LBC specimens, MSAC finds that in comparison to the Papanicolaou (Pap) test, automated LBC testing is safe, is at least as effective but is not cost effective at the price requested. MSAC advises that automated testing of LBC specimens not be supported for public funding.

As such the above statement is the basis of the applicant's clinical claim ie. that the SurePath™ LBC Pap test is equally safe and effective as conventional Pap smear; with the addition that the cell enrichment method is also as safe and effective as the cell filtration method of LBC.

The applicant also states that there is new evidence to differentiate LBC from conventional Pap cytology, but it is unclear what this new evidence will add to the above statements.

A fundamental change in this proposal, compared to previous MSAC reviews of LBC, is the proposed MBS fee for LBC. The applicant (Becton Dickinson Pty Ltd) has proposed that LBC with cell enrichment (SurePath™) be made available on the MBS at the same fee as conventional cytology and that a cost minimisation analysis be undertaken (see Table 3) based on the decision of MSAC outlined in the Public Summary Document for LBC '*is safe, is at least as effective but is not cost effective at the price requested*' (Medical Services Advisory Committee 2009b).

Table 3: Classification of an intervention for determination of economic evaluation to be presented

		Comparative effectiveness versus comparator					
		Superior		Non-inferior	Inferior		
Comparative safety versus comparator	Superior	CEA/CUA		CEA/CUA		Net clinical benefit	CEA/CUA
						Neutral benefit	CEA/CUA*
						Net harms	None [^]
	Non-inferior	CEA/CUA		CEA/CUA*	None [^]		
	Inferior	Net clinical benefit	CEA/CUA	None [^]		None [^]	
		Neutral benefit	CEA/CUA*				
Net harms		None [^]					

Abbreviations: CEA = cost-effectiveness analysis; CUA = cost-utility analysis

* May be reduced to cost-minimisation analysis. Cost-minimisation analysis should only be presented when the proposed service has been indisputably demonstrated to be no worse than its main comparator(s) in terms of both effectiveness and safety, so the difference between the service and the appropriate comparator can be reduced to a comparison of costs. In most cases, there will be some uncertainty around such a conclusion (i.e., the conclusion is often not indisputable). Therefore, when an assessment concludes that an intervention was no worse than a comparator, an assessment of the uncertainty around this conclusion should be provided by presentation of cost-effectiveness and/or cost-utility analyses.

[^] No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this intervention

Outcomes and health care resources affected by introduction of proposed intervention

Outcomes

Health outcomes:

- Overall survival
- Incidence of cervical cancer (including glandular abnormalities, cervical intraepithelial neoplasia grade 3 (CIN3+) and adenocarcinoma in situ)
- Cervical cancer-specific mortality

Diagnostic outcomes

- Detection of HSIL, pLSIL and LSIL, CIN lesions measured as:
 - Test yield
 - Sensitivity and specificity
 - Positive and negative predictive value
 - True positive:false positive
 - Incremental rate of true positive

- Unsatisfactory rates

Proportion of cervical intraepithelial neoplasia (CIN) lesions detected in each cytological category (e.g. HSIL, pLSIL, LSIL)

- Proportion of samples yielding unsatisfactory results

Change in management

- Impact of screening on clinical management (e.g. further investigations, treatment avoided)

Patient outcomes:

- Quality of life
- patient preference
- satisfaction, anxiety
- patient compliance
- safety, adverse events

The above list is based on a cost effectiveness analysis being undertaken.

Health care resources

The key differences in resource usage are expected to be a reduction in repeat testing due to unsatisfactory results and any change in follow-up investigations (either cytological surveillance or colposcopy referral) due to any differences in test performance confirmed by the updated overall evidence reviewed, such as classifying more slides as positive for low-grade lesions (see Table 4).

In addition, the listing of the technology may also reduce the costs borne outside the MBS associated with any duplication of LBC and conventional Pap smear testing.

The provision of health care resources associated with cervical cancer cytology is also being affected by the recent introduction of the HPV vaccine in Australia. The expectation is a decrease in the prevalence of HPV and pre-cancerous cytological abnormalities and also an alteration of the distribution of cytological abnormalities.

Table 4: List of resources to be considered in the economic analysis

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource as a percentage	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other govt budget	Private health insurer	Patient	Total cost
<u>Resources provided to conventional cytology</u>										
- Weighted average costs of a medical consultation	GP/other	outpatient	100	Medicare items						
- Weight average costs of medical consultation (repeat unsat)	GP/other Specialist	outpatient	2.2	Literature						
- Pap test	GP/other Specialist	outpatient	100	Medicare items						
- Initiation of patient episode	Specialist	outpatient	100	Medicare						
<u>Resources provided to deliver LBC (SurePath™)</u>										
- Weighted average costs of a medical consultation	GP/other	outpatient	100	Medicare items						
- Weight average costs of medical consultation (repeat unsat)	GP/other Specialist	outpatient	1.8, 0.50	Literature, applicant						
- Pap test	GP/other Specialist	outpatient	100	Medicare items						
- Initiation of patient episode	Specialist	outpatient	100	Medicare						
<u>Resources provided in association with management of participants testing positive in screening program</u>										
Cost of colposcopy, no biopsy	Specialist	Outpatient	N/A at this time							
Cost of colposcopy, with biopsy	Specialist	Outpatient/ inpatient	N/A at this time							
Cost of cytology performed at colposcopy	Specialist	Outpatient/ inpatient	N/A at this time							
Cost of treating CIN 2/3	Specialist	Inpatient	N/A at this time							
Cost of follow-up for treated CIN 2/3	Specialist	Outpatient/ inpatient	N/A at this time							
Cancer work-up/treatment	Specialist	Inpatient								
- localised			N/A at this time							
- locally advanced/regional			N/A at this time							
- distant			N/A at this time							
Cost of surgery	Specialist	Outpatient/ inpatient	N/A at this time							
Costs of non surgical management	Specialist	Outpatient/ inpatient	N/A at this time							
Costs of work-up	Specialist	Outpatient/ inpatient	N/A at this time							

Proposed structure of economic evaluation (decision-analytic)

Table 5: Summary of PICO to define research question that assessment will investigate

Patients	Intervention	Comparator	Outcomes to be assessed	Healthcare resources to be considered
Women presenting for cervical cytology screening between 18-69 years	Cell enrichment LBC Proposed secondary comparison: Automated versus manual reading of cell enrichment LBC	Conventional cytology Proposed secondary comparison: cell filtration LBC	Health outcomes: Overall survival Incidence of cervical cancer Cervical cancer-specific mortality Diagnostic outcomes: Detection of HSIL, pLSIL and LSIL, CIN lesions measured as: Test yield Sensitivity and specificity Positive and negative predictive value, True positive: false positive Incremental rate of true positive Unsatisfactory rates Proportion of CIN lesions detected in each cytological category Change in management Impact of screening on clinical management Patient outcomes: Quality of life, patient preference, satisfaction, anxiety, patient compliance, safety, adverse events	See Table 4
<p>What is the safety, effectiveness and cost effectiveness of cell enrichment liquid-based cytology using manual reading of slides compared with manual reading of conventionally prepared Pap smear cytology?</p> <p>What is the safety, effectiveness and cost effectiveness of cell enrichment liquid based cytology using automated image analysis systems compared with manual reading of conventionally prepared Pap smear cytology?</p> <p>What is the safety, effectiveness and cost effectiveness of cell enrichment liquid based cytology compared with cell filtration liquid based cell cytology? To what extent, if at all, do these comparisons vary according to whether either method of cytology is assessed using manual reading or automated image analysis systems?</p>				

The economic model used in the 2009 MSAC review of LBC was conducted using a set of linked models to simulate (i) sexual behaviour and HPV transmission in Australia; (ii) the natural history of cervical intraepithelial neoplasia (CIN) and invasive cervical cancer; and (iii) screening, diagnosis and treatment according to practice in Australia (see Figure 2). These models were based on previously published work (Canfell et al 2004; Smith et al 2008) and on a screening model developed for the NZ National Screening Unit (Canfell et al 2008) and was used as a template to assist in developing this consultation decision analytic protocol for cell enrichment liquid based cytology. An erratum which recalculated the model over a lifetime beginning at 18 years of age was subsequently published at:

These models required parameterisation with population, screening, treatment and cost data specific to Australia. Various tests involved in the screening and treatment pathways were also characterised. There may be some variation in these across different settings, so where possible, local data were preferred. Data were also required to model the underlying processes involved in the transitions between health states of HPV infection, CIN and cervical cancer.

The models were used to estimate the incremental cost-effectiveness ratios (ICERs) of (i) automated reading and (ii) manual reading of LBC slides in comparison to current practice of manual reading of conventionally prepared Pap smear cytology samples. The ICERs were based on the lifetime costs and effects of each strategy. These lifetime outcomes were calculated with a cohort model which ran from age 10 until age 84. Life years were the primary outcome measure, but health care resource usage was also predicted. All other screening practices, such as the time between screening tests and the management of abnormal cytology, reflected current practice, taking into account compliance. The analysis used a health services perspective. Future costs and outcomes were discounted at 5 per cent. One-way sensitivity analyses were performed on those parameters for which there was substantial uncertainty, or which could have had a significant influence on the results.

Figure 2 Linked models used to perform economic evaluation

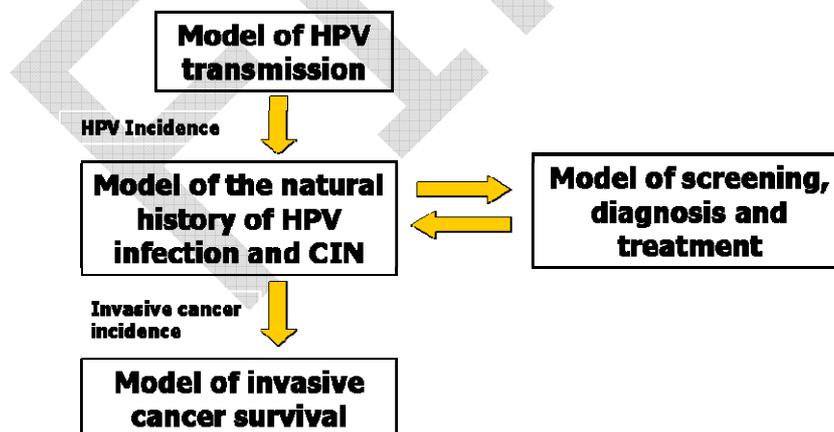
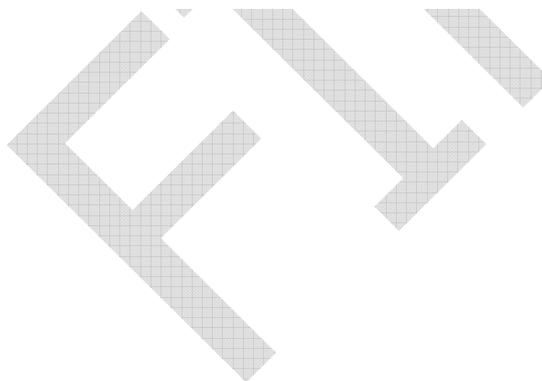
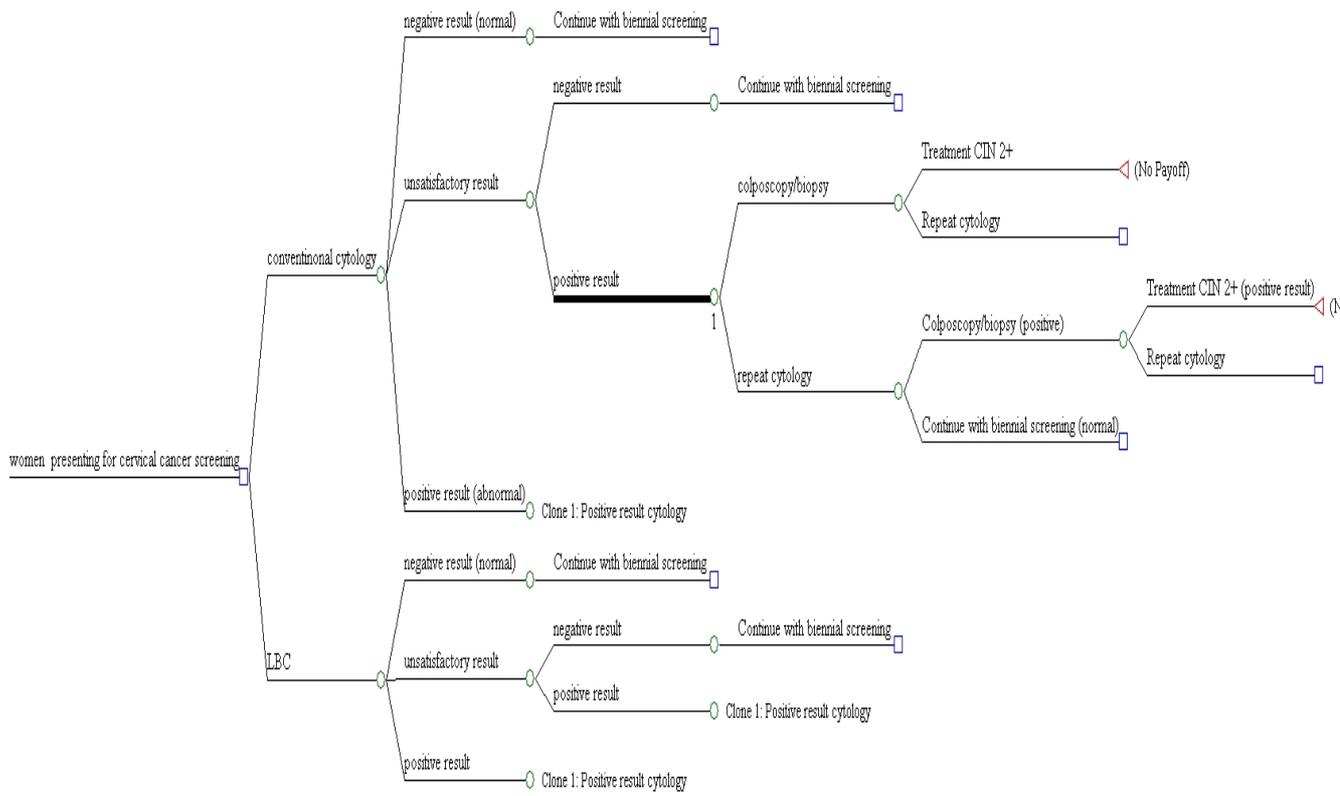


Figure 3 represents a very simplified model of screening, diagnosis and treatment. It does not take into account the model of HPV transmission, history of HPV infection and CIN nor of cancer survival. As can be seen, the only difference in the model is that women receive LBC instead of conventional cytology: as such it is the test characteristics that will drive the differences and the cost.

Figure 3 Simplified decision tree structure of screening, diagnosis and treatment of women presenting for cervical cancer screening



Proposed model

The following points will need to be considered when modelling a decision analysis for cell enrichment LBC:

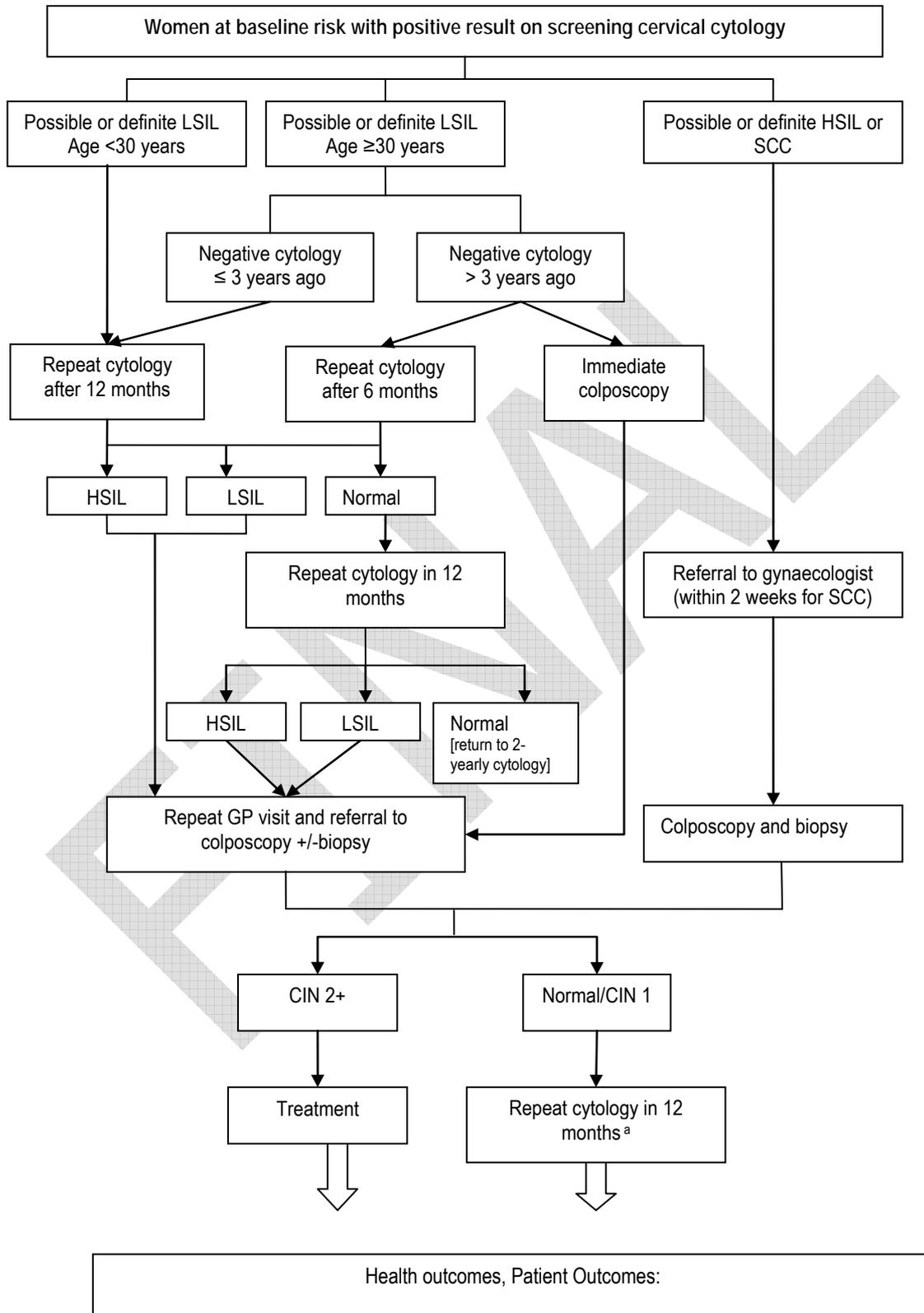
- Model is to be a cost effectiveness model based on the 2009 LBC model
- The MBS fee for cell enrichment LBC is to be identical to conventional cytology (\$19.60). Further explanation will be needed to ensure that the proposed fee is sustainable and is not shifting out of pocket costs to the patient e.g. consideration of women's total out of pocket costs should be considered as part of the economic evaluation.
- Rates of HSIL, LSIL and pLSIL between LBC and conventional cytology is to be based on the overall updated evidence presented rather than as an *a priori* assumption of equivalence or non inferiority.

Sensitivity analysis should be used to address differences in unsatisfactory smear rate and adjunctive testing.

ICERs cannot be calculated without first characterising the accuracy of the test relative to conventional cytology, against an *appropriate* reference standard. More recent studies have been published (Confortini et al 2010; Saraiya et al 2010; Siebers et al 2009; Sykes et al 2008) however it is not known whether these would meet the inclusion criteria of a new review of cell enrichment LBC.

It should be noted that the model to be constructed as part of this review concerns the cell enrichment technique. A wider assessment is being considered by the Department (1276 National Cervical Screening Renewal Assessment) and it is expected that the findings of this review will inform to this future assessment.

Appendix A Management of participants testing positive in screening program (based on(NHMRC 2005)



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