

***Liquid based  
cytology for  
cervical screening***

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**MSAC reference 12a**

**Assessment report**

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The Medical Services Advisory Committee is an independent committee which has been established to provide advice to the Commonwealth Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform Government decisions about which medical services should attract funding under Medicare.

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***MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.***

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# Executive summary

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## The procedure

Liquid-based cytology (LBC) is the production of a thin layer of cervical cells on a microscope slide, suitable for diagnosis of cytological abnormalities. A cytotechnologist carries out manual screening of the preparation under the supervision of a physician.

A gynaecologic sample is obtained using a plastic spatula with either an endocervical brush or a cervical broom in the manner of conventional screening (taken to mean a Pap smear throughout this review) and the sample is rinsed into a vial containing preservative solution. The sample vial is capped, labelled and sent to the laboratory where it is placed into a processor that gently mixes the sample to disperse cells and break up any blood, mucus or non-diagnostic debris present.

The sample is either centrifuged to produce a cell pellet or drawn through a filter under negative pressure to collect cells. The resulting cell sample is fixed onto a glass slide and stained by the Papanicolaou staining method for examination under a microscope.

This report reviews the use of all identified studies investigating LBC, whether preparation of collected cells was by centrifugation or filtration techniques.

## The Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government to strengthen the role of evidence in health financing decisions in Australia. The MSAC advises the Commonwealth Minister for Health and Ageing 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.

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. A team from Monash University's Centre for Clinical Effectiveness, Monash Institute of Health Services Research, and Health Economics Unit, was engaged to conduct a systematic review of literature on liquid-based cytology for cervical screening. A supporting committee with expertise in this area then evaluated the evidence and provided advice to the MSAC.

## The MSAC's assessment of liquid-based cytology

### Clinical need

Cervical cancer is a largely preventable disease which remains a significant cause of morbidity and mortality worldwide. It is usually characterised by a long pre-clinical phase of several years during which it is possible to detect cytological abnormalities which may develop into cancer if untreated. If identified at the pre-cancer stage of cervical intraepithelial neoplasia (CIN), the abnormal cells are usually treatable to prevent the development of cancer. Although CIN can progress to invasive cancer, studies indicate that many of the pre-cancerous lesions will either regress or persist without progression.

Pre-cancerous lesions are asymptomatic, highlighting the importance of screening to detect both pre-cancerous lesions and the early stages of the disease. Although pre-cancerous lesions and early stages of cervical cancer are treatable, the prognosis for later stages of the disease is poor. Persistent disease will ultimately result in death.

Cervical cancer is the ninth most common cancer in Australian women. Figures from 1998 show that there were 868 new cases of cervical cancer in Australia with an age-standardised incidence rate of 8.6 cases per 100,000 women and 269 deaths from cervical cancer, representing an age-standardised mortality rate of 2.5 cases per 100,000 women and 3,693 person-years life lost.

### Safety

The safety issues for cervical screening by LBC are the same as those for Pap smears because the method for collecting cellular material is the same for both. Specific safety issues or risks associated with collection of cervical cells for screening by LBC have not been evaluated and reported in the literature. None of the appraised studies reported these outcomes or technical problems arising for women undergoing cervical screening using these technologies.

### Effectiveness

Secondary studies of LBC concluded that there is insufficient high quality data or evidence to suggest that LBC is better than the Pap smear for cervical screening. However, Sulik et al (2001) suggest that there may be a role for LBC for women who have had abnormal Pap test results or who are at a high risk of cervical cancer due to infrequent screening. Bernstein et al (2001) deduced that the LBC test improved sample adequacy and led to improved diagnosis of low-grade and high-grade squamous intraepithelial lesions but results comparing LBC and Pap tests were not evaluated against a histological reference test. All authors noted that the most frequent study design was the split-sample method and that many of the clinical studies examined were funded partially or completely by manufacturers of LBC technologies.

There were problems associated with the calculation of sensitivity and specificity for all of the published primary studies investigating LBC.

The two studies comparing LBC results with cervical histology (regarded as the appropriate reference test) allowed sensitivity and specificity to be calculated, however, there are issues with the representativeness and completeness of patient samples (Bergeron et al 2001, Park et al 2001; see section 'Critical appraisal of primary studies', page 36). As part of this review, test parameters from the raw data presented by these authors were re-calculated. For the Pap smear, the different thresholds assessed by Bergeron et al (2001) above which cytology results are considered important for further investigation yielded sensitivity values ranging from 39.4 per cent to 86.8 per cent and specificity from 47.8 per cent to 98.9 per cent. For LBC, the corresponding values were sensitivities of 41.7 per cent to 82.6 per cent and specificities of 52.2 per cent to 90.2 per cent.

Diagnostic characteristics were also extracted from Park et al (2001) for a single threshold to give 89.6 per cent sensitivity and 52.1 per cent specificity for the Pap smear and 82.8 per cent sensitivity and 62.0 per cent specificity for LBC. Pooling of diagnostic characteristics was not appropriate due to clinically heterogeneous populations and differing cytology thresholds. Any difference in diagnostic characteristics of the tests must be interpreted with caution due to the failure of the studies to meet several validity criteria and the probable presence of non-appraisable bias as a result.

The five remaining studies (Anton et al 2001, Bai et al 2000, Guidos & Selvaggi 2000, Obwegeser et al 2001, Tench 2000) did not perform the gold standard reference test on subjects who had negative results with LBC, thereby disallowing calculation of either the sensitivity or specificity of LBC (see section 'Accuracy of the tests' on page 20). Without these parameters the studies could not be used in the assessment of test accuracy or performance of LBC.

Without data from a cervical histology reference test it is still possible to calculate some test parameters that provide information on the performance of screening tests relative to each other. The section entitled 'Critical appraisal of primary studies' provides this material. While it demonstrates the performance of LBC as a screening test relative to the Pap smear, the material is not relevant to the present review where the chosen reference is cervical histology.

Many studies failed to define an upper limit to the period over which the histological outcome was determined. It was therefore unclear whether LBC and conventional cytology were being compared on an equivalent basis.

Another important issue is that of interpreting overseas data in the Australian context. The difference in cytology classification systems means that data cannot be directly related, bringing into question the relevance of some data. Specifically, the US Bethesda System is not directly comparable to the cytology classifications used in Australia.

In summary, there is insufficient evidence to enable us to draw conclusions regarding the diagnostic characteristics of LBC and Pap smears for cervical screening. The lack of high quality evidence on the performance of LBC does not permit evaluation of whether it is equal or superior in effectiveness to Pap smears. Further high quality studies using an acceptable reference standard, such as histological confirmation of cytology results, are crucial to allow a valid and reliable judgement concerning the sensitivity and specificity of LBC.

## Cost-effectiveness

A decision-analytic model was used to simulate the cost effectiveness of LBC versus the Pap smear. LBC is associated with greater costs per woman than the Pap smear and there is insufficient evidence to support a claim that LBC is superior to the Pap smear in detecting high-grade lesions or invasive cancer. It follows that there is no evidence to suggest that LBC would be cost-effective at the proposed price. Given the additional cost associated with LBC, the minimum sensitivity at which LBC would produce a cost-effectiveness ratio of \$40,000 or less per life-year saved is 90 per cent compared to 80 per cent for conventional screening, assuming specificity remains constant at 99.4 per cent. There is no evidence to suggest that a difference in sensitivity of this magnitude is likely.

If the evidence is interpreted as suggesting that LBC is no worse than conventional cytology in the detection of high-grade lesions and if it is accepted that there may be savings through fewer unsatisfactory screens and consequently fewer repeat screens, then the question becomes: At what cost for LBC do potential savings exceed the additional cost of LBC over the Pap smear? Total costs for a screen using conventional cytology are estimated at \$19.00. If total costs for LBC were less than \$19.53 and the proportion of unsatisfactory slides was reduced from 3.5 per cent to 0.7 per cent, then LBC could be cost-saving compared to conventional screening.

## Recommendation

Since there is currently insufficient evidence pertaining to liquid-based cytology for cervical screening, the MSAC recommends that public funding should not be supported at this time for this screening test.

The Minister for Health and Ageing accepted this recommendation on 16 October 2002.

# Introduction

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The Medical Services Advisory Committee (MSAC) has reviewed the use of liquid-based cytology (LBC) for cervical screening as a replacement for the Papanicolaou (Pap) smear. The MSAC evaluates new health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. The MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

The MSAC's terms of reference and membership are in Appendix A. The MSAC is a multidisciplinary expert body, comprising members drawn from disciplines such as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for cervical screening with LBC.

# Background

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This report presents an evaluation of the clinical effectiveness and cost-effectiveness of LBC as a replacement for the Pap smear in cervical screening. This report integrates a submission made to the MSAC from the technology manufacturer and a request made to the MSAC from within the Commonwealth Department of Health and Ageing.

A submission was made to the MSAC to consider the merits of replacing the Pap smear with LBC as the cervical screening test for possible listing on the Medicare Benefits Schedule (MBS). The predecessor of the MSAC, the Australian Health Technology Advisory Committee, previously investigated some aspects of these technologies (AHTAC 1998). The AHTAC report was updated and reassessed by the New Zealand Health Technology Agency (Broadstock 2000). The current report incorporates the AHTAC and NZHTA assessments and also presents data published after May 2000 when database searching ceased for Broadstock (2000).

## Cervical Screening

Cervical cancer is one of the most common cancers among women throughout the world. One in 101 Australian women will develop cancer of the cervix in their lifetime. Although the incidence of cervical cancer is decreasing in Australia due to the introduction of screening programs, it still remains the ninth most common form of cancer in Australian women. Almost 1,000 new cases of cervical cancer are identified each year and 269 women died from the disease in 1998 (AIHW 2000).

Cervical cancer was the first, and remains the only, cancer to be recognised as being virally induced. The International Agency for Research on Cancer has designated human papillomavirus (HPV) infection as a necessary but not sufficient cause of cervical cancer (<http://www-dep.iarc.fr/>). Squamous cell carcinoma is the most frequent type of cervical cancer, comprising about 85 per cent of currently reported cases. The other 15 per cent are adenocarcinomas (NHMRC 1994; Jelfs 1995; AHTAC 1998). Squamous cell cervical cancers are usually found in the transformation zone of the cervix which consists of columnar cells that undergo metaplasia to squamous cells. The variety of pathological changes seen in the transformation zone may be benign and inflammatory due to the presence of bacteria, fungi or *Chlamydia*. HPV causes characteristic cell changes. Cervical intraepithelial neoplasia (CIN) is graded into three levels of severity CIN I, CIN II and CIN III. It is recognised as a treatable pre-cancerous lesion with the potential to progress to invasive cervical cancer. Micro-invasive carcinoma is the earliest stage of invasive cervical cancer.

Cervical cancer is a disease in which normal cell division and renewal is replaced by uncontrolled development of malignant cells as a result of persistent infection with high-risk types of HPV (AIHW 1998; Jelfs 1995; Galloway 1999; WHO 1995; Southern & Herrington 1998; Pfister 1996). These cancer cells multiply in an uncontrolled manner to form a tumour which may expand locally by invasion or systemically by metastasis via the lymphatic and/or vascular systems (Jelfs 1995). The major symptom of cervical cancer is unusual bleeding from the vagina, sometimes accompanied by an unusual vaginal discharge.

## Natural history of the development of pre-cancerous lesions and cancer

Cervical cancer is associated with women across different age groups but tends to be more prevalent among women in their fifth or sixth decade with a mean age of 54 years at diagnosis (Canistra & Niloff 1996). By contrast, the precursors of invasive cervical cancer usually occur in women under the age of 40. These precursor lesions (CIN) are characterised by dysplastic changes confined to the epithelium.

The natural history of CIN is extremely variable. Untreated CIN may either return to normal or progress to invasive cervical cancer. About one-third to one-half of cases of CIN I and CIN II spontaneously regress (Channen 1990). The time for CIN III to progress to invasive cancer has been reported as ranging from one to 30 years, although it is now accepted that abnormalities detected by screening only develop into invasive cervical cancer if high-risk subtypes of HPV persist over a number of years (Zielinski et al 2001, Nobbenhuis et al 1999, Liaw et al 1999). Persistent infection with high-risk subtypes of HPV is an established, significant risk factor for the development of cervical cancer.

High-risk HPV types are found in 99.7 per cent of cervical cancers worldwide (Bosch et al 1995; Walboomers et al 1999; CDC 1999; Cuzick et al 1999). Women infected with high-risk HPV types, compared with those who are not infected, have relative risks of 12 to 350 for the development of high-grade cervical disease, with the higher values applicable to those with persistent HPV infection (Cuzick et al 1999; Liaw et al 1999; Nobbenhuis et al 1999). Prospective studies have demonstrated that infection with high-risk HPV types consistently precedes the development of CIN II/III (Cuzick et al 1999; Liaw et al 1999; Nobbenhuis et al 1999; Munoz & Bosch 1996; Koutsky et al 1992; Ho et al 1995). These studies are further supported by molecular studies identifying the mechanisms by which high-risk HPV types contribute to carcinogenesis (Cuzick et al 1999; Liaw et al 1999).

High-risk HPV types contain genomic sequences E6 and E7 which are consistently retained and expressed in cancers. Increased expression of the E6 and E7 proteins affects cell growth because these proteins bind to cellular tumour suppressor proteins – E6 with p53 and E7 with the retinoblastoma gene product – causing their inactivation and ultimately the disruption of normal cell cycle control (Galloway 1999; Southern & Herrington 1998; CDC 1999). Integration of HPV DNA into the host's cellular DNA occurs in the majority of cervical cancers. This event generally disrupts the HPV E2 transcription regulatory gene and enhances the stability of HPV mRNA by attaching it to cellular sequences.

The epidemiological and molecular evidence was regarded as sufficiently strong for the World Health Organization and the European Research Organisation on Genital Infection and Neoplasia to issue a joint statement (WHO 2000) that included the following:

1. Cervical cancer is a rare complication of cervical infection with a high-risk HPV type; and
2. A persistent high-risk HPV infection is necessary for the development, maintenance and progression of a cervical cancer precursor lesion (high-grade cervical intraepithelial lesion, CIN III).

## Detection and treatment

The Pap smear is the most common screening method for the detection of pre-cancerous changes. The test involves a general practitioner or gynaecologist inserting a speculum into the vagina and gently scraping the surface and outer canal of the cervix. The collected cells are transferred to a microscope slide for assessment at a pathology laboratory. If a pre-cancerous change is suggested by the cervical smear, the woman is referred to a gynaecologist who undertakes an examination of the cervix with a magnifying instrument called a colposcope to highlight any suspicious pre-cancerous or cancerous areas. At this stage a biopsy can be taken for examination by a pathologist.

Pre-cancerous changes are relatively easy to treat and are almost always curable. The type of treatment depends on whether the observed change is low-grade or high-grade, the woman's age and general health, whether the woman wishes to have children and the woman's preferences. The range of treatments for pre-cancerous changes includes cryosurgery, cauterisation, laser surgery or loop or cone biopsies. In a small number of cases a hysterectomy may be necessary.

Despite the widespread availability of screening in Australia since the 1960s, it was estimated in 1991 that only 46 per cent of cases of invasive disease were being prevented (AHMAC 1991). It should be noted that it is difficult to compare cervical abnormalities using different grading systems. For example, the Australian classification system is not directly comparable to the US Bethesda System. Instead, the 'Australian' classification of low-grade epithelial abnormalities can best be described as a hybrid of the Bethesda System classifications of low-grade squamous intraepithelial lesion (LSIL) and atypical squamous cells of undetermined significance (ASCUS; Table 1).

## New screening technologies

It is essential that appropriate evaluation is conducted to ensure that the introduction of a new technology benefits those women receiving the test, produces savings overall or produces significant clinical or financial gains. In some cases, the introduction of a new technology may produce savings across the entire screening program that offset the increased cost of the test (American Society of Cytopathology 2000).

For example, increasing the sensitivity of the screening test could make it possible to lengthen the screening interval and reduce the cost of the program overall. The average time from appearance of screen-detectable abnormalities to development of invasive cervical cancer is considered to be about 10 years. However, the relatively short screening interval is needed because of the number of false negative tests. Women need to be re-tested two to three years after a normal smear, not because of rapid development of the disease but to reduce the chance of missing an existing abnormality. While increasing the sensitivity of the test would appear to benefit those women whose abnormalities would not otherwise have been detected on that smear, the gain is not clear cut – the abnormalities may have regressed before the next Pap smear or may be picked up on the next Pap smear with no adverse effect on prognosis.

A technology that made it possible to identify more accurately women at very low-risk of cervical cancer could potentially reduce costs through an increase in the screening interval. However, costs would only be reduced if the level of compliance was high with a longer screening interval. Thirty five to 40 per cent of women are currently being re-

screened within two years of a normal smear. A technology which circumvented the need for repeat Pap smears as a result of unsatisfactory smears would also reduce the overall costs of a screening program if women and gynaecologists had sufficient confidence in using the alternative technology.

## National Health & Medical Research Council guidelines

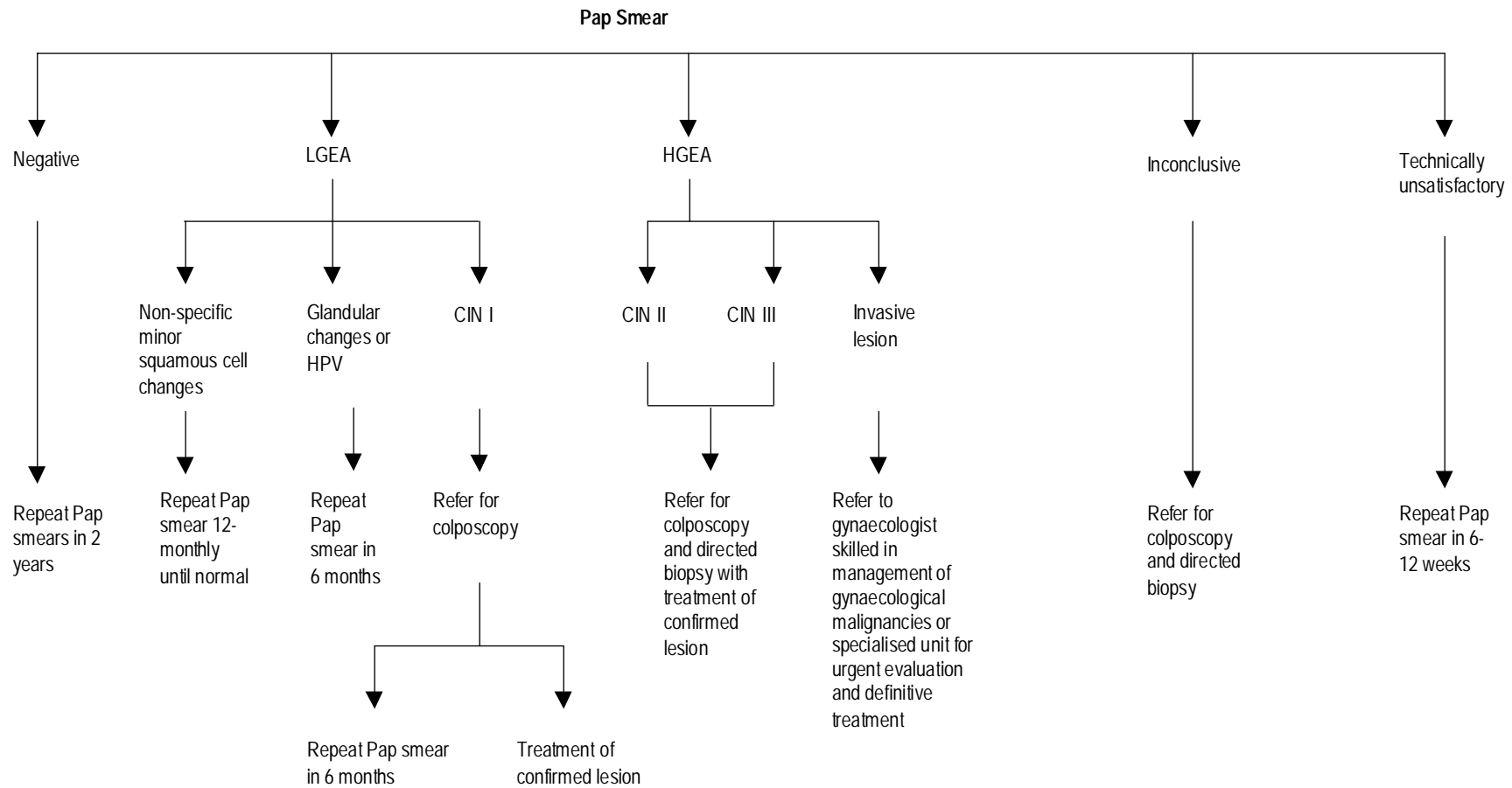
Currently, patients who test positive for low-grade epithelial abnormalities (LGEA) are recommended for treatment in line with the Australian National Health and Medical Research Council (NHMRC) guidelines, shown in Figure 1. The standard treatment of lesions confirmed as CIN I on colposcopy and biopsy, or HPV only, is equivocal. Traditionally a large proportion of CIN I-confirmed lesions have been treated in Australia whereas Canada, Holland and the United Kingdom manage these lesions solely by close observation (NHMRC 1994).

Table 7 presents a breakdown of the use of cervical cytology (MBS Item number 73053) conducted between January 1997 and April 2000 and billed to the Health Insurance Commission. Table 8 presents a similar breakdown of the extent of cervical cytology carried out due to detected abnormalities (MBS Item number 73055). This is used when a Pap smear is not specifically for cervical screening and covers cytological examinations undertaken due to the management, follow-up or investigation of a previous abnormal cytology report; due to the presence of symptoms, signs or recent history suggestive of abnormal cervical cytology are also included, as are repeat smears required due to an unsatisfactory test. Further details regarding these item numbers are provided on page 16. These figures do not include work performed in the public sector.

Public sector work could account for about 15 per cent of all smears undertaken. As illustrated in Tables 7 and 8, the number of HIC claims in 2000 for Item Nos 73053 and 73055 = 1,307,062 + 245,695 = 1,552,757. Also for 2000, the Royal College of Pathologists of Australasia's Cytopathology Quality Assurance Program (RCPA QAP) publication 'Performance Standards for Australian Laboratories Reporting Cervical Cytology 2001 - Data for January 1 to December 2000' lists 1,992,282 smears on page 2 as the total number of specimens for the year. This gives the public sector proportion (not billed to Medicare) as 22 per cent. However, the Performance Standards figure includes post-hysterectomy smears (Item no 73057) which are not included in the 1,552,757 HIC claims. In addition, since 2000, all public sector labs other than the Victorian Cytology Service and those that remain in non-privatised public hospitals have been moved to billing the HIC and are loosely considered to be 'private sector'. For these reasons the public sector proportion has probably fallen.

## Management of high-grade abnormalities

There are two main treatment options for high-grade intraepithelial abnormalities, or HGEA (NHMRC, 1994). These include ablative modalities involving the destruction of the abnormal cervical epithelium by physical means and excisional modalities involving the removal of the abnormal cervical epithelium. Ablative modalities include cryocautery using carbon dioxide or nitrous oxide, electrocoagulation diathermy and carbon dioxide laser. Excisional modalities include cone biopsy using a scalpel or laser, loop electro-excisional procedures including large loop excision of transformation zone, loop electro-surgical excisional procedure, Cartier loop excision and hysterectomy.



**Figure 1** Current NHMRC guidelines for the management of women with screen detected abnormalities  
 Abbreviations: LGEA=low-grade epithelial abnormalities; HGEA=high-grade epithelial abnormalities; CIN=cervical intraepithelial neoplasia

**Table 1 Categories of reporting cervical smears in Australia**

<p><b>High-grade epithelial abnormalities (HGEA)</b></p> <p><b>1. Intraepithelial lesions (HSIL*)</b></p> <p>Squamous cell changes comprising smears indicating moderate dysplasia (CIN II) and severe dysplasia or carcinoma-in-situ (CIN III)</p> <ul style="list-style-type: none"><li>• Squamous cell changes of severe dysplasia or CIN III with features of possible invasion</li><li>• Glandular cell changes comprising smears indicating significant columnar cell dysplasia and adenocarcinoma-in-situ</li><li>• Mixed intraepithelial lesions with squamous and glandular components</li></ul> <p><b>2. Invasive lesions</b></p> <ul style="list-style-type: none"><li>• Squamous cell carcinoma</li><li>• Adenocarcinoma</li><li>• Undifferentiated carcinoma of small-cell or large-cell type</li><li>• Mixed carcinoma</li></ul> <p><b>High-grade, non-epithelial abnormalities</b></p> <ul style="list-style-type: none"><li>• Sarcomas, lymphomas, malignant melanoma, etc</li></ul> <p><b>Inconclusive</b></p> <ul style="list-style-type: none"><li>• Smears with abnormal cells suggesting a high-grade abnormality, but in which a confident cytological diagnosis is not possible (ASCUS*)</li></ul> <p><b>Low-grade epithelial abnormalities (LGEA)</b></p> <p><b>1. Squamous cell changes</b></p> <ul style="list-style-type: none"><li>• Smears showing non-specific minor changes with some features that may be associated with HPV or minimal dysplasia but lacking stringent criteria of HPV effect or dysplasia (ASCUS*)</li><li>• Smears showing stringent criteria of HPV effect (LSIL*)</li><li>• Smears indicating mild dysplasia (CIN I) with or without criteria of associated HPV effect (LSIL*)</li></ul> <p><b>2. Glandular cell changes</b></p> <ul style="list-style-type: none"><li>• Smears showing minor changes in endocervical glandular cells including changes attributable to HPV effect (AGUS*)</li></ul> <p><b>Negative</b></p> <ul style="list-style-type: none"><li>• Smears in which no abnormal cells are detected</li><li>• Smears with changes which are readily attributable to reactive processes (within normal limits – WNL*)</li></ul> <p><b>Technically unsatisfactory</b></p> <ul style="list-style-type: none"><li>• Smears which cannot be assessed at all due to the paucity of the sample, or a covering of blood or inflammatory exudate, or poor fixation</li></ul>
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Source: NHMRC (1994). \*Bethesda categorisation system. Abbreviations: HSIL=high-grade intraepithelial lesions; LSIL=low-grade intraepithelial lesions; CIN=cervical intraepithelial neoplasia; ASCUS=atypical squamous cells of undetermined significance; HPV=human papillomavirus; AGUS= atypical glandular cells of undetermined significance.

## Management of low-grade abnormalities

There is no consensus regarding treatment of LGEAs, be they lesions confirmed as HPV only or as CIN I on colposcopy/biopsy. The two usual treatments for biopsy-confirmed CIN I are observational management by repeat smears or active management by ablation or excision of the lesion. Current management according to NHMRC guidelines for LGEA smears varies depending on the cellular changes observed on the smear.

Although a repeat Pap smear can be performed in 6 to 12 months to see whether the LGEA finding persists, the repeat smear may not be sensitive enough for disease detection and delayed testing may result in patient anxiety, loss to follow-up and disease progression.

It is generally accepted in Australia that approximately five per cent of Pap smears are reported as LGEA; however, this is likely to be an under-estimate because this is based on the number of women with claims for MBS item number 73053 to the Health

Insurance Commission. Of all LGEA smears detected in NSW in 1998, 21.7 per cent were reported to be HGEA or cancer following histological examination. However, review of the data revealed that only 3.8 per cent of LGEA smears were actually HGEA or cancer on histology (NSW Cervical Screening Program and NSW Pap Test Register Annual Statistical Report, 1998). Therefore, the proportion of Australian women with predictions of LGEA who actually have HGEA is unknown. Based on available data, the percentage of Pap smears with predictions of LGEA who have HGEA can be assumed to lie between 3.8 per cent and 21.7 per cent.

## Cervical screening in Australia

Cervical cytology terminology in Australia is different from that in the US and the UK. For example Australia uses only the two categories 'satisfactory' and 'unsatisfactory' in reporting the quality of smears. There are other major differences between Australia and the US which must be considered when comparing studies and screening programs, and how results might be generalisable to women in Australia. Some of these major differences are reported in Table 2.

**Table 2 Major differences in cervical screening programs in Australia and the US**

Factor	Australia	USA
Program organisation	Formal, comprehensive, nationally-coordinated	No formal program
Monitoring/recruitment of women	Special programs/registers in all States and Territories monitor and follow-up women undergoing regular screening	Mostly ad hoc; no systematic effort to recruit or promote the regular participation of women
Terminology for reporting cervical cytology	Unique to Australia – not directly comparable to the Bethesda System	The Bethesda System
Quality of specimens collected	Annual feedback to smear-takers is an NPAAC requirement	No formal requirement
Quality of laboratory reporting	Laboratories must meet quantifiable Performance Standards measured on their routine work for NATA accreditation	No measures of quality based on routine laboratory work used in accreditation
Maximum number of slides screened per day	70 per cytologist	100 per cytologist plus review slides
Follow-up of women with abnormalities	Safety net function undertaken by State and Territory Pap test registers	No formal requirement

NPAAC=National Pathology Accreditation Advisory Council; NATA=National Association of Testing Authorities.

## National Cervical Screening Program

Organised cervical screening using the Pap smear and the appropriate management of screen-detected abnormalities have been shown to be effective in reducing morbidity and mortality from cervical cancer. The Australian National Cervical Screening Program (NCSP) has reduced the mortality from cervical cancer by 40 per cent in the past 10 years. Data from the International Agency for Research on Cancer suggest that very few comparable countries have lower incidence and mortality rates from cervical cancer than Australia (<http://www-dep.iarc.fr/>).

Studies of invasive cervical cancer have shown that at least a third of women with the disease had never been screened (Wain et al 1992). A recent Victorian Cervical Cytology Registry report provided evidence that only one quarter of the women with

microinvasive cancer had received adequate screening (Mitchell et al 2002). Improving the rate of adequate screening offers the greatest potential for saving lives.

### Australian cytology and histology data

The Policy and Cost-Effectiveness Working Group (“the Working Group”) of the National Advisory Committee to the National Cervical Screening Program is currently overseeing several studies, including a review of the NHMRC guidelines on the management of women with screen-detected abnormalities (1994). To minimise the replication of tasks and assessments, the National Advisory Committee to the National Cervical Screening Program authorised sharing with the MSAC of relevant data collected by the Working Group. The data presented below were requested by the National Advisory Committee to the National Cervical Screening Program from State and Territory cervical screening registries in response to the following two-part question:

- a) For how many women in the most recent 12-month period are data available with any cervical histology results within six months of an abnormal Pap smear by level of abnormality (first abnormal smear in the 12-month period); and
- b) For the women in a), please provide a cross-tabulation between histology and any cytology test performed by the level of abnormality for the most recent 12 month period for which data are available.

#### Cytology categories requested:

- Minor non-specific changes in squamous cells (MNSC);
- HPV (when HPV is the only abnormality present);
- CIN I;
- CIN II;
- CIN III;
- Inconclusive, possible HGEA;
- Adenocarcinoma in situ;
- Micro-invasive cancer; and
- Invasive cancer.

#### Histology categories requested:

- HPV detected (when HPV is the only abnormality present);
- Minor non-specific changes in squamous cells (MNSC);
- CIN I;
- CIN II;
- CIN III;
- Adenocarcinoma in situ;
- Micro-invasive cancer;

- Invasive cancer; and
- Negative/benign. The data supplied

The 'most recent 12 month period for which data are available' referred to in the question turned out to be 1999 for all States and Territories. In addition, detailed notes regarding classification of cytology results can be found in Appendix D.

Not all States and Territories supplied data, nor were data supplied in the same range of cytology or histology categories. Tables 3 and 4 show the actual data supplied by cytology and histology categories. A few key points should be noted:

- Queensland data were too late for inclusion in our study;
- The NSW data provided a single figure for the following cytology categories: CIN II, CIN III and all three cancer categories, and a single figure for the following histology categories: CIN II and CIN III; as shown in Appendix C; and
- Many States provided categories of cytology or histology results that differed from those requested. These were re-allocated according to rules described below.

Rules for re-allocating 'non-standard' cytology categories:

- 'Reactive/inflammatory changes' becomes 'negative'; and
- 'Atypia' and 'HPV possibly present' become 'other low-grade changes'

Rules for re-allocating 'non-standard' histology categories:

- 'Atypia' and 'HPV possibly present' become 'other low-grade changes';
- 'CIN Not Otherwise Specified – most likely will be CIN I'; becomes CIN I;
- 'Mature or immature squamous metaplasia with/without inflammation' becomes 'negative';
- 'Not applicable' – omitted as most likely not a cervical sample;
- For NSW, where CIN II and CIN III are not differentiated, apply the other States' proportions;
- 'Endocervical dysplasia' becomes 'atypia', i.e. 'other low-grade changes'; and
- 'Micro-invasive' and 'invasive' are combined (although most people consider micro-invasive to be more like CIN III).

**Table 3 Cytology/histology correlations for all States and Territories except NSW and QLD**

Cytology	Histology									
	HPV	MNSC	CIN I	CIN II	CIN III	AIS	MICROINV	INVAS	NEG/BEN	TOTAL
MNSC	511	551	654	284	176	7	2	4	1015	3204
HPV	535	31	311	96	33	1	0	0	302	1309
CIN I	901	208	1829	842	372	8	1	0	968	5129
CIN II	203	66	542	1048	734	5	5	1	321	2925
CIN III	76	40	146	428	1526	34	22	17	150	2439
INCONC	137	119	210	233	364	30	3	14	403	1513
AIS	3	1	3	2	6	28	6	4	8	61
MICROINV	1	0	3	7	66	4	5	30	4	120
INVAS	3	1	2	5	43	6	9	70	6	145
<b>TOTAL</b>	<b>2370</b>	<b>1017</b>	<b>3700</b>	<b>2945</b>	<b>3320</b>	<b>123</b>	<b>53</b>	<b>140</b>	<b>3177</b>	<b>16845</b>

Abbreviations: MNSC=minor non-specific changes in squamous cells; HPV=human papillomavirus; CIN=cervical intraepithelial neoplasia; INCONC=inconclusive; AIS=adenocarcinoma *in situ*; MICROINV=microinvasive cancer; INVAS=invasive cancer

**Table 4 Cytology/histology correlations for all States and Territories except QLD<sup>a</sup>**

Cytology	Histology									
	HPV	MNSC	CIN I	CIN II	CIN III	AIS	MICROINV	INVAS	NEG/BEN	TOTAL
MNSC	1115	551	1325	526	418	7	2	11	2033	5987
HPV	832	31	659	209	146	1	0	3	615	2496
CIN I	1296	208	2779	1198	728	8	1	1	1373	7591
CIN II	258	66	695	1556	1242	5	10	60	411	4303
CIN III	122	40	272	848	1946	34	26	66	224	3579
INCONC	252	119	411	561	692	30	6	36	688	2795
AIS	3	1	3	2	6	28	6	4	8	61
MICROINV	3	0	9	27	86	4	5	32	7	173
INVAS	6	1	11	34	72	6	9	73	11	225
<b>TOTAL</b>	<b>3887</b>	<b>1017</b>	<b>6164</b>	<b>4961</b>	<b>5336</b>	<b>123</b>	<b>65</b>	<b>286</b>	<b>5371</b>	<b>27209</b>

<sup>a</sup>=NSW breakdown between CIN I, II, III and cancer categories imputed from proportions given by total of the six States and Territories excluding QLD.

## The Procedure

Liquid-based cytology is the production of a thin layer of cervical cells on a microscope slide, suitable for diagnosis of cytological abnormalities. A cytotechnologist carries out manual screening of the preparation under the supervision of a physician.

A gynaecologic sample is obtained using a plastic spatula with either an endocervical brush or a cervical broom in the manner of conventional screening and the sample is rinsed into a vial containing preservative solution. The sample vial is capped, labelled and sent to the laboratory where it is placed into a processor that gently mixes the sample to disperse cells and break up any blood, mucus or non-diagnostic debris present.

To collect a thin layer of cells suitable for diagnosis, the sample is either centrifuged to produce a cell pellet or drawn through a filter under negative pressure to collect cells. The resulting cell sample is fixed onto a glass slide and stained by the Papanicolaou staining method for examination under a microscope (Gardner 2001).

Proponents argue that LBC yields a more representative cell sample by reducing the amount of extraneous material. Others argue that LBC processing machines cause the loss of patterns of natural cell arrangements on the slides, making them harder to read. Neither this slide reading issue, nor that of centrifugation versus filtration in the preparation of the cell sample for LBC was addressed in any of the studies identified in this report.

## Methods for collecting cervical cell specimens

Cell samples for LBC are collected using one of two methods: the split-sample or direct-to-vial. Most studies have used the split-sample method in which cervical cells are first transferred to a conventional slide after collection, then any residual cells are transferred from the cell-collecting device to the LBC preservation fluid. The two samples are then compared for the percentage of abnormalities detected. It has been argued that this method underestimates the effectiveness of LBC since most of the cells are transferred to the conventional slide (Brown & Garber 1998, Corkill et al 1997, AHTAC 1998).

With the direct-to-vial method, cells collected from a cervical scraping are transferred directly to the LBC preservative fluid. Controls for this LBC method are sometimes historical but are more often a contemporaneous but non-randomised control group.

Clinical trials have shown an increase in the detection by LBC of low-grade and more severe abnormalities, as well as an increase in the number of technically satisfactory smears. However these findings have generally not been confirmed by biopsy, so there is no way of determining the significance of the increased detection of abnormalities.

## Collection device

Traditionally, a Pap smear has been taken with a wooden spatula, most commonly the Ayre spatula. For the last 15 years, a combination of spatula and plastic cyto-brush has typically been used to take the cervical smear. The latest devices are thought to combine the roles of the spatula and cyto-brush for collection of both ectocervical and endocervical cells. There is evidence that the device used to collect cervical cell specimens for LBC plays a significant role in determining the sensitivity and specificity of the test (Austin & Ramsey 1998). The traditional wooden spatula is thought to reduce the sensitivity of LBC because of the absorptive properties of the wood (Martin-Hirsch et al 1999). Cervical cell collection using a cotton-tipped swab would arguably produce similar results for the same reasons.

The basis for use of a particular cervical cell collection device is subjective. The reliability of retrieving consistent cervical cell samples with different collection devices has not been thoroughly investigated. In one study investigating the role of the cell collection device in the adequacy of the specimen processed for LBC, there was a significant difference in the quality of the sample prepared following cell collection with spatulas, brooms, brushes or combinations thereof (Selvaggi et al 2000).

## Intended purpose

Cervical screening utilising LBC is intended to replace the Pap smear test for detecting cancerous lesions and also pre-cancerous cells so that treatment may be initiated before the disease progresses to an inoperable stage.

In Australia, screening for cervical abnormalities has been available since the 1960s. In 1991 a National Cervical Screening Programme (NCSP) was implemented with a policy of screening sexually active women every two years (AIHW 2000). Age-standardised mortality from cervical cancer in Australia fell by 40 per cent between 1983 and 1996 (AIHW 2000), with a large proportion of this decline directly related to the introduction of the NCSP.

Cervical cytology screening has several different applications. The primary use is detection of cervical cancer and its precursor lesions from either indicative cervical smears or in population-based screening programmes. However, cervical cytology screening continues to be useful in the management of women after treatment in whom abnormal cytology persists and also for the detection of residual or recurrent cervical lesions (Meijer & Walboomers 2000).

## Clinical need/burden of disease

Cervical cancer is a preventable disease. It is a slow growing cancer that usually takes a decade or more to fully develop from normal epithelium. If identified in its pre-cancerous stage (CIN), the abnormal cells are almost always easily treated and cancer does not develop.

While CIN can progress to invasive cancer (McIndoe et al 1984), studies indicate that many of the detected lesions will either regress or persist without progression. CIN is graded from I to III according to the severity of the lesion, with CIN III being the most serious. The more severe an abnormality, the lower the likelihood of regression.

Currently, screening is based on the Pap smear with the aim of detecting and treating high-grade pre-cancerous lesions (CIN II and CIN III). The identification by screening of individuals with lesser abnormalities raises the likelihood of unnecessary treatment of women whose minor abnormalities have a high probability of regression.

Cervical cancer remains a significant cause of morbidity and mortality worldwide. Early cervical cancer can be asymptomatic, highlighting the extreme importance of screening to detect early stages of the disease. Where present, symptoms include discomfort or bleeding during or after sexual intercourse, an unusual vaginal discharge, pelvic pain, excessive tiredness, swollen legs or backache. However, these symptoms can also be due to more common problems and are sometimes overlooked. Although the early stages of cervical cancer are treatable, the prognosis is less favourable for later stages of the disease. Persistent disease will ultimately result in death.

## Incidence and prevalence

Cervical cancer is one of the most common cancers worldwide and is the ninth most common cancer in Australian women (DHAC 1998). Figures from 1998 show that there were 868 new cases of cervical cancer in Australia with an age-standardised incidence rate of 8.6 cases per 100,000 women and 269 deaths from the disease, representing an age-standardised mortality rate of 2.5 cases per 100,000 women and 3,693 person-years life lost (PYLL, AIHW 2000). Tables 5 and 6 report the breakdown of the number of women in Australia identified with cervical abnormalities in 1997 and 1998.

**Table 5** Number of low-and high-grade abnormalities on histology for women aged 20-69 years, by State and Territory, 1997

Severity of Abnormality	State or Territory						Australia
	NSW	Vic	WA	SA	Tas	NT	
Low-grade	6,447	3,419	2,209	2,370	543	326	15,314
High-grade	3,601	3,388	1,432	1,310	430	231	10,392
Ratio of low-grade/high-grade	1.79	1.01	1.54	1.81	1.26	1.41	1.47

**Table 6** Number of low-and high-grade abnormalities on histology for women aged 20-69 years, by State and Territory, 1998

Severity of Abnormality	State or Territory						Australia
	NSW	Vic	WA	SA	Tas	NT	
Low-grade	5,799	3,329	2,090	2,179	756	258	14,411
High-grade	3,960	2,994	1,414	1,505	534	298	10,705
Ratio of low - grade/high-grade	1.46	1.11	1.48	1.45	1.42	0.87	1.35

## Existing procedures

### Papanicolaou (Pap) smear test

In Australia, cervical screening has been performed using the Pap smear since the 1960s. This test is susceptible to three main types of error:

- Sampling errors when cells are either not adequately collected or are discarded with the sampling device without transferral to the slide;
- Preparation errors when cells are not evenly distributed onto the microscope slide; and
- Interpretation errors that commonly arise due to blood, mucus or other diagnostic debris being transferred to the slide. In addition, cell overlapping and distortion due to air-drying can complicate the evaluation of cell changes.

These errors can lead to Pap smears giving inconclusive or ambiguous results.

The Pap smear involves evaluation for abnormalities of cells obtained from the cervix. Smear abnormalities are categorised according to Table 1. This categorisation is an Australian modification of the internationally recognised Bethesda system for categorising reports (Solomon et al 2002). As the majority of published articles use the Bethesda system, the Bethesda categories have been indicated alongside the Australian categories in Table 1.

Women are managed in various ways after evaluation of the Pap smear, including a repeat Pap smear every two years for women with a negative result, early repeat Pap smears for abnormalities less than CIN 1 or colposcopic referral for women with abnormalities of CIN 1 or worse, including all HGEAs. Figure 1 outlines the current NHMRC guidelines for the management of women with screen-detected abnormalities.

#### Limitations of the Pap smear

The Pap smear consists of the removal of exfoliated cells from the appropriate area of the cervix by means of a brush and/or spatula. The cells are smeared onto a slide which is sprayed with a fixative and transported to the laboratory for staining and microscopic examination by a cytotechnician. The test is not 100 per cent sensitive and gives a proportion of false negative results. Data from the US Agency for Healthcare Research and Quality indicate that the sensitivity of the Pap smear ranges from 50 per cent to 80 per cent, meaning that the false negative rate – or the probability of failing to detect abnormalities – ranges from 20 per cent to 50 per cent (McRory et al 1999).

These figures do not necessarily apply in Australia where there is more control over laboratories and quality control is more stringent. Comparable figures for accuracy of the Pap smear in an Australian setting do not exist, although the 2001 publication 'Performance Standards for Australian Laboratories Reporting Cervical Cytology' from the Royal College of Pathologists of Australia (RCPA) states that in 2000, the average false negative rate for women with histologically-confirmed CIN III was 17.9 per cent, giving a sensitivity of 82.1 per cent. Data from the same report enable calculation of the average laboratory false negative rate of 5.9 per cent, giving a laboratory sensitivity of 94.1 per cent.

## Marketing status of the technology

LBC screening tests are exempt from the regulatory requirements of the Therapeutic Goods Administration (TGA) because of their description as *in vitro* diagnostic tests that are not of human origin.

## Current reimbursement arrangement

Cervical screening is currently funded under the Medicare Benefits Scheme under Item numbers 73053 and 73055 (Tables 7 and 8). There is currently no listing on the MBS relating to any LBC test.

Table 7 gives a breakdown of the use of cervical cytology screening procedures throughout Australia from 1997 to April 2002 and billed to the Health Insurance Commission. Cytological examinations carried out under MBS item number 73053 should be in accordance with the agreed National Policy on Screening for the Prevention of Cervical Cancer. This policy provides for:

- (1) 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
- (2) Cessation of cervical smears at 70 years for women who have had two normal results within the last five years. Women over 70 years who have never been examined, or who request a cervical smear, should be examined.

**Table 7 Requested Medicare item number 73053 processed from January 1997 to April 2002**

Year	Number of services for Medicare item number 73053								Total
	NSW	VIC	QLD	SA	WA	TAS	ACT	NT	
1997	512,684	265,243	269,436	87,449	139,243	44,809	28,964	11,053	1,358,881
1998	523,831	270,231	284,994	84,314	150,004	43,484	28,951	10,777	1,396,586
1999	501,618	264,496	275,356	79,853	143,677	42,679	21,412	10,531	1,339,622
2000	485,029	248,949	264,717	90,054	143,759	40,989	22,764	10,801	1,307,062
2001	501,832	230,181	287,109	129,071	149,048	42,660	26,141	11,296	1,377,338
2002	160,993	69,996	92,538	42,848	49,965	13,259	8,181	3,930	441,710
<b>Total</b>	<b>2,685,987</b>	<b>1,349,096</b>	<b>1,474,150</b>	<b>513,589</b>	<b>775,696</b>	<b>227,880</b>	<b>136,413</b>	<b>58,388</b>	<b>7,221,199</b>

73053- Cytology of smears from cervix: a) for detection of pre-cancerous or cancerous changes in women with no symptoms, signs or recent history suggestive of cervical neoplasia; or (b) due to an unsatisfactory smear taken in the circumstances defined in para (a) above; or (c) if there is inadequate information provided to use item 73055; each examination. Source: <http://www.hic.gov.au/>

Table 8 presents a similar breakdown of the extent of cervical cytology carried out due to detected abnormalities (MBS Item number 73055).

**Table 8 Requested Medicare item number 73055 processed from January 1997 to April 2002**

Year	Number of services for Medicare item number 73055								Total
	NSW	VIC	QLD	SA	WA	TAS	ACT	NT	
1997	88,936	22,563	71,459	8,924	37,154	5,218	1,583	4,515	240,352
1998	86,916	22,825	74,052	10,638	33,946	5,258	1,726	4,843	240,204
1999	93,690	22,328	75,062	11,902	30,555	5,238	4,428	4,900	248,103
2000	90,954	22,107	74,424	13,830	29,148	4,929	5,249	5,054	245,695
2001	87,209	47,575	80,885	25,291	26,389	4,710	5,978	5,255	283,292
April 2002	28,600	19,060	26,301	7,739	8,397	1,478	2,114	1,742	95,431
<b>Total</b>	<b>476,305</b>	<b>156,458</b>	<b>402,183</b>	<b>78,324</b>	<b>165,589</b>	<b>26,831</b>	<b>21,078</b>	<b>26,309</b>	<b>1,353,077</b>

73055-Cytology not associated with item 75053, of smears from cervix in association with: (a) the management of previously detected abnormalities including pre-cancerous or cancerous conditions; or (b) the investigation of women with symptoms, signs or recent history suggestive of cervical neoplasia; for each test. Source: <http://www.hic.gov.au/>

# Approach to assessment

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## Review of literature

### Search strategy

The medical literature was searched to identify relevant studies and reviews for the period between January 2000 and April 2002. The year 2000 was chosen as the date from which to commence the search because of the publication in that year of a systematic review of cervical screening devices (Broadstock 2000). The electronic databases searched to provide a list of citations are listed in Table 9.

**Table 9 Electronic databases (including version) accessed for this review**

Database	Period covered
Cochrane Library including: The Cochrane Database of Systematic Reviews (CDSR) Database of Abstracts of Reviews of Effectiveness (DARE) The Cochrane Controlled Trials Register (CCTR) Health Technology Assessment Database (HTA) NHS Economic Evaluation Database (NHS EED)	2002, Issue 1
Medline	2000 to April Wk 4 2002
PreMedline	April 29 2002
Current Contents	2000 Wk 1 to 2002 Wk 15
Biological Abstracts	2000 to Mar 2002
CINAHL	2000 to Apr Wk 4 2002
EBM Reviews - Cochrane, ACP Journal Club, CCTR and DARE	1st Quarter 2002

Additionally, the Internet was searched for health technology assessment (HTA) databases and HTA agency websites. The Internet sites are listed in Appendix E. Table 10 lists the search terms used to identify the citations. The search terms were combined using the Boolean operators 'and', 'or' and 'not'. All articles identified by this strategy were retrieved.

**Table 10 Search terms used to identify citations for review of LBC**

Cervical screening terms	Cytology terms	Cancer terms	Diagnostic terms	Economic terms
Cytolog\$ techni\$.mp.	Fluid\$based.mp.	Neoplas\$.mp	Sensitivity and specificity/	Economics/
Cytological techniques/	Thin\$layer.mp.	Cancer\$.mp	Sensitivity.mp.	Costs and cost analysis/
Histocytological preparation techniques/	Thin\$prep.mp.	Dysplasi\$.mp	Specificity.mp.	Economic value of life.sh
Cytodiagnosis/	Liquid\$based.mp.	Tumo\$.mp	di.fs	Economics, medical and nursing
Pap\$ adj (smear\$ or test\$).mp.	Cytyc.mp.	Carcinoma.mp	ri.fs	(economic\$ or cost or costs or costly or costing).mp.
Cervi\$.mp.	Labonord.mp.	CIN.mp	du.fs	(expenditure\$ not energy).mp.
Vaginal smears/	Cytoscreen.mp.	SIL.mp	Diagnosis/	(value adj1 money).mp.
Mass screening/	Surepath.mp.	Cervix neoplams/		budget\$.mp.
	Cytorich.mp.	Cervical intraepithelial neoplasia/		
	Autocyte.mp.	Cervix dysplasia/		
	Prepstain.mp.	Cervi\$ cancer.mp.		
	Autocyte\$prep.mp.			
	Cytorich.mp.			
	Cyteasy.mp.			
	Preserv\$cyt.mp.			
	Thin\$layer.mp.			
	Mono\$layer.mp.			

tw=text word, di=diagnosis, du=diagnostic use, fs or sh=floating subject heading. The dollar sign (\$) is a wildcard symbol representing truncation. Terms were searched as text words. A medical subject heading (MeSH) term search was conducted if allowed by the database.

## Entry criteria

The following criteria were developed *a priori* to determine eligibility of relevant studies for critical appraisal of the diagnostic characteristics and clinical effectiveness of LBC.

### Subject characteristics:

- **Inclusion:** women undergoing screening for cervical cancer for which LBC is used to replace the Papanicolaou smear; and
- **Exclusion:** women undergoing cervical screening for which LBC is not used; pregnant women.

### Characteristics of the study test:

- **Inclusion:** use of filter-based or centrifuge-based LBC tests.
- **Exclusion:** no LBC tests used; HPV DNA diagnostic tests; automated or semi-automated slide reading/analysing technologies.

### Characteristics of the outcome:

- **Inclusion:** all outcomes, with special reference to those examining comparative diagnostic accuracy and reliability, plus clinical effectiveness and cost-effectiveness.

### Characteristics of the study design

- Inclusion: health technology assessments, systematic reviews, meta-analyses, randomised controlled trials, comparative or cohort studies (including case series) that evaluate the diagnostic characteristics of LBC tests in cervical screening for abnormalities including non-specific minor cell changes, possible CIN I, mild dysplasia, CIN II, CIN III and cervical cancer detected by cervical histology. Histology of cervical biopsy was the gold standard reference for this review.
- Exclusion: case studies, narrative reviews, editorials, letters, publications in a language other than English, articles identified as preliminary reports when results are published in later versions, articles published in abstract form only, studies published before 2000.

## Search results

Initial assessment of the abstracts was performed to allow exclusion of articles that did not meet the selection criteria. Ambiguous or unclear citations were included in the next assessment stage for examination in full text. Two reviewers examined each citation for inclusion. Discrepancies in selection were discussed and resolved through consensus. A final decision to reject or accept articles was based on a thorough reading of the complete article. Only studies that passed this process have been included.

The search for studies that examined the effectiveness and cost-effectiveness of LBC screening compared with conventional screening initially retrieved 963 articles of which 840 were rejected, leaving 123 articles to be assessed in full text. Of these, 15 met the inclusion criteria and are cited in Appendix F. Appendix G cites articles that were excluded after assessment of full text and the reason for exclusion.

No published economic analyses were considered appropriate for the purpose of informing the decision as to whether cervical screening using LBC should be included in the MBS as an alternative to cervical screening using Pap smears.

## Assessment of validity

The Cochrane Methods Working Group on Systematic Review of Screening and Diagnosis (1996) states that the most rigorous study design for assessing the validity of evidence pertaining to diagnostic tests is a prospective blind comparison of the test with a reference, or gold standard, in a consecutive series of patients from a relevant clinical population (Jaeschke et al 1994, Sackett et al 2000).

The Cochrane Methods Working Group specifically recommends the following criteria for assessing the validity of evidence pertaining to diagnostic tests:

- that the study test is compared with a reference standard;
- that the study test and reference test are measured independently, or blind, of each other;
- that the choice of patients assessed by the reference standard be made independently of the study test's results;

- that the study test be measured independently of all other clinical information;
- that the reference standard be measured before the commencement of any interventions based on test results; and
- that tests be compared in a valid study design:
  - tests done independently on each person (most valid);
  - different tests done on randomly-allocated individuals;
  - all tests done on each person but not assessed independently;
  - different tests on different individuals; and
  - not randomly allocated (least valid).

The validity of the studies in all included articles was assessed according to criteria that focus on the important aspects of study design for diagnostic studies (Jaeschke et al 1994, Cochrane Methods Working Group on Systematic Review of Screening and Diagnosis 1996, Sackett et al 2000), as indicated in Table 11.

**Table 11 Criteria and definitions for assessing validity of diagnostic studies**

Validity criterion	Definition
Test is compared with a reference standard	Patients in the study should have undergone both the diagnostic test in question and a reference test that would provide confirmatory proof to confirm that they do or do not have the target disorder
Appropriate spectrum of consecutive patients	Study included patients that the test would normally be used on in clinical practice, i.e. patients covering the spectrum of mild to severe cases of the target disorder, early and late cases, and patients with other commonly confused diagnoses. An inappropriate spectrum compares patients already known to have the disorder with a group of normal non-diseased patients (case-control) or with patients diagnosed with another condition
Masked assessment of study and reference test results	The study test and the reference test should be interpreted separately by persons unaware of the results of the other to avoid review bias
All study subjects tested with both study and reference tests	The reference test should be applied regardless of the result from the study test to avoid work-up/verification bias
Study test measured independently of clinical information	The person interpreting the test should be masked to clinical history and results of any other tests performed previously
Reference test measured prior to any interventions	No treatment interventions initiated before the application of the reference (or study) test

## Accuracy of the tests

The accuracy of a diagnostic test is primarily determined by its ability to identify the target disorder compared to the recognised reference test. Accuracy is measured by diagnostic characteristics such as sensitivity and specificity. In this review the diagnostic characteristics of each test were reviewed when the study tested the subjects with at least two of the diagnostic tests under investigation and reported sufficient data. The minimum requirement for determining sensitivity was the availability of sufficient data to compute the proportion of subjects with the disorder whose tests were correctly identified as positive. For specificity, sufficient data were required to compute the proportion of patients without the disorder whose tests were correctly identified as negative.

Diagnostic test results are summarised in two-by-two tables as described in Table 12. Individuals who tested positive for the disease in both the study test and the reference test are represented in cell *a* are called true positives (TP). Individuals without the disease who test negative in both tests (the *d* cell) are called true negatives (TN).

A diagnostic test may produce discordance between the test result and the true disease status of the subject. When this occurs a false result is reported. These situations are illustrated by cells *b* and *c* in Table 12. In *b*, the test is positive in individuals without the disease; in *c*, the test is negative in diseased individuals. These two sets of false results are called false positives (FP) and false negatives (FN), respectively.

**Table 12 The generic relationship between results of the diagnostic test and disease status**

Study Test Results	True Disease Status (Reference test)		
	Diseased	Not Diseased	Total
Positive	a	b	a+b
Negative	c	d	c+d
Total	a+c	b+d	a+b+c+d

\*Abbreviations: a=number of diseased individuals detected by the test; b=number of individuals without disease detected by the test; c=number of diseased individuals not detected by the test; d=number of individuals without disease not detected by the test; a+b=total number of individuals testing positive; c+d=total number of individuals testing negative; a+c=total number of diseased individuals; b+d=total number of individuals without disease; a+b+c+d=total number of individuals studied.

Sensitivity is the proportion of diseased individuals who test positive. It is a measure of the probability of correctly diagnosing a case, or the probability that any given case will be identified by the test. Referring to Table 12,

$$Sen = \frac{a}{a+c} = \frac{TP}{TP+FN}$$

Specificity is the proportion of individuals without disease who test negative. It is the probability of correctly identifying a non-diseased person with the study test.

$$Spe = \frac{d}{b+d} = \frac{TN}{TN+FP}$$

The complement of specificity is called the false positive rate (FPR).

$$FPR = 1 - Spe$$

Note that calculating sensitivity and specificity requires data in each cell of Table 12. Particularly, values are required for the FN (*d*) to calculate sensitivity and for the TN (*d*) to calculate specificity. Neither of these values is available from studies that fail to perform the reference test on subjects who had negative results for the test under investigation.

Likelihood ratios (LRs), which indicate by how much a given diagnostic test result will raise or lower the pre-test probability of the target disorder, were also computed if the necessary data were extractable from the published studies. Likelihood ratios express the odds that a given level of a test result would be expected in a patient with the condition compared to one without the condition.

The LR for a positive test result is calculated by:  $LR+ = \frac{Sen}{FPR}$

The LR for a negative test result is calculated by:  $LR- = \frac{1 - Sen}{Spe}$

Note that positive LRs of 10 or greater, or negative LRs of less than 0.1 indicate large changes in disease likelihood. If the likelihood ratio for a positive test is less than two and the likelihood ratio for a negative test result is greater than 0.5, there is little or no chance that the test will enable diagnosis of the disease.

### Pooling sensitivities and specificities

When clinical and statistical heterogeneity are acceptable, summary estimates of sensitivity and specificity can be calculated by combining weighted averages of the sensitivities and specificities using methods described by Deeks (2001).

### Relative true and false positive rates

Although the accuracy of a diagnostic test is primarily determined by its ability to identify the target disorder compared with the recognised reference test, in some cases the reference test is invasive. In such cases, it may be considered unethical or unacceptable to subjects and also impractical and costly to apply the reference test to asymptomatic participants with negative test screening results (Frommer et al 1988). This can lead to a situation in which some of the information necessary to calculate diagnostic characteristics is absent from the study results.

To allow comparison of screening tests in the absence of a reference test, Schatzkin et al (1987) have developed a method in which ratios of sensitivities and specificities are derived and compared. Their method requires that all the positives (for either screening test) are assessed with the reference test and that both screening tests are performed on each woman. The McNemar's test is used to determine the statistical significance of the differences in sensitivities and specificities. The relative true positive rate (TPR) and relative FPR provide measures of the relative accuracy of one test to another. To calculate the relative TPR and FPR the following formulae are used (Table 13):

$$\text{Relative TPR (Test 2: Test1)} = (a+b)/(a+c)$$

$$\text{Relative FPR (Test2: Test1)} = (A+B)/(A+C)$$

**Table 13** Sampling scheme where only those testing positive on either screening test are investigated with the reference standard (from Chock et al 1997)

	Reference standard positive			Reference standard negative		
	Test 1 +	Test 1 -	Total	Test 1 +	Test 1 -	Total
Test 2 +	a	b	a+b	A	B	A+B
Test 2 -	c	[d]	[c+d]	C	[D]	[C+D]
<b>Total</b>	a+c	[b+d]	[n]	A+C	[B+D]	[N]

[ ]: unknown variables are in square brackets

One of the Cochrane Methods Working Group (1996) recommended criteria for assessment of validity of evidence pertaining to diagnostic tests (refer to Table 11) is that all study subjects are tested with both study and reference tests where the reference test should be applied regardless of a positive or negative result from the study test. However, this criterion may not be applicable to cervical screening as it may be considered unethical to perform biopsies on women that test negative to both screening tests. Therefore, an additional validity criterion was considered based on the assumption of the method to calculate the relative true positive and false positive rates, i.e. that all the positives (for either screening test) are tested with the reference test and that both screening tests are performed on each woman.

### Critical appraisal of secondary studies

In addition to primary studies, published secondary studies identified by the search strategies including systematic reviews, meta-analyses and health technology assessments which met inclusion criteria, were also critically appraised. Critical appraisal of systematic reviews was performed against both a modified checklist recommended by the Quality of Reporting of Meta-Analyses (QUOROM) group (Moher et al 1999, Table 14) and recognised qualitative criteria (Chalmers & Altman 1995, Greenhalgh 1997, Sackett et al 2000). Qualitative criteria are designed to assess whether the systematic review was performed in the optimal way to minimise bias. Criteria assess whether the systematic review contains an explicit statement of the objectives and methods and whether the methods are reproducible. Specific criteria assessed included whether the review asked a focused question, if the eligibility criteria for included trials were explicit, the type of search strategy used, the way the validity of included trials was assessed and whether results of included trials were similar.

### Expert advice

A supporting committee with expertise in cervical screening was established to evaluate the evidence and provide advice to the MSAC from a clinical perspective. In selecting members for supporting committees, the MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations for nominees. Membership of the supporting committee is provided at Appendix B.

### Limitations of this review

This review was conducted using the systematic review methodology outlined above. However, due to the time frame available, the search was limited to English language articles only. Members of the Supporting Committee were available to provide advice on current work or publications not accessible via electronic search methods, however, no attempt was made to systematically search the 'grey literature'.

**Table 14 Quality of reporting of published systematic reviews and health technology assessments (based on Moher et al 1999).**

<b>Section</b>	<b>Descriptor</b>
<b>Title</b>	Identify the report as a systematic review
<b>Abstract</b>	Use of a structured format Explicit description of clinical question Description of databases and other information sources Description of selection criteria Description of methods for validity assessment Description of methods for data abstraction Description of study characteristics Description of quantitative data synthesis Description of characteristics of included and excluded studies Description of quantitative findings Description of qualitative findings Description of results of subgroup analysis
<b>Introduction</b>	Explicit description of clinical problem Explicit description of biological rationale for intervention Explicit description of rationale for review
<b>Methods</b>	Detailed description of information sources Detailed description of restrictions on searching Description of inclusion and exclusion criteria Description of criteria and process used for validity assessment Description of processes used for data abstraction Description of study characteristics Description of methods of assessment of clinical heterogeneity Description of principal measures of effect Description of methods of combining results Description of methods used to handle missing data Description of methods of assessment of statistical heterogeneity Description of rationale for <i>a priori</i> sensitivity testing and subgroup analysis Description of methods to assess publication bias
<b>Results</b>	Description of profile of trial flow Presentation of descriptive data for each trial Report of agreement on the selection of studies Report of agreement on validity assessment Presentation of simple summary results Presentation of data needed to calculate effect sizes and confidence intervals
<b>Discussion</b>	Summary of key findings Discussion of clinical inferences based on internal and external validity Interpretation of the results in the light of the totality of available evidence Description of potential biases in the review process Suggestions for future research agenda

## Results of assessment

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### Is it safe?

The safety issues are the same for cervical screening with LBC, as for Pap smears because cells are collected by the same method. The difference between the two technologies lies in the way the samples of cervical cells are prepared and examined.

Although Pap smears are generally regarded as safe, scarring of the cervix, mucosal tears or perforation of the mucosa or vagina may result, dependent largely on the expertise and confidence of the physician performing the procedure.

Prevalence or incidence figures of such risks are not available, although clear definition of risks or complications associated with the procedure would be useful, particularly with respect to training, experience and quality control of operators.

In summary, the safety or risks associated with collection of cervical cells for an LBC test for cervical screening has not been evaluated and reported in the literature. None of the appraised studies reported these outcomes or technical problems arising for women undergoing primary screening using this technology, although any risk is likely to be associated with collection of cervical cells and not the tests themselves.

## Is it effective?

This report assessed the effectiveness of LBC tests for cervical screening.

### Critical appraisal of secondary studies

Five reviews were identified: three systematic reviews (Hartmann et al 2001, Sulik et al 2001, Moseley & Paget 2002), one meta-analysis (Bernstein and Sanchez-Ramos 2001), and one health technology assessment by the New Zealand Health Technology Agency (Broadstock 2000). Assessment of validity of each review against the modified QUOROM group checklist (Moher et al 1999) is summarised in Table 15.

Three of the reviews rated well and two rated poorly against the QUOROM checklist. The systematic reviews by Broadstock (2000) and Sulik et al (2001) met the most criteria followed by the meta-analysis of Bernstein et al (2001). The remaining two systematic reviews (Hartmann et al 2001, Moseley & Paget 2002) rated poorly for content and structure of their abstracts, plus they were not identified as systematic reviews in their titles.

As the QUOROM checklist is a nominal scale reflecting the reporting of systematic reviews, an assessment of the reviews against qualitative criteria (Chalmers & Altman 1995, Greenhalgh 1997, Sackett et al 2000) was also applied. The reviews varied in their validity. Detailed descriptions of the appraised secondary studies are shown in Table 16. The qualitative criteria examined were:

- Was a focused question addressed, ie were PICO elements (patient, intervention/diagnostic or screening test of interest, comparator, outcomes of interest) identified?
- Were study inclusion and exclusion criteria explicit and considered *a priori*?
- Did the study report an explicit and comprehensive search strategy?
- Did the study address the validity of the included trials?
- Summary of main results.
- Strengths and limitations of study.

**Table 15 Quality of reporting of published secondary studies**

Section	Descriptor	Broadstock 2000	Hartmann 2001	Sulik 2001	Moseley 2002	Bernstein 2001
<b>Title</b>	Identify the report as a systematic review	☑	☐	☑	☐	☑
<b>Abstract</b>	Use of a structured format	☑	☐	☑	☐	☑
	Explicit description of clinical question	☑	☑	☑	☐	☑
	Description of databases and other information sources	☑	☐	☑	☐	☑
	Description of selection criteria	☑	☐	☑	☐	☑
	Description of methods for validity assessment	☑	☐	☑	☐	☑
	Description of methods for data abstraction	☑	☐	☑	☑	☑
	Description of study characteristics	☑	☐	☑	☐	☑
	Description of quantitative data synthesis	☑	☑	☑	☐	☑
	Description of characteristics of included and excluded studies	☑	☐	☑	☐	☑
	Description of quantitative findings	☑	☑	☑	☐	☐
	Description of qualitative findings	☑	☑	☐	☐	☐
	Description of results of subgroup analysis	☐	☐	☐	☐	☐
	<b>Introduction</b>	Explicit description of clinical problem	☑	☑	☑	☑
Explicit description of biological rationale for intervention		☑	☑	☑	☐	☑
Explicit description of rationale for review		☑	☑	☑	☑	☑
<b>Methods</b>	Detailed description of information sources	☑	☑	☑	☑	☑
	Detailed description of restrictions on searching	☑	☑	☑	☑	☑
	Description of inclusion and exclusion criteria	☑	☑	☑	☑	☑
	Description of criteria and process used for validity assessment	☑	☑	☑	☐	☑
	Description of processes used for data abstraction	☑	☑	☑	☑	☑
	Description of study characteristics included	☑	☑	☑	☑	☑
	Description of methods of assessment of clinical heterogeneity	☑	☐	☑	☐	☑
	Description of principal measures of effect	☑	☑	☑	☑	☑
	Description of methods of combining results	☐	☑	☑	☐	☑
	Description of methods used to handle missing data	☐	☐	☐	☐	☐
	Description of methods of assessment of statistical heterogeneity	☐	☐	☑	☐	☑
	Description of rationale for <i>a priori</i> sensitivity testing and subgroup analysis	☐	☐	☐	☐	☐
	Description of methods to assess publication bias	☐	☐	☐	☐	☐
<b>Results</b>	Description of profile of trial flow	☑	☑	☑	☑	☑
	Presentation of descriptive data for each trial	☑	☑	☑	☑	☑
	Report of agreement on the selection of studies	☑	☑	☑	☐	☐
	Report of agreement on validity assessment	☑	☐	☑	☐	☐
	Presentation of simple summary results	☑	☑	☑	☑	☑
	Presentation of data needed to calculate effect sizes and confidence intervals	☑	☑	☐	☑	☑
<b>Discussion</b>	Summary of key findings	☑	☑	☑	☑	☑
	Discussion of clinical inferences based on internal and external validity	☑	☑	☑	☑	☑
	Interpretation of the results in the light of the totality of available evidence	☑	☑	☑	☑	☑
	Description of potential biases in the review process	☐	☑	☑	☐	☑
	Suggestions for future research agenda	☑	☑	☑	☑	☑

**Table 16 Validity reviews of secondary studies**

**Reference:** Sulik, S. M., Kroeger, K. et al, (2001). 'Are fluid-based cytologies superior to the conventional Papanicolaou test? A systematic review', *Journal of Family Practice*, 50, 1040-6.

<p><b>Focused question?</b> (ie PICO elements: patient, intervention/diagnostic or screening test of interest, comparator, outcomes of interest)</p>	<p><b>Patient:</b> Women undergoing testing for cervical cancer (age not specified). Assumed for primary screening and evaluation of previous abnormal test result</p> <p><b>Diagnostic test:</b> liquid-based cytology (LBC)</p> <p><b>Comparison:</b> Pap test</p> <p><b>Outcomes:</b> Sensitivity, specificity, area under the receiver operating characteristic curve (AuROC), the proportion of satisfactory, unsatisfactory, and 'satisfactory but limited by' test results. AuROC is a measure of overall diagnostic accuracy (1.0 is a perfect test and 0.5 is a test no better than chance).</p> <p><b>Reference test:</b> Colposcopy, biopsy, consensus by cytologists</p>
<p><b>Inclusion and exclusion criteria?</b> (including <i>a priori</i>)</p>	<ul style="list-style-type: none"> <li>• Included studies compared both conventional and LBC samples in which tests were simultaneously applied to the same group of women, or one group of women who received Pap was compared with a group that received LBC</li> <li>• Subset of articles comparing the 2 tests with a reference standard was identified for the evaluation of LBC accuracy. Also included studies that provided colposcopy to a random sample of women with normal Pap or LBC tests and those that subjected normal tests to an independent consensus review by a panel of experienced cytology professionals. Articles were excluded unless they reported colposcopy and biopsy results for at least 50% of the women with a finding of high-grade squamous intraepithelial lesions or higher on either Pap or LBC.</li> <li>• Two investigators independently reviewed the titles and each article to determine if it met the inclusion criteria</li> </ul>
<p><b>Explicit comprehensive search strategy?</b> (did review incorporate a search strategy comprehensive enough that it was unlikely to have missed studies?)</p>	<ul style="list-style-type: none"> <li>• Used medical subject headings and text words</li> <li>• Published English studies (1985 and November 1999)</li> <li>• Searched Medline, Best Evidence, EMBASE, Biological Abstracts/RRM, and The Cochrane Library. Also searched the bibliographies of the retrieved articles</li> <li>• Contacted LBC manufacturers for additional articles and abstracts; authors of articles with incomplete data were contacted to obtain missing information</li> <li>• Search terms included: "monolayer technology", "ThinPrep", "CytoRich", "Cytotprep", "AutoPrep", "AutoCyte", "Papanicolaou/Pap smear", "liquid-based cytology", "fluid-based cytology", "cervical cancer screening", "vaginal smears"</li> <li>• Overall comprehensive search strategy</li> </ul>
<p><b>Assessed validity of included trials?</b></p>	<ul style="list-style-type: none"> <li>• Developed criteria and assessed quality of studies addressing accuracy (max score=13)</li> <li>• Two reviewers independently assessed quality of each article (differences resolved by consensus)</li> <li>• Three reviewers independently extracted data using a structured form (differences resolved by consensus)</li> <li>• Performed homogeneity analyses</li> </ul>
<p><b>Summary of main results</b></p>	<ul style="list-style-type: none"> <li>• Five studies included a comparison with a reference standard and both tests were performed at the same time in all patients. Three of the five studies systematically compared LBC and Pap results with colposcopy and biopsy. The remaining two used consensus between independent reviewers of the Pap and LBC test results as the reference standard, with biopsy for at least 50% of the women with significant abnormalities on either or both tests</li> <li>• The total quality assessment scores of the five studies ranged from 7 to 10 out of a possible maximum score of 13</li> <li>• <b>Sensitivity and Specificity:</b> No significant difference in AuROC between the two methods (Pap=0.93, LBC=0.91; p=0.37; 95% CI -0.33, 0.80). LBC demonstrated higher sensitivity, 90% (95% CI 0.77, 0.96) versus 79% (95% CI 0.50, 0.91) for Pap. LBC had a lower specificity, 85% (95% CI 0.74, 0.92) versus 89% (95% CI 0.75, 0.96) for Pap</li> <li>• <b>Specimen Adequacy:</b> LBC specimens were more likely to be reported as satisfactory [Risk Differences (RD)=0.06; 95% CI 0.03, 0.09]. No difference in number of unsatisfactory test results. There was a 6% higher rate of absence of endocervical cells (RD=0.06; 95% CI 0.02, 0.10) but a 10% decrease in reports of satisfactory but limited (RD = -0.10; 95% CI -0.13, -0.06) with LBC. The increase in absence of endocervical cells for LBC specimens was seen in all split-sample studies (RD=0.08; 95% CI 0.06, 0.11) but not in the cohort studies (RD = 0.01; 95% CI -0.07, 0.05)</li> </ul>
<p><b>Strengths and limitations</b></p>	<ul style="list-style-type: none"> <li>• Search was comprehensive but restricted to English language articles</li> <li>• The aims and inclusion criteria were clearly stated</li> <li>• Summary estimates of test sensitivity and specificity were calculated</li> <li>• The methodological qualities of the included studies were assessed</li> <li>• The authors highlighted the limitations associated with the five studies reviewed</li> <li>• No study addressed the issue of blinding in the interpretation of the reference standard</li> <li>• The patients included in the studies came from high-risk populations</li> <li>• The results may not be generalisable to women at low risk who receive Pap tests</li> </ul>

**Table 16 (cont) Validity reviews of secondary studies**

**Reference:** Moseley, R.P. & Paget, S. (2002). 'Liquid based cytology: is this the way forward for cervical screening? ', *Cytopathology*, 13, 71-82.

<p><b>Focused question?</b> (ie PICO elements: patient, intervention/diagnostic or screening test of interest, comparator, outcomes of interest)</p>	<p>Not explicitly stated in the review. Implied as:  <b>Patient:</b> Women undergoing testing for cervical cancer, age not specified. Assumed for primary screening and evaluation of previous abnormal test result  <b>Diagnostic test:</b> LBC  <b>Comparison:</b> Conventional Pap smear  <b>Outcomes:</b> Sensitivity, specificity, smear adequacy  <b>Reference test:</b> Histology, colposcopy</p>
<p><b>Inclusion and exclusion criteria?</b> (including <i>a priori</i>)</p>	<ul style="list-style-type: none"> <li>• Fourteen split-sample and 12 direct-to-vial studies met the inclusion criteria and were reviewed</li> <li>• Abstracts, reviews and clinical studies reporting less than 1000 cases were excluded. Four clinical studies reporting more than 1000 cases were also excluded because: data for two studies could not be converted to United Kingdom's National Health Service Cervical Screening Programme (NHSCSP) terminology, one study was an early report of a published study, and one study did not provide data for squamous dyskaryosis</li> <li>• Not clear how many of the investigators independently assessed each study to be included in the review</li> </ul>
<p><b>Explicit comprehensive search strategy?</b> (did review incorporate a search strategy comprehensive enough that it was unlikely to have missed studies?)</p>	<ul style="list-style-type: none"> <li>• Medline (1990-2001), UK HTA report, manual search of journals from 1995-2001 (Cytopathology, Diagnostic Cytopathology, Acta Cytologica, Cancer Cytopathology)</li> <li>• Used search terms: "liquid-based cytology", "ThinPrep", "AutoCyte PREP"</li> <li>• The following were not included as search terms: "Pap smear", "Papanicolaou", "fluid-based cytology", "cervical cancer screening" or "vaginal smear"</li> <li>• Language restrictions not stated</li> </ul>
<p><b>Assessed validity of included trials?</b></p>	<ul style="list-style-type: none"> <li>• Method for evaluating validity (methodological quality) of the included studies was not stated</li> <li>• No quality score was used to evaluate the included studies</li> <li>• Validity was assessed descriptively</li> </ul>
<p><b>Summary of the main results</b></p>	<p>Authors described results from included studies which are summarised as follows:</p> <ul style="list-style-type: none"> <li>• <b>Sensitivity of LBC compared with Pap smear:</b> Although several split-sample studies report increased detection of abnormalities with LBC, in the majority of these studies there are sparse or non-existent histology follow-up data so the true clinical yield of epithelial abnormalities is unknown. In these circumstances false positive test results may be misinterpreted as increased sensitivity. Where a histological reference standard has been employed, test evaluation has frequently been limited to discordant test results where one test is negative and the other positive. There is potential bias with both types of analysis.</li> <li>• <b>Specificity of LBC compared with Pap smear:</b> In most of the studies evaluated, there were no histological data available. Where they were available, outcome data for colposcopic referral were substantially incomplete and/or the number of women referred to colposcopy was not clearly stated. Positive predictive value (PPV) for high-grade histology following colposcopic referral with an abnormal smear could not therefore be reliably assessed. Authors reported PPV for high-grade histology only for the five studies in which women were biopsied, PPV ranged from 35% to 100% for Pap and 40% to 91% for LBC. They concluded there was no evidence to suggest that LBC is more or less specific than Pap smear.</li> <li>• The authors concluded that analysis of existing data did not support the nationwide implementation of LBC at present and that predominantly USA studies and results may not be applicable to other countries due to different screening practices</li> </ul>
<p><b>Strengths and limitations</b></p>	<ul style="list-style-type: none"> <li>• Did not use broad search terms such as Pap smear, vaginal smear, etc relevant to the research question</li> <li>• Search confined to one database and may have missed relevant articles</li> <li>• Heterogeneity was not tested and reported</li> <li>• Attempts were not made to locate unpublished studies</li> <li>• Search was likely to be restricted to English language articles</li> <li>• Not clear how the investigators would be able to retrieve all articles related to Pap smear when their search terms did not include the keyword "Pap smear"</li> </ul>

**Table 16 (cont) Validity reviews of secondary studies**

**Reference:** Hartmann, K.E., Nanda, K. et al, (2001). 'Technologic advances for evaluation of cervical cytology: is newer better?', *Obstetrical & Gynecological Survey*, 56, 765-774.

<p><b>Focused question?</b> (ie PICO elements: patient, intervention/diagnostic or screening test of interest, comparator, outcomes of interest)</p>	<p>Yes, explicitly stated in the review</p> <p><b>Patient:</b> Women undergoing primary screening and evaluation of previous abnormal test result (age not specified)</p> <p><b>Diagnostic test:</b> Liquid-based thin layer cytology (ThinPrep)</p> <p><b>Comparison:</b> Conventional Pap smear</p> <p><b>Outcomes:</b> Diagnostic test characteristics, sensitivity, specificity, predictive values, likelihood ratios</p> <p><b>Reference test:</b> Colposcopy and/or cervical biopsy</p>																																																																											
<p><b>Inclusion and exclusion criteria?</b> (including <i>a priori</i>)</p>	<ul style="list-style-type: none"> <li>• Searched forward for new articles addressing new methods for preparing or evaluating cytology subsequent to the AHCPR report on evaluation of cervical cytology (McRory et al 1999)</li> <li>• Studies that used clinical confirmation of cytology by colposcopy, cervical biopsy, or both</li> <li>• Two individuals independently reviewed titles and abstracts. Full text article was reviewed and the final decision was made if disagreement</li> <li>• Two individuals reviewed the included studies and agreement was sought</li> <li>• Investigators worked with authors of 1999 AHCPR report and applied same criteria and data extraction techniques</li> </ul>																																																																											
<p><b>Explicit comprehensive search strategy?</b> (did review incorporate a comprehensive search strategy?)</p>	<ul style="list-style-type: none"> <li>• Searched MEDLINE database (1995-March 2001)</li> <li>• Searched for English-language articles</li> <li>• Search terms were: "cervical neoplasm", "cervical dysplasia", "vaginal smears", "screening"</li> <li>• Searched forward from 1999 AHCPR report</li> <li>• Also included studies from AHCPR report which searched MEDLINE (from 1966), EMBASE (from 1980), HealthSTAR (from 1975), CancerLit (from 1983), and CINAHL (from 1983) through December 31, 2000</li> </ul>																																																																											
<p><b>Assessed validity of included trials?</b></p>	<ul style="list-style-type: none"> <li>• Validity assessment not explicitly described, but selection criteria contain some validity criteria</li> <li>• Two team members selected studies and resolved discrepancies by consensus. The new method being evaluated had to be: 1) obtained as a screening test or as an adjunct to screening; 2) compared with colposcopy/biopsy reference standard; 3) verified by colposcopy and/or biopsy within a 3-month interval from screening; and 4) reported in a fashion that allowed completion of 2x2 tables relating findings of new method to colposcopy/biopsy.</li> <li>• Methodological qualities of the included studies not evaluated and reported</li> <li>• Applied criteria and data extraction techniques similar to the 1999 AHCPR</li> </ul>																																																																											
<p><b>Summary of results</b></p>	<ul style="list-style-type: none"> <li>• Identified only one population based study of LBC that used a reference standard (colposcopy with histology) to assess subset of women with normal screening results. The following table from Hartmann et al (2001) summarises test characteristics:</li> </ul> <p><b>TABLE 2 Performance of liquid-based cytology in a prospective cohort*</b></p> <table border="1" data-bbox="427 1346 1406 1585"> <thead> <tr> <th rowspan="2">Liquid-Based Cytology Threshold†</th> <th rowspan="2">Final Diagnosis</th> <th rowspan="2">No. With Diagnosis (%)</th> <th rowspan="2">Inclusion of Equivocal Final Diagnosis§</th> <th rowspan="2">Sens (%)</th> <th colspan="5">Estimated</th> </tr> <tr> <th>Spec (%)</th> <th>PPV (%)</th> <th>NPV (%)</th> <th>+LR</th> <th>-LR</th> </tr> </thead> <tbody> <tr> <td>≥ ASCUS</td> <td>≥ LSIL</td> <td>323 (3.7)</td> <td>With Normal</td> <td>87.9</td> <td>90.2</td> <td>25.9</td> <td>99.5</td> <td>9.0</td> <td>0.13</td> </tr> <tr> <td>≥ ASCUS</td> <td>≥ LSIL</td> <td>1019 (11.8)</td> <td>With LSIL</td> <td>55.4</td> <td>93.0</td> <td>51.6</td> <td>94.0</td> <td>7.9</td> <td>0.48</td> </tr> <tr> <td>≥ LSIL</td> <td>≥ LSIL</td> <td>323 (3.7)</td> <td>With Normal</td> <td>79.6</td> <td>97.7</td> <td>57.8</td> <td>99.2</td> <td>35.2</td> <td>0.21</td> </tr> <tr> <td>≥ LSIL</td> <td>≥ LSIL</td> <td>1019 (11.8)</td> <td>With LSIL</td> <td>42.7</td> <td>99.9</td> <td>97.8</td> <td>92.9</td> <td>325.2</td> <td>0.57</td> </tr> <tr> <td>≥ LSIL</td> <td>≥ HSIL</td> <td>137 (1.6)</td> <td>With &lt; HSIL</td> <td>83.9</td> <td>96.1</td> <td>25.8</td> <td>99.7</td> <td>21.6</td> <td>0.17</td> </tr> <tr> <td>≥ HSIL</td> <td>≥ HSIL</td> <td>137 (1.6)</td> <td>With &lt; HSIL</td> <td>67.2</td> <td>99.3</td> <td>61.3</td> <td>99.5</td> <td>98.4</td> <td>0.33</td> </tr> </tbody> </table> <p>ASCUS = Atypical squamous cells of uncertain significance; LSIL = low-grade squamous intraepithelial lesion; HSIL = high-grade squamous intraepithelial lesion; Sens = sensitivity; Spec = specificity; PPV = positive predictive value; NPV = negative predictive value; +LR = the likelihood ratio for a positive test; -LR = likelihood ratio for a negative test.</p> <p>* Data from Hutchinson ML et al. (11) test characteristics were calculated from data in their publication.</p> <p>† Thresholds indicate the comparisons made in the 2 x 2 contingency table constructed to calculate performance characteristics for that row. For instance, in the second to last row, ≥ LSIL indicates that cytology findings of LSIL and more severe abnormalities were grouped together as a positive test result and compared to the final diagnosis of HSIL and more severe abnormalities that are grouped together and considered a positive reference standard diagnosis.</p> <p>§ The equivocal column indicates the group in which women with equivocal final diagnoses were included for calculation of the performance characteristics in a specific row. See text for further details.</p> <ul style="list-style-type: none"> <li>• Authors concluded current evidence is inadequate to suggest LBC is better than Pap smear</li> </ul>	Liquid-Based Cytology Threshold†	Final Diagnosis	No. With Diagnosis (%)	Inclusion of Equivocal Final Diagnosis§	Sens (%)	Estimated					Spec (%)	PPV (%)	NPV (%)	+LR	-LR	≥ ASCUS	≥ LSIL	323 (3.7)	With Normal	87.9	90.2	25.9	99.5	9.0	0.13	≥ ASCUS	≥ LSIL	1019 (11.8)	With LSIL	55.4	93.0	51.6	94.0	7.9	0.48	≥ LSIL	≥ LSIL	323 (3.7)	With Normal	79.6	97.7	57.8	99.2	35.2	0.21	≥ LSIL	≥ LSIL	1019 (11.8)	With LSIL	42.7	99.9	97.8	92.9	325.2	0.57	≥ LSIL	≥ HSIL	137 (1.6)	With < HSIL	83.9	96.1	25.8	99.7	21.6	0.17	≥ HSIL	≥ HSIL	137 (1.6)	With < HSIL	67.2	99.3	61.3	99.5	98.4	0.33
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<p><b>Strengths and limitations</b></p>	<ul style="list-style-type: none"> <li>• The aims and inclusion criteria were clearly stated</li> <li>• Search was not comprehensive and may have missed relevant, including unpublished articles (publication bias)</li> <li>• Only Medline searched but included studies from AHCPR report that searched several databases</li> <li>• Attempts weren't made to locate unpublished studies</li> </ul>																																																																											

**Table 16 (cont) Validity reviews of secondary studies**

**Reference:** Broadstock, M. (2000) 'Effectiveness and cost-effectiveness of automated and semi-automated cervical screening devices: a systematic review of the literature.' Christchurch: New Zealand Health Technology Assessment. *New Zealand Health Technology Assessment (NZHTA) Report*.

<p><b>Focused question?</b> (ie PICO elements: patient, intervention/diagnostic or screening test of interest, comparator, outcomes of interest)</p>	<p><b>Patient:</b> All women (screening)</p> <p><b>Diagnostic test:</b> Liquid based slide preparation (ThinPrep, AutoCyte)</p> <p><b>Comparison:</b> Conventional Pap test</p> <p><b>Outcomes:</b> Sensitivity, specificity, relative true positive rate, relative false positive rate, PPV at a threshold of HSIL+ for both cytology and reference standard</p> <p><b>Standard test:</b> Histology (biopsy), cytology by expert panel review</p>
<p><b>Inclusion and exclusion criteria?</b> (including <i>a priori</i>)</p>	<ul style="list-style-type: none"> <li>• Included studies comparing the clinical or cost-effectiveness of LBC and Pap tests and used a reference standard</li> <li>• Excluded non-English studies, correspondence, abstracts, single case studies, those with poor description of methods and results, those cited in the Australian Health Technology Advisory Committee (AHTAC) review (1998), and evaluated devices, techniques or strategies</li> <li>• Studies evaluating slides taken from samples were excluded (such as women with previous abnormal samples, never been screened, pregnant, or those less than 18 years of age)</li> </ul>
<p><b>Explicit comprehensive search strategy?</b> (did review incorporate a search strategy comprehensive enough that it was unlikely to have missed studies?)</p>	<ul style="list-style-type: none"> <li>• Searched Medline, EMBASE, HealthSTAR, Current Contents, Science Citation Index, CancerLit, EconLit, Cochrane Library, Database of Abstracts of Reviews of Effectiveness, NHS Economic Evaluation and HTA database, US National Library of Medicine, North Thames Regional Library (UK), and World Health Organization. The National Bibliographic database, Ministry of Health website and library, university and medical library catalogues and the NZHTA in-house collection. Internet websites were also searched.</li> <li>• Restricted to English articles (January 1, 1997 - May 31, 2000) to update the 1998 AHTAC review</li> <li>• Search terms included: "cervix neoplasms", "vaginal smears", "mass screening", "cytological techniques", "Pap", "ThinPrep", "AutoCyte"</li> </ul>
<p><b>Assessed validity of included trials?</b></p>	<ul style="list-style-type: none"> <li>• Critically appraised the methodological qualities of the studies (study sample recruitment, blind verification, reference standard used, extent of verification)</li> <li>• Studies were rated according to a revised hierarchy of evidence adapted from the recommendations of the Cochrane Methods Working Group on systematic review of screening and diagnostic tests</li> <li>• Rigorous validity assessment</li> </ul>
<p><b>Summary of the main results</b></p>	<ul style="list-style-type: none"> <li>• Six systematic reviews and/or meta-analyses and 15 primary research studies were identified and appraised</li> <li>• All used histology by biopsy as reference standard to verify positive diagnoses, though no study verified negatives at a threshold of HSIL. Verification of positives was commonly limited to test results, which were discordant (ie one screening test gave a positive result and the other gave a negative result).</li> <li>• The reviewers concluded that given limitations in study quality, the clinical effectiveness of ThinPrep and AutoCyte Prep for detection of high-grade abnormalities could not be reliably determined from the current evidence base. Moreover, it was not possible to say whether one device has advantages over another in terms of considered outcomes. Valid estimates of test sensitivity and test specificity of these devices await further research</li> </ul>
<p><b>Strengths and limitations</b></p>	<ul style="list-style-type: none"> <li>• Employed a comprehensive search strategy</li> <li>• Included a comprehensive literature search</li> <li>• Attempted to search for unpublished studies</li> <li>• Stated aims and inclusion criteria clearly</li> <li>• Rigorous, explicit systematic review</li> <li>• The authors reported the following limitations associated with their review: publication limited to January 1997 to May 2000, inclusive; publications in English language; unknown local applicability of results from studies, all of which were conducted outside of New Zealand; the impact of HPV testing was not considered</li> </ul>

**Table 16 (cont) Validity reviews of secondary studies**

**Reference:** Bernstein, S.J., Sanchez-Ramos, L. & Ndubisi, B. (2001). 'Liquid-based cervical cytologic smear study and conventional Papanicolaou smears: a meta-analysis of prospective studies comparing cytologic diagnosis and sample adequacy', *American Journal of Obstetrics & Gynecology*, 185, 308-317.

<p><b>Focused question?</b> (ie PICO elements: patient, intervention/diagnostic or screening test of interest, comparator, outcomes of interest)</p>	<p><b>Patient:</b> Women undergoing testing for cervical cancer (age not specified); assumed for primary screening and evaluation of previous abnormal test result</p> <p><b>Diagnostic test:</b> LBC</p> <p><b>Comparison:</b> conventional Pap smears</p> <p><b>Outcomes:</b> Cytologic diagnosis, sample adequacy</p> <p><b>Reference test:</b> Not used</p>
<p><b>Inclusion and exclusion criteria?</b> (including <i>a priori</i>)</p>	<ul style="list-style-type: none"> <li>• Prospective studies evaluating ThinPrep and Pap smears based on the Bethesda system nomenclature</li> <li>• Data from split-sample and direct-to-vial (case-cohort) studies were assessed</li> <li>• Studies were excluded if different thin-layer technology was used; no comparison with conventional smears and specific outcome measures were not evaluated</li> </ul>
<p><b>Explicit comprehensive search strategy?</b> (did review incorporate a search strategy comprehensive enough that it was unlikely to have missed studies?)</p>	<ul style="list-style-type: none"> <li>• MEDLINE, PubMed, Silver Platter and references from published articles</li> <li>• English articles (January 1990 to April 2000)</li> <li>• Search terms included: "ThinPrep", "liquid-based cytology", "Pap smear"</li> </ul>
<p><b>Assessed validity of included trials?</b></p>	<ul style="list-style-type: none"> <li>• Studies were evaluated for their methodological qualities, inclusion and exclusion criteria, description of sampling protocols, definition of reported outcomes, and statistical analyses. Methods were not described</li> <li>• A heterogeneity test was performed to evaluate ability to pool individual trial data (Breslow &amp; Day 1980)</li> </ul>
<p><b>Summary of the main results</b></p>	<ul style="list-style-type: none"> <li>• Forty nine publications on LBC were identified: 24 were excluded on the basis of use of different thin-layer technology, lack of comparison to conventional smears, and lack of evaluation of specific outcome measures</li> <li>• 24 articles and one abstract met the inclusion criteria</li> <li>• No difference in the rate of atypical cells of undetermined significance diagnosis between ThinPrep and Pap smears (odds ratio (OR) 1.03; 95% CI 0.99, 1.06). In split-sample trials, the rate was higher in ThinPrep than in Pap smear when ThinPrep Processor Beta model and ThinPrep 2000 were combined (OR 1.20; 95% CI 1.13, 1.27). When ThinPrep 2000 alone was compared with Pap smear, there was no difference (OR 1.05; 95% CI 0.95, 1.16)</li> <li>• ThinPrep was significantly better than Pap smear in the cytologic diagnosis of low-grade squamous intraepithelial lesions in direct-to-vial studies: OR 2.15; 95% CI 2.05, 2.26. In split-sample trials, ThinPrep was favoured in both the combined models (OR 1.27; 95% CI 1.21, 1.32) and the ThinPrep 2000 trials (OR 1.27; 95% CI 1.21, 1.34). Similarly, when high-grade squamous intraepithelial lesions were analysed, ThinPrep was favoured over Pap smear in direct-to-vial studies (OR 2.26; 95% CI 2.06, 2.47) and in both sets of split-sample trials (OR 1.09; 95% CI 1.00, 1.18; OR 1.14; 95% CI 1.00, 1.29).</li> <li>• The overall adequacy was significantly improved in the ThinPrep group in all trials - direct-to-vial (OR 2.11; 95% CI 2.07, 2.15), split-sample ThinPrep Processor Beta model + ThinPrep 2000 (OR 1.64; 95% CI 1.53, 1.76), and split-sample ThinPrep 2000 (OR 1.65; 95% CI 1.54, 1.78).</li> </ul>
<p><b>Strengths and limitations</b></p>	<ul style="list-style-type: none"> <li>• The research question, aims and inclusion criteria were clearly stated</li> <li>• Search was restricted to English articles</li> <li>• No attempt was made to identify unpublished articles</li> <li>• Search was restricted to a limited number of databases (Medline and PubMed)</li> <li>• Summary estimate was calculated for each outcome</li> <li>• Although the authors state that included studies were evaluated for methodologic quality, the methodology of this evaluation and subsequent reporting of results were not presented</li> <li>• Good description of the statistical method used for pooling results</li> <li>• Highlighted the need for further research</li> <li>• The reported results associated with both LBC and Pap smear were not evaluated against a reference test</li> </ul>

## Validity of secondary studies

### Focused question

The reviews focused on a clear research question, providing an explicit statement of the patient group, intervention (cervical screening) and focused outcomes (sensitivity, specificity, etc). Four of the reviews compared LBC (also called fluid-based cytology) and conventional Pap smears with a reference test (Hartmann et al 2001, Sulik et al 2001, Moseley & Paget 2002, Broadstock 2000). In the review by Bernstein et al (2001) the two types of screening tests were compared but not evaluated against a reference test.

### Inclusion and exclusion criteria

Some of the reviews provided explicit *a priori* details of the studies that were to be included and excluded from the review. Hartmann et al (2001) focused on studies that used clinical confirmation of cervical cytology by colposcopy, cervical biopsy or both. Sulik et al (2001) reviewed studies comparing both conventional Pap smear samples and LBC samples in which tests were either simultaneously applied to the same group of women, or a group of women who received Pap tests was compared with a group that received LBC.

The inclusion criteria adapted by Moseley & Paget (2002) were broad. They excluded abstracts, reviews or clinical studies reporting less than 1,000 cases and four clinical studies of more than 1,000 cases for reasons cited in Table 16. Bernstein et al (2001) included prospective studies evaluating LBC and Pap smears based on the Bethesda system nomenclature. They excluded studies if a different LBC technology was used, if there was no comparison to conventional smears and if specific outcome measures were not evaluated. Broadstock (2000) evaluated studies comparing the clinical effectiveness of LBC and Pap smears that also used a reference standard. Among excluded studies were abstracts, single case studies, studies with a poor description of methods and results and studies cited in the 1998 AHTAC review. Excluded studies were those that evaluated devices, techniques or strategies, and those that assessed slides taken from particular groups of women: with previous abnormal samples, never been screened, pregnant or under 18 years of age.

### Explicit comprehensive search strategy

This criterion addresses whether the search strategy used to gather information for the review was sufficiently comprehensive to minimise the likelihood of studies being missed. The search strategy was described in all reviews but varied across them. The searches were restricted to English language articles in all reviews. The most thorough search strategies were undertaken by Hartmann et al (2001), Sulik et al (2001) and Broadstock (2000). The search by Moseley & Paget (2002) was confined to Medline as the only database, one UK HTA report and four journals. In addition, the keywords "Pap smear", "Papanicolaou", "cervical cancer screening" or "vaginal smear" were not included in the search terms. Bernstein et al (2001) searched Medline and PubMed and references from published articles. In only two reviews did authors attempt to identify and retrieve unpublished articles or data (Sulik et al 2001, Broadstock 2000), suggesting that the remaining reviews may have been subject to publication bias.

### Assessed validity of included trials

Three reviews (Sulik et al 2001, Bernstein et al 2001, Broadstock 2000) thoroughly and explicitly assessed the validity of their included studies. Hartmann et al (2001) included some validity criteria in the selection criteria. Moseley & Paget (2002) evaluated but did not explicitly report on validity criteria of the included studies.

### Results of secondary study evaluations

All five studies attempted to evaluate the test performance of LBC compared to the conventional Pap test.

Although Hartmann et al (2001) found no studies that met their inclusion criteria, they discuss three studies. One of these was a population-based study of LBC using colposcopy and histology as reference standards to assess a random subset of women with normal screening results. Calculations of sensitivity, specificity, PPV and NPV were based on a presumption of no false negatives and no comparison was made with conventional Pap smears. In the other two studies only a sample of women were selected for biopsy and the authors did not specify how they were identified. The LBC and conventional Pap smears were undertaken on separate non-randomised individuals. Hartmann et al concluded that the current evidence is inadequate to gauge whether new technologies are better than conventional cytology.

Sulik et al (2001) based their evaluation on five studies – three comparing LBC and Pap smear results with a reference test of colposcopy and biopsy and two using expert consensus as the reference standard, with biopsy for at least 50 per cent of the women showing significant abnormalities on either or both tests. In none of the five studies was there a significant difference between the two methods as determined by the area under the receiver operating characteristic curve (AuROC; refer to Table 15). Compared to Pap test, LBC showed higher sensitivity (90 versus 79 per cent) and a lower specificity (85 versus 89 per cent). LBC specimens were more likely to be reported as satisfactory. No difference in the number of unsatisfactory test results for Pap smear or LBC was reported. With LBC there was a six per cent higher rate of absence of endocervical cells but a 10 per cent decrease in reports of 'satisfactory but limited by exudate and inflammatory material'. The increase in absence of endocervical cells for LBC specimens was seen in all split-sample studies but not in the cohort studies.

The review by Moseley & Paget (2002) identified several split-sample studies reporting increased detection of abnormalities with LBC. The majority of these studies presented sparse or non-existent biopsy/histology follow-up data so the true clinical yield of epithelial abnormalities is unknown. In these circumstances, false positive test results may be misinterpreted as increased sensitivity. Where a histological reference standard was employed, test evaluation was frequently limited to discordant test results where one test was negative and the other positive. There is potential bias associated with the analyses for both of these situations.

The authors also attempted to compare the specificity of LBC and Pap smears. In most of the studies evaluated, there were no histological data. Where these were available, outcome data for colposcopic referral was substantially incomplete and/or the number of women referred to colposcopy was not stated. Positive predictive value for high-grade histology following colposcopic referral for an abnormal smear could therefore not be reliably assessed. For the five studies in which women were biopsied, PPV for high-grade histology ranged from 35 to 100 per cent for Pap smears and 40 to 91 per cent for LBC.

The meta-analysis by Bernstein et al (2001) reported no difference in the rate of atypical cells of undetermined significance diagnosis between LBC and Pap smears. In split-sample trials, the rate was higher with LBC than with Pap smears when the ThinPrep Processor Beta model and ThinPrep 2000 were combined (OR 1.20; 95 per cent CI 1.13, 1.27). When ThinPrep 2000 alone was compared with Pap smears, there was no difference. LBC was significantly more sensitive than Pap smears in the cytologic diagnosis of low-grade squamous intraepithelial lesions in direct-to-vial studies (OR 2.15; 95 per cent CI 2.05, 2.26). In split-sample trials, LBC was more sensitive in both the combined models (OR 1.27; 95 per cent CI 1.21, 1.32) and the ThinPrep 2000 trials (OR 1.27; 95 per cent CI 1.21, 1.34).

Similarly, when high-grade squamous intraepithelial lesions were analysed, LBC was more sensitive than Pap smears in direct-to-vial studies (OR 2.26; 95 per cent CI 2.06, 2.47) and in both sets of split-sample trials (OR 1.09; 95 per cent CI 1.00, 1.18 and OR 1.14; 95 per cent CI 1.00, 1.29 respectively). The overall adequacy was significantly improved in the LBC group in all trials direct-to-vial (OR 2.11; 95 per cent CI 2.07, 2.15), split-sample ThinPrep Processor Beta model + ThinPrep 2000 (OR 1.64; 95 per cent CI 1.53, 1.76) and split-sample ThinPrep 2000 (OR 1.65; 95 per cent CI 1.54, 1.78).

The NZHTA review (Broadstock 2000) identified several studies relevant to LBC but concluded that estimates of test sensitivity and specificity for the new devices could not be reliably determined because of methodological limitations associated with the appraised studies.

Limitations of the critically appraised secondary studies are summarised below:

- All were restricted to English language articles so relevant studies may have been missed from the review (potential for publication bias);
- Inclusion criteria were relaxed in one review allowing the inclusion of studies with poor methodology;
- The search strategy was not comprehensive in some of the reviews;
- Some of the reviews did not attempt to locate unpublished articles or data;
- The methodological quality of the included and evaluated studies was not explicitly stated in some reviews;
- One review did not use a reference test to evaluate the results of both Pap smears and LBC;
- The issue of blinding in the interpretation of the reference standard was not addressed in some reviews; and
- Some reviews did not define or clarify who the patients were or whether they came from high-risk or low-risk populations.

## Critical appraisal of primary studies

The search strategy identified 21 primary studies published after the NZHTA report (Broadstock 2000) of which only seven met the inclusion criteria (Appendix F).

Table 17 lists the descriptive characteristics of the included studies. Four of the included studies were conducted in the United States. The remainder were conducted in France (Bergeron et al 2001), Switzerland (Obwegeser & Brack 2001) and South Korea (Park et al 2001). One of the studies specified a consecutive series of patients (Bergeron et al 2001) whereas the others recruited either a random (Obwegeser & Brack 2001) or a non-random population-based sample (Park et al 2001, Bai et al 2000, Tench 2000, Anton et al 2000 and Guidos & Selvaggi 2000).

Although the study designs varied, the papers generally described the clinical characteristics of the women screened, their ages and selection criteria. Bergeron et al (2001) and Park et al (2001) described split-sample studies, Obwegeser & Brack (2001) reports on a randomised controlled trial, Bai et al (2000) and Tench (2000) used historical controls, Guidos & Selvaggi (2000) used historical controls in addition to prospective recruitment of controls, and Bergeron et al (2001) and Anton et al (2001) recruited all patients prospectively.

Critical appraisal of the seven included studies against the validity criteria (Table 18) revealed that none of the studies met all of them. Failure to meet validity criteria adequately suggests non-appraisable bias in the results of the study (Lijmer et al 1999). Two studies (Bai et al 2000, Tench 2000) recruited an appropriate spectrum of patients, however not all patients testing positive for either screening test were tested with the reference test. Both Bergeron et al (2001) and Park et al (2001) masked assessment of the screening test results and tested all subjects with both the screening tests, but only Bergeron et al (2001) tested every patient with the reference test (after the start of treatment). However the study subjects described by Bergeron were inappropriate. They included women referred for loop electrosurgical excision procedure (LEEP) of the cervix for the following reasons: high-grade cervical intraepithelial neoplasm (CIN) on biopsy, abnormal cytology and unsatisfactory colposcopy status after menopause, persistent abnormal cytology after laser therapy and high-grade squamous intraepithelial lesion (SIL) on a smear with a normal biopsy.

Park et al (2001) did not test every patient with the reference test. Instead colposcopically-directed biopsies were performed only when there were discrepancies in cytological diagnoses and when at least one slide was abnormal. Also, a large proportion of abnormal cases were included in the study as clinicians were asked to favour the selection of patients with previous abnormal conventional smear diagnoses or suspected abnormalities. Obwegeser & Brack (2001) masked assessment of the screening test results but only applied the reference test to women with a cytological diagnosis of high-grade squamous intraepithelial lesions.

**Table 17 Descriptive characteristics of included studies**

First Author and Year of publication	Setting, dates of enrolment	Spectrum of patients		Selection criteria
		Sample size	Age (years) Mean (SD), range	
Anton 2001	USA, not stated	590 (Pap) 137 (LBC)	Not stated	Women were recruited from the patients of a large group of gynaecologists in private practice. Patients with a diagnosis of ASCUS within follow-up biopsies or cytologies within a one-year period were followed up. Patients who had follow-up cytologies consisting only of ASCUS or AGUS were excluded.
Bai 2000	USA, May 1996 to June 1998	82,752 (Pap) 82,252 (LBC)	42.6, 22-88 (Patients testing positive for atypical glandular cells of undetermined significance of endocervical cell type (AGUS-EC) Pap smear) 40.2, 18-93 (Patients testing positive for AGUS-EC LBC)	All cases diagnosed as AGUS-EC from both the conventional Pap smears and the LBC from a computerised database of the Laboratory of Women and Infants' Hospital of Rhode Island. Glandular abnormalities of endometrial origin on cytology were not included.
Bergeron 2001	France, not stated	500	Not stated	Consecutive women referred for loop electrosurgical excision procedure of the cervix: women who had high grade cervical intraepithelial neoplasm (CIN) on biopsy, women who had an abnormal cytology and unsatisfactory colposcopy status after menopause, women who had persistent abnormal cytology after laser therapy and women who had high grade squamous intraepithelial lesion (SIL) on a smear with a normal biopsy.
Guidos 2000	USA, not stated (prospective recruitment) & January 1996 to February 1997 (retrospective recruitment)	29,589 (LBC) 16,139 (Pap) 8,981 (retrospective Pap)	45-90 (patients with endometrial lesions) 23% of 50+ (LBC) 29% of 50+ (Pap)	The patient population consisted of a mixture of asymptomatic women who received annual routine gynaecological examinations, high-risk women and symptomatic patients.
Obwegeser 2001	Switzerland, mid-July 1998 to September 1998	1,002 (Pap) 997 (LBC)	Not stated	Patients were recruited from 15 private practices and included patients with a previous abnormal Pap smear.
Park 2001	South Korea, March 1998 to February 1999	483	Not stated	Patients were recruited from a referral hospital with a relatively large proportion of patients with known or suspected cervical abnormalities. Clinicians were asked to favour the selection of patients with previous abnormal screening diagnoses or suspected abnormalities therefore a large proportion of abnormal cases was included in the study.
Tench 2000	USA, January 1999 to April 1999 (Pap), January 2000 to April 2000 (LBC)	10,367 (Pap) 2,231 (LBC)	Not stated	Patients attending a two-hospital district in San Diego county.

**Table 18** Validity of included studies

First Author Year	Validity of study methods							
	Appropriate spectrum of study subjects	Masked assessment of study and reference test results	Masked assessment of study test results	All study subjects tested with both study tests	All study subjects tested with study and reference test	All positive subjects tested with reference test	Study test independent of clinical information	Reference test measured before intervention
Anton 2001	No	NS	NS	No	No	No	No	NS
Bai 2000	Yes	NS	NS	No	No	No	NS	NS
Bergeron 2001	No	Yes	Yes	Yes	Yes	Yes	No	No
Guidos 2000	No	NS	NS	No	No	No	No	Yes
Obwegeser 2001	No	Yes	NS	No	No	No	NS	NS
Park 2001	No	Yes	Yes	Yes	No	Yes	No	NS
Tench 2000	Yes	NS	NS	No	No	No	Yes	Yes

NS – Not stated

Table 19 lists the test results extractable for each threshold level. The diagnostic characteristics are listed in Table 20.

Sensitivity and specificity could only be calculated from data in Bergeron et al (2001) and Park et al (2001) as subjects with both positive and negative LBC and Pap test results were verified using the biopsy reference test. Sensitivity and specificity are likely to be over-estimated if the reference test is not used on all patients or different reference tests are used to verify positive and negative results (Lijmer et al 1999). For the conventional Pap test, sensitivity for different thresholds varied from 39.4 to 86.8 per cent and specificity varied from 47.8 to 98.9 per cent. For the LBC test the respective figures were sensitivity 41.7 to 82.6 per cent and specificity 52.2 to 90.2 per cent (Bergeron 2001).

Diagnostic characteristics were also extracted from Park et al (2001) for a single threshold (positive cytology defined as  $\geq$  ASCUS): 89.6 per cent sensitivity and 52.1 per cent specificity for the conventional Pap test and 82.8 per cent sensitivity and 62.0 per cent specificity for the LBC test. Pooling of diagnostic characteristics was not appropriate due to the clinically heterogeneous populations and differing cytology thresholds. Any difference in diagnostic characteristics of the tests must be interpreted with caution due to the failure of the studies to meet several validity criteria (Table 18) and therefore the probable presence of non-appraisable bias.

**Table 19 Test results with histology as the reference test**

First author, year	Number tested with reference test		Threshold	True positives		False positives		True negatives		False negatives	
	Pap	LBC		Pap	LBC	Pap	LBC	Pap	LBC	Pap	LBC
Anton 2001	276	86	Negative=within normal limits, benign cellular changes Positive=No pathologic change, LSIL, HSIL	187	68	89	48	-	-	-	-
Bai 2000	72	35	Negative=unremarkable/benign lesions Positive=all other lesions	23	14	49	21	-	-	-	-
			Negative=unremarkable/benign lesions, LSIL Positive=HSIL, ungraded squamous dysplasia, AIS, dysplastic glandular lesions, adenocarcinoma	19	14	53	21	-	-	-	-
Bergeron 2001	500	500	Negative=normal Positive=unsatisfactory, ASCUS/AGUS, LSIL, HSIL	354	337	48	45	44	47	54	71
			Negative=normal/limited by unsatisfactory specimen Positive= ASCUS/AGUS, LSIL, HSIL	308	334	36	44	56	48	100	74
			Negative=normal/limited by unsatisfactory specimen, ASCUS/AGUS Positive= LSIL, HSIL	249	273	14	25	78	67	159	135
			Negative=limited by unsatisfactory specimen, ASCUS/AGUS, LSIL Positive= HSIL	161	170	1	9	91	83	247	238
Guidos 2000	NS	16	Negative=normal Positive=adenocarcinoma	1	14	0	1	-	-	-	-
Obwegeser 2001	12	11	(Positive cytology = HSIL) Negative=no SIL Positive=LSIL, HSIL	12	10	0	1	-	-	-	-
			(Positive cytology HSIL) Negative=no SIL, LSIL Positive=HSIL	12	10	0	1	-	-	-	-
Park 2001	158	158	(Positive cytology ≥ ASCUS) Negative=chronic cervicitis Positive=CIN I, CIN II, CIN III, carcinoma	78	72	34	27	37	44	9	15
Tench 2000	NS	30	Negative=normal, ASCUS, unsatisfactory specimen, satisfactory specimen but limited by scant squamous cellularity Positive=LSIL, HSIL	-	29	-	1	-	-	-	-

AGUS= atypical glandular cells of undetermined significance; AIS=adenocarcinoma in situ; ASCUS=atypical squamous cells of undetermined significance; HSIL=high-grade squamous intraepithelial lesion; LSIL=low-grade squamous intraepithelial lesion; SIL=squamous intraepithelial lesion.

**Table 20 Diagnostic characteristics of included studies**

LBC technology	First author, year	Threshold	Rel TPR	Rel FPR	Sensitivity		Specificity		LR+	LR-
					Pap (%)	LBC (%)	Pap (%)	LBC (%)		
Not specified	Anton 2001	Negative=within normal limits, benign cellular changes Positive=(no pathologic change), LSIL, HSIL	1.17 (p<0.01)	1.73 (p<0.2)	-	-	-	-	-	-
Thin Prep	Bai 2000	Negative=unremarkable/ benign lesions Positive=all other lesions	1.25 (p<0.005)	0.88 (p<0.005)	-	-	-	-	-	-
		Negative=unremarkable/ benign lesions, LSIL Positive=HSIL, ungraded squamous dysplasia, AIS, dysplastic glandular lesions, adenocarcinoma	1.52 (p<0.025)	0.82 (p<0.025)	-	-	-	-	-	-
Thin Prep	Guidos 2000	Negative=normal Positive=adenocarcinoma, carcinoma	a	a	-	-	-	-	-	-
Thin Prep	Obwegeser 2001	(Positive cytology = HSIL) Negative=No SIL Positive=LSIL, HSIL	0.91 (p<0.0005)	a	-	-	-	-	-	-
		(Positive cytology = HSIL) Negative=No SIL, LSIL Positive=HSIL	0.91 (p<0.0005)	a	-	-	-	-	-	-
Thin Prep	Park 2001	(Positive cytology ≥ASCUS) Negative=chronic cervicitis Positive=CIN1, CIN2, CIN3, carcinoma	-	-	89.6	82.8	52.1	62.0	1.87 (Pap) 2.18 (LBC)	0.20 (Pap) 0.28 (LBC)
Auto Cyte PREP	Tench 2000	Negative=normal, ASCUS, unsatisfactory specimen, satisfactory specimen but limited by scant squamous cellularity Positive=LSIL, HSIL	a	a	-	-	-	-	-	-
Auto Cyte PREP	Bergeron 2001	Negative=normal Positive=unsatisfactory specimen, ASCUS/AGUS, low-grade SIL, high-grade SIL	-	-	86.8	82.6	47.8	52.2	1.66 (Pap) 1.73 (LBC)	0.28 (Pap) 0.33 (LBC)
		Negative=normal/limited by unsatisfactory specimen Positive=ASCUS/AGUS, low-grade SIL, high-grade SIL	-	-	75.5	81.9	60.9	52.2	1.9 (Pap) 1.7 (LBC)	0.40 (Pap) 0.35 (LBC)
		Negative=normal/limited by unsatisfactory specimen, ASCUS/AGUS Positive=LSIL, HSIL	-	-	61.0	66.9	84.8	72.8	4.0 (Pap) 2.5 (LBC)	0.46 (Pap) 0.45 (LBC)
		Negative=normal/limited by unsatisfactory specimen, ASCUS/AGUS, LSIL Positive=HSIL	-	-	39.4	41.7	98.9	90.2	35.9 (Pap) 4.3 (LBC)	0.61 (Pap) 0.65 (LBC)

<sup>a</sup> Cannot be calculated; AGUS= atypical glandular cells of undetermined significance; ASCUS=atypical squamous cells of undetermined significance; HSIL=high-grade squamous intraepithelial lesion; LR+=positive likelihood ratio; LR-=negative likelihood ratio; LSIL=low-grade squamous intraepithelial lesion; Rel TPR=relative true positive rate (LBC compared to Pap); Rel FPR=relative false positive rate (LBC compared to Pap); SIL=squamous intraepithelial lesion.

The failure of Anton et al (2001), Bai et al (2000) and Obwegeser & Brack (2001) to meet several validity criteria, as well as the limitation imposed by application of the reference test only to those who tested positive on either screening test, hampered interpretation of these studies. The TPR and FPR calculated from Anton et al (2001) were 1.17 and 1.73, respectively (LBC compared to Pap), with LBC tests having a higher detection rate than the conventional Pap test. The LBC test also had a correspondingly higher FPR that was not statistically significant. The ranges for both thresholds in Bai et al (2000) were 1.25 to 1.52 for TPR and 0.82 to 0.88 for FPR, with LBC tests having a higher detection rate and a lower FPR. The TPR calculated from Obwegeser & Brack (2001) was 0.91 for both thresholds, with LBC tests having a lower detection rate than the conventional Pap test. The FPR could not be calculated from Obwegeser & Brack (2001).

Guidos & Selvaggi (2001) and Tench (2000) reported insufficient data for the calculation of any diagnostic characteristics.

## Summary of results

### Secondary studies

Secondary studies investigating LBC concluded that, to date, there is insufficient high quality data or evidence to suggest that LBC is better than the Pap smear for cervical screening. However, Sulik et al (2001) suggest that there may be a role for LBC for women who have had abnormal Pap test results or who are at a high risk of cervical cancer due to infrequent screening.

Bernstein et al (2001) deduced that the LBC test improved sample adequacy and led to improved diagnosis of low-grade and high-grade squamous intraepithelial lesions but results comparing LBC and Pap tests were not evaluated against a histological reference test. All authors noted that the most frequent study design was the split-sample method and that many of the clinical studies examined were funded partially or completely by manufacturers of LBC technologies.

### Primary studies

Sensitivity and specificity could only be calculated from two primary studies investigating LBC (Bergeron et al 2001, Park et al 2001). For the Pap smear, the different thresholds assessed by Bergeron et al (2001) above which cytology results are considered important for further investigation yielded sensitivity values ranging from 39.4 to 86.8 per cent and specificity from 47.8 to 98.9 per cent. For LBC, the corresponding values were 41.7 to 82.6 per cent sensitivity and 52.2 to 90.2 per cent specificity.

Diagnostic characteristics were also extracted from Park et al (2001) for a single threshold to give 89.6 per cent sensitivity and 52.1 per cent specificity for the Pap smear and 82.8 per cent sensitivity and 62.0 per cent specificity for LBC. Pooling of diagnostic characteristics was not appropriate due to clinically heterogeneous populations and differing cytology thresholds. Any difference in diagnostic characteristics of the tests must be interpreted with caution due to the failure of the studies to meet several validity criteria and the probable presence of non-appraisable bias as a result.

The relative TPR and FPR (LBC compared to Pap) were calculated from three studies. The TPR and FPR calculated from Anton et al (2001) were 1.17 and 1.73, respectively, indicating that LBC has a higher detection rate than conventional cytology, but also a correspondingly higher FPR. However, the FPR was not statistically significant. For both

thresholds in the Bai (2000) study, the range of TPR values was 1.25 to 1.52 and that for FPR values was 0.82 to 0.88, indicating that LBC has a higher detection rate and a lower FPR than conventional cytology. The TPR from Obwegeser & Brack (2001) was 0.91 for both thresholds, demonstrating that LBC has a lower detection rate than conventional cytology. Pooling of diagnostic characteristics was not appropriate due to the clinically heterogeneous populations and differing cytology thresholds.

The failure of the studies to meet several validity criteria and the limitation of having applied the reference test only to those who tested positive on either screening test made interpretation difficult.

Many studies failed to define an upper limit to the period over which the histological outcome was determined. It was therefore unclear whether LBC and conventional cytology were being compared on an equivalent basis.

In addition to the above limitations, the issue of relating overseas data to the Australian context is important. The difference in cytology classification, particularly between the US Bethesda System and that used in Australia, means that data cannot be directly compared and may be of questionable relevance.

In summary, there is insufficient evidence to enable us to draw conclusions regarding the diagnostic characteristics of LBC and Pap smears for cervical screening. Further high quality studies using an acceptable reference standard, such as histological confirmation of cytology results, are crucial to allow a valid and reliable judgement concerning test sensitivity and specificity of LBC.

## What are the economic considerations?

### Review of previous considerations

The Australian Health Technology Advisory Committee evaluated the safety, effectiveness and cost-effectiveness of automated and semi-automated devices including LBC for cervical screening (AHTAC, 1998). An indicative economic model based on Australian data and experience was developed. However, because the new technologies were used in addition to conventional cervical screening practice in the model, the results from this analysis are of limited relevance to the current consideration of whether LBC should replace conventional cytology.

Broadstock (2000) extended and updated the AHTAC evaluation of the safety, effectiveness and cost-effectiveness of automated and semi-automated devices including LBC for cervical screening for the New Zealand Health Technology Assessment (NZHTA) Clearing House. This review concluded that estimates of test sensitivity and test specificity for the new devices could not be reliably determined from the available evidence. Thus, estimates of test sensitivity and specificity were the main source of uncertainty in the economic models investigating the cost-effectiveness of new devices. A review of economic models that assumed improved detection using the new devices suggested that the impact of new devices on survival was extremely small for women screened at three-yearly intervals (the cycle used in New Zealand's national cervical screening program). Cost-effectiveness may be even poorer in Australia where re-screening is conducted biennially rather than triennially.

### Review of submitted models

An application was submitted to the MSAC requesting listing on the MBS for an LBC test, defined as being for cytology of a sample of cervical cells collected into a liquid medium (instead of first being smeared onto a slide), filtered and then transferred to a glass slide and fixed with a preservative solution. This test is referred to as LBC in the current report. Included in the submission was an analysis of the cost-effectiveness of cervical screening using the LBC test versus cervical screening with conventional cytology using a decision-analytic model .

A supplementary submission made to the MSAC in June 2002 provided a re-analysis of the incremental cost-effectiveness of LBC over conventional cytology using the same fundamental model presented in the original submission.

No application has been received requesting Medicare listing of cytology of a sample of cervical cells that are collected into a liquid medium (instead of first being smeared on a slide), *centrifuged* and then transferred to a glass slide and fixed with a preservative solution (LBC/centrifugation). However, the evidence for the methods using either filtration or centrifugation in the sample preparation was included in the assessment of LBC in this report.

A detailed assessment based on a consideration of the economic models provided in the submission and supplementary submission to the MSAC is provided in Appendix H. Several problems were identified with the fundamental structure of the submitted models

and the transition probabilities driving these models. Thus, the calculations based on the submitted models are not considered reliable. Note that all values reported throughout this report refer to Australian dollars.

### Alternate model

In view of the lack of an appropriate model in the published literature and the problems identified with the models presented in the submissions to the MSAC, a new model has been constructed for this report to address issues raised in regard to the models described in the submissions. The model is not specific to the LBC test, but rather is designed for any LBC test (including LBC/centrifugation) in the absence of comparative data for differing LBC methods.

### Model structure

A decision-analytic model was used to simulate the health and economic impact of LBC versus conventional cytology for cervical screening. The population in the model is a cohort of women representative of the population that will participate in a cervical screening program. Women who choose not to participate in a screening program are not included in the model. This model is used to calculate the incremental cost of LBC or LBC/centrifugation over conventional cytology per extra woman with a detected high-grade lesion. The results from this analysis can be extrapolated to cost per extra case of cancer avoided and further extrapolated to cost per additional life-year saved if necessary. The model implicitly assumes that conventional cytology and the current program for screening for cancer of the cervix are cost-effective compared with no screening.

The model can be extended beyond two years by modification to a Markov process. This would permit comparisons of cost-effectiveness of various slide preparation techniques over a variety of time horizons. However, one of the major limitations of a Markovian model is that it maintains no memory of previous events. As a result, women given a false negative cytological prediction in one Markov cycle re-enter the model with an unaltered probability of having an abnormality detected. Modifying the Markov model structure to take account of the past can increase the complexity of the model. Furthermore, the data that would enable derivation of the transition probabilities required to populate a model with a longer time horizon are lacking. Given these limitations and the degree of uncertainty around estimates of comparative sensitivity and specificity of LBC versus conventional cytology, results presented in this report are limited to a two-year time horizon.

The fundamental structure of the model is based on clinical practice consistent with the NHMRC guidelines (1994). According to these guidelines, women undergoing a screening test either by conventional cytology or LBC can have one of the following cytological predictions of true condition:

- Negative or minor reactive & inflammatory changes;
- Mild atypia or HPV effects (alone);
- CIN I (including equivocal and possible CIN I predictions);

- CIN II (including inconclusive results);
- CIN III;
- Possible invasive cancer; or
- Endocervical or other non-squamous abnormality present.

These cytological predictions have been simplified to the following two classifications for the purposes of modelling:

1. Negative (assumed to be no different from NHMRC category) or delayed negative (which relates to cytological predictions of low grade abnormality other than CIN I that spontaneously resolve according to repeat screening).

Women in this group are assumed to have either a true negative or a false negative result. All women with a negative cytological prediction are assumed not to undergo any further assessments for two years. The women with cytological predictions of low-grade abnormality other than CIN I that resolve spontaneously (three per cent of all satisfactory screens – see 2. for explanation of derivation) are assumed to have two repeat screens over the two-year cycle.

A classification including both of these groups is appropriate because in practice the majority of cytological predictions of low-grade abnormality, in particular cytological predictions of minor reactive or inflammatory changes and mild atypia, are managed by observation and resolve spontaneously.

2. Abnormality requiring active investigation (assumed to include women in all other NHMRC categories, ie women with cytological prediction of CIN I or greater abnormalities and women with persistent cytological predictions of low-grade abnormality other than CIN I).

It is assumed that all women in this group will be actively investigated by colposcopy/biopsy. The NHMRC guidelines (1994) recommend that women with cytological predictions of CIN I (or higher) lesions and those with persistent other changes undergo active investigation by colposcopy/biopsy. The RCPA Cytopathology Quality Assurance Program reports for Performance Standard 2(b) that the mean percentage of smears reported as abnormal was 6.01 per cent in 2000 such that 93.99 per cent of smears were negative. The proportion of smears reported as abnormal includes those reported as being indicative of a high grade abnormality (0.55 per cent) and those reported as being indicative of a possible high grade abnormality (0.52 per cent). Thus, the proportion of smears reported as cytological prediction of low-grade abnormality can be estimated at 4.94 per cent (6.01 per cent - 0.55 per cent - 0.52 per cent).

The Cervical Cancer Screening in New South Wales Annual Statistical Report (1999) indicates that 16.1 per cent of cytological predictions of low-grade abnormalities are CIN I and 83.9 per cent are not CIN I. The Victorian Cervical Cytology Registry Statistical Report (2000) indicates that 33 per cent of cytological predictions of low-grade abnormality will be CIN I predictions. Pooled Victorian and NSW data suggest that CIN I cytological predictions make up 21.4 per cent of the combined predictions of mild atypia and CIN I. The majority of CIN I cytological predictions will be actively investigated but only the

persistent cytological predictions of low grade but not CIN I abnormality will be investigated, so it seems reasonable to anticipate that approximately 40 per cent of cytological predictions of low grade abnormality plus all cytological predictions of high grade and possible high grade abnormality will be investigated by colposcopy and biopsy. Thus, it is assumed that approximately 50 per cent ( $[0.55 \text{ per cent} + 0.52 \text{ per cent} + 0.40 \times 4.94 \text{ per cent}] / 6.01 \text{ per cent}$ ) of abnormal smears (ie three per cent of all smears) will be actively investigated by colposcopy/biopsy. The remaining 97 per cent of smears fall into the categories of negative (94 per cent) or spontaneously resolved cytological prediction of low-grade abnormality (three per cent).

According to the NHMRC guidelines (1994), women undergoing colposcopy and directed biopsy could be assumed to have one of the following histological confirmations and recommended management:

- Normal or benign cell structure – it is recommended that these women be managed by a repeat screen after six months.
- HPV effects alone (including equivocal HPV results) - it is recommended that these women be managed by observation, which involves repeat screening at six-monthly intervals, until two consecutive six-monthly screens are reported as negative. After two further annual negative smears, women revert to screening every two years.
- CIN I/mild dysplasia – it is recommended that these women be managed by either observational or active treatment. Observation involves repeat screening at six-monthly intervals until two consecutive six-monthly screens are reported as negative. The clinician may suggest a further colposcopy for some women. After two further annual negative smears, women revert to screening every two years.
- CIN II – it is currently recommended that these women, after two negative smears, and one or two negative colposcopies, have an annual Pap smear for life.
- CIN II/III – it is currently recommended that these women, after two negative smears, and one or two negative colposcopies, have an annual Pap smear for life.
- CIN III – it is currently recommended that these women, after two negative smears, and one or two negative colposcopies, have an annual Pap smear for life.
- Micro-invasive cancer of the cervix.
- Invasive cancer of the cervix.

It is acknowledged that some women undergoing colposcopy will be determined not to require biopsy. The NHMRC guidelines recommend that these women be managed by repeat screening at six-monthly intervals until two consecutive negative six-monthly screens are reported. The clinician may suggest a further colposcopy for some of these women. After two further annual negative smears, these women revert to the standard screening schedule and are screened every two years.

These histological outcomes have been simplified to the following classifications for modelling purposes:

- Normal or benign cell structure (as per NHMRC classification) – it is assumed that these women are managed by a repeat screen after six months;
- Low-grade lesion (which includes HPV effects, equivocal CIN and CIN I histology) – it is assumed that 50 per cent of these women are actively treated with ablative or excisional procedures and the remainder are managed by observation. This estimate was derived by assuming that the majority of CIN I patients will be managed by active treatment as has been the case historically in Australia (NHMRC 1994). From Table 22, it can be estimated that approximately 47 per cent of low-grade lesions confirmed by histology are in the CIN I classification.
- High-grade lesion (which includes CIN II, CIN II/III, CIN III histology, microinvasive and invasive cancer of the cervix) – it is assumed that these women are actively treated with ablative or excisional procedures. It is assumed that cervical screening will be repeated at six-monthly intervals for 12 months and again 12 months after active treatment of lesions.

Figure 2 summarises the fundamental structure of the alternate model.

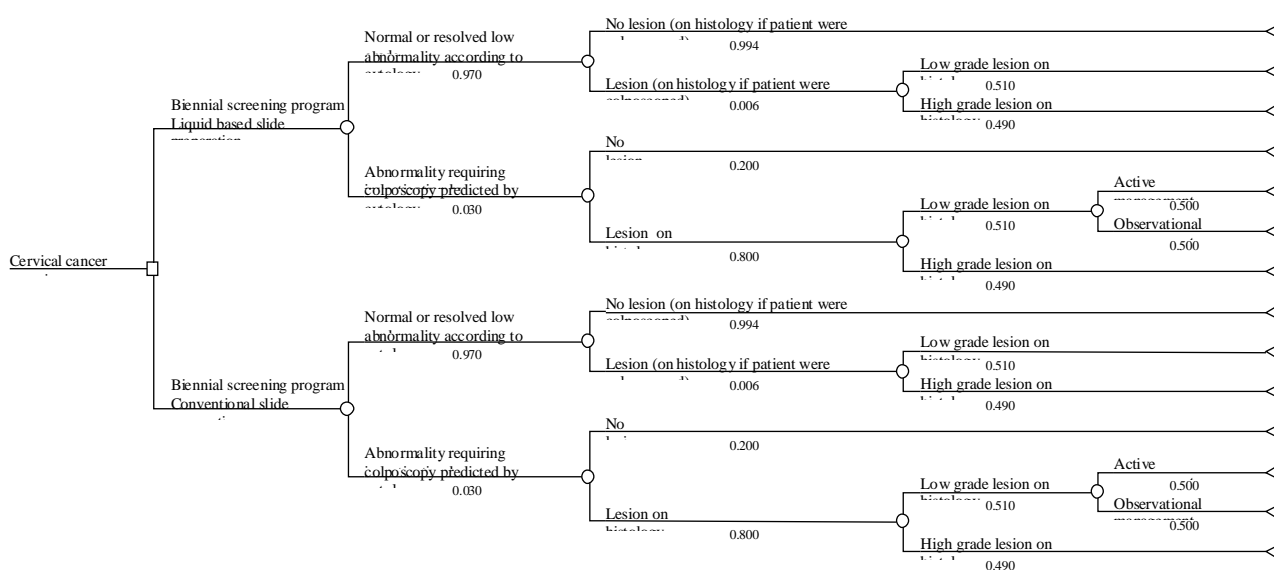


Figure 2 Structure of the alternate model

## Resource variables

The resource variables included in the analysis are summarised in Table 21.

**Table 21 Resource variables included in model**

Description	CC arm (\$)	LBC arm (\$)
Cost of screening by conventional smears or LBC (also applies to re-screening)	55.75	67.25
Cost of actively investigating a cytological prediction of an abnormality	238.50	238.50
Total cost of actively managing a cytologically-predicted low grade abnormality	503.00	537.50
Cost to treat a lesion	1,021.25	1,055.75

CC=conventional cytology; LBC=liquid-based cytology

The estimation of costs of screening and re-screening in the case of an inadequate sample have been based on \$19.00 for conventional cytology (derived from the November 2001 MBS schedule fee for MBS item 73053) and \$30.50 for LBC (derived from the submission to the MSAC which requests a fee of \$30.50). It has been assumed that a patient episode initiation (PEI) fee of \$8 (as per MBS item 73901 in the November 2001 MBS) will be charged in addition to these items. In addition, women are assumed to require a GP visit at a cost of \$28.75, consistent with the fee for MBS item 23 which is appropriate as it relates to a standard GP visit.

Patients with cytological predictions of low-grade abnormality other than CIN I are assumed to require two additional screens over the two-year time horizon of the model. This will include patients with resolution of cytologically-predicted abnormalities (three per cent of all smears) and those with persistent non-CIN I low grade abnormalities eventually requiring investigation (0.9 per cent = [40 per cent - 21.4 per cent] × 4.94 per cent).

The following assumptions were made in the derivation of costs to investigate actively an abnormal result on cytology:

- Referral to a specialist is assumed for all women with cytological reports suggesting an abnormality requiring further investigation. This assumption is generally consistent with recommendations contained in the NHMRC guidelines (1994). The cost of a specialist visit was estimated at \$67.65. This estimate is consistent with the fee for MBS item 104 which is appropriate as it relates to an initial visit to a specialist.
- All women will require colposcopy and directed biopsy. The average cost for colposcopy and biopsy was estimated at \$75.85, derived by assuming the following costs and that the multiple operation rule will apply (see Note T8.5, p112, November 2001 MBS).
  - The cost of colposcopy is \$50.50 (this estimate corresponds to the fee for MBS item 35614 which is appropriate as it relates to colposcopy following an abnormal cervical smear); and
  - The cost of biopsy is \$50.60 (this estimate corresponds to the fee for MBS item 35608 which is appropriate as it relates to biopsy of the cervix); and

- The procedure will be conducted in the specialist's rooms without anaesthesia.

The fees for two or more operations listed in Group T8 (other than Subgroup 12 of that Group) performed on a patient on the one occasion, except as provided in paragraph T8.5.3, are calculated by the following rule:

- 100% for the item with the greatest Schedule fee
  - Plus 50% for the item with the next greatest Schedule fee
  - Plus 25% for each other item.
- Histopathological examination of biopsies will be conducted. The cost of this examination is estimated at \$95.00, which corresponds to the fee for MBS item 72823 which is appropriate as it relates to examination of complexity level 4 biopsy material, including cervical samples.

The following assumptions were made in the derivation of costs to treat a high-grade lesion by ablation or excision. The same costs were assumed for women who have low-grade lesions actively treated by ablation or excision. Women will be hospitalised under DRG N09Z. A hospital cost of \$878 is assumed, consistent with private sector costs as reported in the National Hospital Cost Data Collection Cost Report for 1999/2000 (2001, \$1,039 for the public sector and \$878 for the private setting). Three visits to the GP for follow-up screening over the next two years were also included. The costs of treating lesions may have been over-estimated as hospitalisation is not always required for these procedures. Instead, the procedures are often conducted in a specialist's rooms or an outpatient clinic. On the other hand, total costs for treatment of lesions are likely to be an under-estimate because they do not incorporate costs for women who have lesions that relapse. Costs for treatment of lesions are varied in a sensitivity analysis.

The NHMRC guidelines (1994) estimate the cost of active management of a low-grade lesion by colposcopy/biopsy followed by a period of observation to be \$503. A presumption was made that this would include costs of follow-up, further investigation and treatment of relapsed cases where appropriate. This cost was assumed to be the total cost incurred by women whose confirmed low-grade lesion was managed by observation rather than ablation/excision in the conventional cytology arm. The costs of health technologies and procedures may not change predictably over time as advances in procedures and technology can result in a decrease rather than an increase in costs. We have not used standard inflators to adjust costs over time. For the LBC arm, the additional cost of \$34.50, or three times the differential cost between a test using LBC methods and that using conventional cytology methods, assumed that three follow-up screens will be conducted in these women. Costs for management of low-grade lesions could be varied in a sensitivity analysis.

## Outcome variables

One of the 'Performance Standards for Australian Laboratories Reporting Cervical Cytology' requires that between 0.5 per cent and 5 per cent of all smears should be reported as unsatisfactory (PSALRCC, 2001). The RCPA Cytopathology Quality Assurance Program (2001) reports that the median percentage of technically unsatisfactory specimens received was 1.9 per cent (range: 0.35 - 8.99 per cent) in 2000. An Australian study by Roberts et al (1997) can be used to provide an indication of the maximum improvement in the rate of unsatisfactory screens if LBC were used in place of conventional cytology. Roberts et al (1997) reported that 3.5 per cent of conventional smears were found to be unsatisfactory but only 0.7 per cent of those using the LBC test were unsatisfactory. The proportion of technically-unsatisfactory specimens in the two arms of the model is assumed from Roberts et al (1997).

Table 22 summarises the correlation between histology/colposcopy findings and cytological prediction of abnormality according to Pap smear tests in Australian women in 1999. These are aggregated data from the States and Territories (except Queensland - see Tables 3 and 4 and Appendices C and D).

**Table 22 Cross-tabulation of histology/colposcopy findings and cytological prediction of abnormality according to Pap smear for 1999 for all States and Territories except QLD<sup>a</sup>**

Cytology	Histology									
	NEG/BEN	HPV	MNSC	CIN I	CIN II	CIN III	AIS	MICROINV	INVAS	TOTAL
MNSC	2,033	1,115	551	1,325	526	418	7	2	11	5,987
HPV	615	832	31	659	209	146	1	0	3	2,496
CIN I	1,373	1,296	208	2,779	1,198	728	8	1	1	7,591
CIN II	411	258	66	695	1,556	1,242	5	10	60	4,303
CIN III	224	122	40	272	848	1,946	34	26	66	3,579
INCONC	688	252	119	411	561	692	30	6	36	2,795
AIS	8	3	1	3	2	6	28	6	4	61
MICROINV	7	3	0	9	27	86	4	5	32	173
INVAS	11	6	1	11	34	72	6	9	73	225
<b>TOTAL</b>	<b>5,371</b>	<b>3,887</b>	<b>1,017</b>	<b>6,164</b>	<b>4,961</b>	<b>5,336</b>	<b>123</b>	<b>65</b>	<b>286</b>	<b>27,209</b>

Abbreviations: NEG/BEN=negative/benign; MNSC=Minor non-specific changes in squamous cells; HPV=human papilloma virus (when HPV is the only abnormality present); INCONC=Inconclusive, possible high grade epithelial abnormality; AIS=adenocarcinoma in situ; MICROINV=micro-invasive cancer; INVAS=invasive cancer.

<sup>a</sup> NSW breakdown between CIN I, II, III and cancer categories imputed from proportions given by total of the other six States and Territories (ie excluding Queensland).

These cross-tabulations can be used to calculate estimates of PPV of screening using conventional cytology with a cut-off of minor non-specific changes as summarised in Table 23 which includes estimates of the proportion of low-grade and high-grade lesions.

**Table 23 Transition probabilities derived from cytology-histology cross-tabulated data**

Cytological prediction	Histological finding	Probability	Histological finding	Probability
Abnormality requiring active investigation	Negative (NEG/BEN)	20% (5,371/27,209)	-	-
	Positive (1-NEG/BEN)	80%	Low grade lesion (HPV, MNSC, CIN I)	51%
			High grade lesion (CIN II, CIN III, AIS, MICROINV, INVAS)	49%

Should an extrapolation to cases of cancer avoided or life-years gained be required, it is important to note that the proportion of abnormalities found to be low and high grade lesions on histology may not be applicable to abnormalities not detected by cytology (ie false negatives) because low-grade lesions are more likely to given a negative cytological prediction than high grade lesions. Soost et al (1991) report that the sensitivity of screening is lower for mild and moderate dysplasia (78.1 per cent) than it is for severe dysplasia and cancer (81.4 per cent). The assumption that the same proportion would be applicable will bias the model in favour of the more sensitive screening test.

Information in Table 23 suggests that the PPV for screening using conventional Pap slide preparation techniques is 80 per cent. These data can be used to populate a 2x2 table (Table 24) which shall be developed over Tables 24-27.

**Table 24 2x2 table for cervical screening using conventional cytology**

Results predicted by cytology	Results on histology		
	Lesion	Negative	Totals
Abnormality	80	20	100
Negative	-	-	-
Totals	-	-	-

The 'Performance Standards for Australian Laboratories Reporting Cervical Cytology' state that not more than 14 per cent of technically-satisfactory smears collected by general practitioners and nurses should be reported as abnormal (PSALRCC, 2001). This standard is intended to refer to smears collected from asymptomatic women taking part in routine screening. To best approximate the requirements of this standard, only data relating to smears taken by general practitioners and nurses are included. The RCPA Cytopathology Quality Assurance Program (2001) states that the mean percentage of satisfactory smears reported as abnormal for laboratories returning data against this measure was six per cent (range: 1 -50 per cent). It was estimated that 50 per cent of these cytologically-predicted abnormalities, or three per cent of all satisfactory smears, are investigated by colposcopy/biopsy (see discussions under Model structure). This estimate has been used for the conventional cytology arm of the model. Thus, it can be calculated that for every 100 cytological predictions of abnormality requiring active investigation there should be 3,233 cytological predictions of normal, or resolved histology. Further details for the 2x2 table can be filled out, as per Table 25.

**Table 25** 2x2 table for cervical screening using conventional slide preparation techniques

Results predicted by cytology	Results on histology		
	Lesion	Negative	Totals
Abnormality	80	20	100
Negative	-	-	3,233
Totals	-	-	3,333

Estimates to include in the remaining cells can only be determined from the literature. The published estimates of sensitivity of screening using conventional cytology are wide-ranging. A sensitivity of 80 per cent as per Soost et al (1991) was assumed for the model because the data they used to derive estimates was population based. Furthermore, reasonable assumptions were made where no data were available. Inclusion of the estimate of sensitivity in Table 25 gives Table 26. If 80 women with lesions report positive, then 20 will test negative.

**Table 26** 2x2 table for cervical screening using conventional slide preparation techniques

Results predicted by cytology	Results on histology		
	Lesion	Negative	Totals
Abnormality	80	20	100
Negative	20	-	3,233
Totals	100	-	3,333

The remaining cells in the table can now be calculated to give a complete 2x2 table (Table 27). This table suggests that specificity of screening using conventional cytology is 99.4 per cent (3,213/3,233), which is within the range reported in the literature. This estimate coincides exactly with the estimate by Soost et al. In addition, the prevalence of a true lesion can be estimated to be approximately three per cent (100/3,333).

**Table 27** 2x2 table for cervical screening using conventional slide preparation techniques

Results predicted by cytology	Results on histology		
	Lesion	Negative	Totals
Abnormality	80	20	100
Negative	20	3,213	3,233
Totals	100	3,233	3,333

The values reported for sensitivity and specificity of screening using LBC in the few studies that use histological or colposcopic reference standards are within the range of sensitivity and specificity reported for the conventional Pap test. Therefore, no differences in these parameters are assumed in the base case model. Table 28 summarises the transition probabilities assumed in the model.

**Table 28 Transition probabilities assumed in the alternate model**

Description	Source	Value (%)
Probability that a woman has an abnormality on histology (pAbnormalityonHisto)	Derived from Table 27	3
Probability of an unsatisfactory sample when conventional slide preparation techniques are used (pUnsatisfactoryPap)	Derived from Roberts et al 1997	3.5
Probability of an unsatisfactory sample when LBC preparation techniques are used (pUnsatisfactoryThinPrepLBC/filtration)	Derived from Roberts et al 1997	0.7
Probability of active management of a low-grade lesion detected on histology (pActiveMgtPostactiveInvestig)	Derived by assuming that the majority of CIN I patients will be managed by active treatment. From Table 22, it can be estimated that approximately 47% of low-grade lesions confirmed on histology are in the CIN I classification.	50
Probability that a woman with an abnormality has a low-grade lesion (pLGLgivenabnormality)	Derived from Table 23	51
Probability that a woman with an undetected abnormality has a low-grade lesion (pLGLgivenUndetecAbnorm)	See discussion under Table 23	60
Probability that a woman with an abnormality has a high grade lesion (pHGLgivenabnormality)	Derived from Table 23	49
Probability that a woman with an undetected abnormality has a high-grade lesion (pHGLgivenUndetecAbnorm)	See discussion under Table 23	40
Sensitivity of screening test using conventional slide preparation techniques (SensitivityPap)	Derived from the literature	80
Sensitivity of screening test using liquid based slide preparation techniques (SensitivityTP)	=SensitivityPap (given that there is inadequate evidence for assumption of any difference)	80
Specificity of screening test using conventional slide preparation techniques (SpecificityPap)	Derived from Table 27	99.4
Specificity of screening using LBC methods (SpecificityTP)	=SpecificityPap (given that there is inadequate evidence for assumption of any difference)	99.4
Probability of a prediction of an abnormality requiring investigation on cytology for screening using conventional slide preparation methods ( $\_p$ AbnormalityPredictionPap)	Derived using Bayes theorem: $((1-pAbnormalityonHisto) \times (1-SpecificityPap)) + (pAbnormalityonHisto \times SensitivityPap)$	3
Probability of a prediction of an abnormality on cytology for screening using LBC methods ( $\_p$ AbnormalityPredictionTP)	Derived using Bayes theorem: $((1-pAbnormalityonHisto) \times (1-SpecificityTP)) + (pAbnormalityonHisto \times SensitivityTP)$	3
Probability of a false negative result using conventional slide preparation methods ( $\_p$ FalseNegPap)	Derived using Bayes theorem: $(pAbnormalityonHisto \times (1-SensitivityPap)) / (((1-pAbnormalityonHisto) \times SpecificityPap) + (pAbnormalityonHisto \times (1-SensitivityPap)))$	0.6
Probability of a false negative result using LBC methods ( $\_p$ FalseNegTP)	Derived using Bayes theorem: $(pAbnormalityonHisto \times (1-SensitivityTP)) / (((1-pAbnormalityonHisto) \times SpecificityTP) + (pAbnormalityonHisto \times (1-SensitivityTP)))$	0.6
Probability of a false positive result using conventional slide preparation methods ( $\_p$ FalsePosPap)	Derived using Bayes theorem: $((1-pAbnormalityonHisto) \times (1-SpecificityPap)) / (((1-pAbnormalityonHisto) \times (1-SpecificityPap)) + (pAbnormalityonHisto \times SensitivityPap))$	20
Probability of a false positive result using LBC methods ( $\_p$ FalsePosTP)	Derived using Bayes theorem: $((1-pAbnormalityonHisto) \times (1-SpecificityTP)) / (((1-pAbnormalityonHisto) \times (1-SpecificityTP)) + (pAbnormalityonHisto \times SensitivityTP))$	20
Probability of a prediction of normal histology on cytology for screening using conventional slide preparation methods ( $\_p$ NormalPredictionPap)	Derived using Bayes theorem: $((1-pAbnormalityonHisto) \times SpecificityPap) + (pAbnormalityonHisto \times (1-SensitivityPap))$	97

**Table 28 (cont) Transition probabilities assumed in the alternate model**

Description	Source	Value (%)
Probability of a prediction of normal histology on cytology for screening using conventional slide preparation methods ( $\_pNormalPredictionTP$ )	Derived using Bayes theorem: (((1-pAbnormalityonHisto)×SpecificityTP) +(pAbnormalityonHisto×(1-SensitivityTP)))	97
Probability that a woman with a negative cytology prediction on cytology using conventional slide preparation will have normal histology ( $\_pTrueNegPap$ )	Derived using Bayes theorem: (((1-pAbnormalityonHisto)×SpecificityPap)/ (((1-pAbnormalityonHisto)×SpecificityPap)+(pAbnormalityonHisto×(1-SensitivityPap))))	99.4
Probability that a woman with a negative cytology prediction on cytology using LBC will have normal histology ( $\_pTrueNegTP$ )	Derived using Bayes theorem: (((1-pAbnormalityonHisto)×SpecificityTP)/ (((1-pAbnormalityonHisto)×SpecificityTP) +(pAbnormalityonHisto×(1-SensitivityTP))))	99.4
Probability that a woman with an abnormal cytology prediction on cytology using conventional slide preparation will have a lesion on histology ( $\_pTruePosPap$ )	Derived using Bayes theorem: (pAbnormalityonHisto×SensitivityPap)/ (((1-pAbnormalityonHisto)×(1-SpecificityPap)) +(pAbnormalityonHisto×SensitivityPap))	80
Probability that a woman with an abnormal cytology prediction on cytology using LBC will have a lesion on histology ( $\_pTruePosTP$ )	Derived using Bayes theorem: (pAbnormalityonHisto×SensitivityTP)/ (((1-pAbnormalityonHisto)×(1-SpecificityTP)) +(pAbnormalityonHisto×SensitivityTP))	80

## Results from the alternate model

Table 29 summarises the results generated by the alternate model.

**Table 29 Results of cost-effectiveness analysis using model**

Type of cytology	Costs per woman (\$)	Proportion of women with high-grade lesion detected	Incremental cost/woman with high-grade lesion detected
Liquid-based cytology (LBC)	101.23	0.012	
Conventional cytology (Pap)	89.42	0.012	
Incremental (LBC-Pap)	11.81	No difference	LBC DOMINATED, Pap DOMINATES

According to this model, LBC is associated with greater costs per woman than conventional cytology. Furthermore, there is insufficient evidence to support any claim that LBC is superior to conventional cytology in detecting either high-grade lesions or invasive cancer. Currently, LBC cannot be demonstrated to be cost-effective at the proposed price because it costs more to detect a high-grade lesion using LBC than with conventional cytology and there is insufficient evidence that its use improves detection of high-grade lesions.

Listing of LBC on the MBS on a cost-minimisation basis should only be considered if the evidence can be interpreted as suggesting that LBC is no worse than conventional cytology in the detection of high-grade lesions.

In this situation the costs of performing LBC must be no greater than those of performing conventional cytology. In estimating total costs for each of the techniques for cytology, it would be appropriate to consider the potential savings with LBC as a result of a decreased requirement for repeat screens after an unsatisfactory initial screen.

If it is accepted that 3.5 per cent of screens are inadequate with the conventional Pap smear and need to be repeated, then the cost of performing a satisfactory test is \$19.665 ( $\$19 + \$19 \times 3.5\%$ ). If it is accepted that LBC will reduce the proportion of unsatisfactory slides from 3.5 per cent to 0.7 per cent as suggested by Roberts et al (1997) or from the current rate of unsatisfactory slides of 1.9 per cent according to RCPA Cytopathology Quality Assurance Program to 0.7 per cent, then savings of \$0.665 per test and \$0.361 per test respectively could be generated by replacing conventional slide preparation techniques by LBC methods.

Total costs for a screen using conventional slide preparation techniques are estimated at \$19.00. Constraint of the cost for LBC to \$19.53 ( $19.665/1.007$ ) if the proportion of unsatisfactory slides were reduced from 3.5 per cent to 0.7 per cent, or to \$19.23 ( $(\$19 + (1.9\% \times \$19))/1.007$ ) if the proportion of unsatisfactory slides were reduced from 1.9 per cent to 0.7 per cent, may justify listing of LBC on the MBS. However, as stated, this is only appropriate if the available evidence can be interpreted as suggesting that LBC is no worse than conventional cytology in detecting cases of high-grade lesions.

### Sensitivity analysis

Figure 3 summarises the results of a sensitivity analysis that examines the incremental cost per high-grade lesion detected for a range of values for sensitivity of LBC. Specificity is assumed to be 99.4 per cent. The sensitivity and specificity of screening using conventional cytology is kept constant at 80 per cent and 99.4 per cent, respectively. In addition, the prevalence of a true lesion is held constant at 3.0 per cent and the proportions of low-grade and high-grade lesions are kept constant at 51 per cent and 49 per cent, respectively.

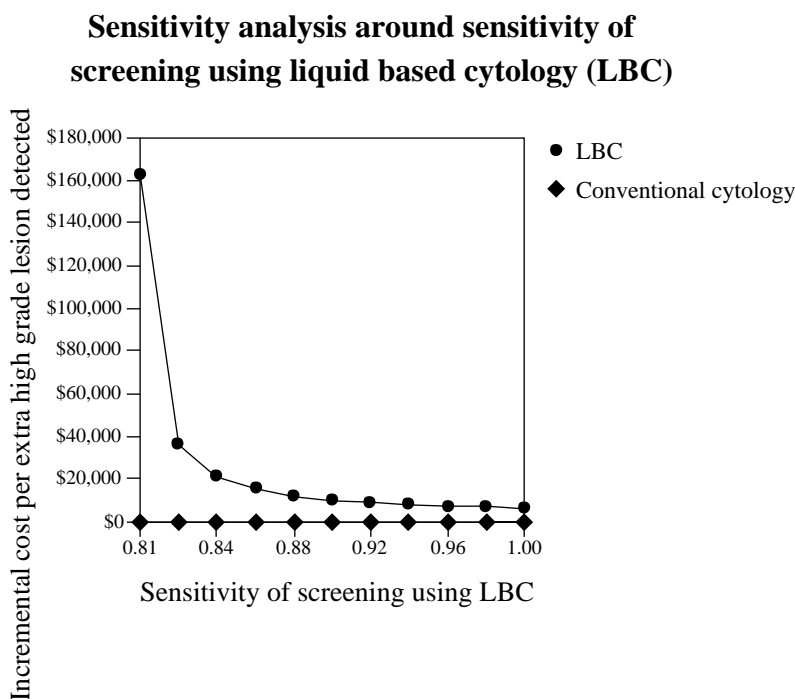


Figure 3 Sensitivity analysis around sensitivity (low-grade abnormality cut-off) of screening using LBC methods

The sensitivity analysis can be converted to incremental cost-effectiveness measured in terms of incremental cost per additional cancer avoided or incremental cost per additional life-year gained. However, this would require an assumption regarding the number of cases of cancer that would be avoided by detection of high-grade lesions and the number of life-years that would be gained by avoiding an invasive cancer.

The number of cancers avoided will depend on the proportion of high-grade lesions that are invasive cancer on detection and the proportion of high-grade lesions that would progress to invasive cancer over the two-year time horizon of the model. The number of life-years gained will depend on the effectiveness of treatments available for invasive cancer of the cervix. The more effective the treatment, the fewer life-years gained. If patients have a high mortality rate, then more life-years are likely to be saved. It is beyond the scope of this report to make an accurate assessment of these variables. However, an indicative analysis is presented in Figure 4 assuming that four per cent of additional high grade lesions would be, or would progress to, cancer over two years and that six (discounted) life-years would be gained by avoidance of an invasive cancer.

The estimate that four per cent of high grade lesions would be, or would progress to, cancer over two years was obtained by considering that between two per cent and three per cent of high grade lesions detected would be invasive cancer (according to Tables 3 and 4) and that Melnikow et al (1998) estimated the risk of progression from high grade lesion to invasive cancer at 24 months to be 1.44 per cent (95 per cent CI: 0, 3.95).

**Sensitivity analysis around sensitivity of screening using LBC**

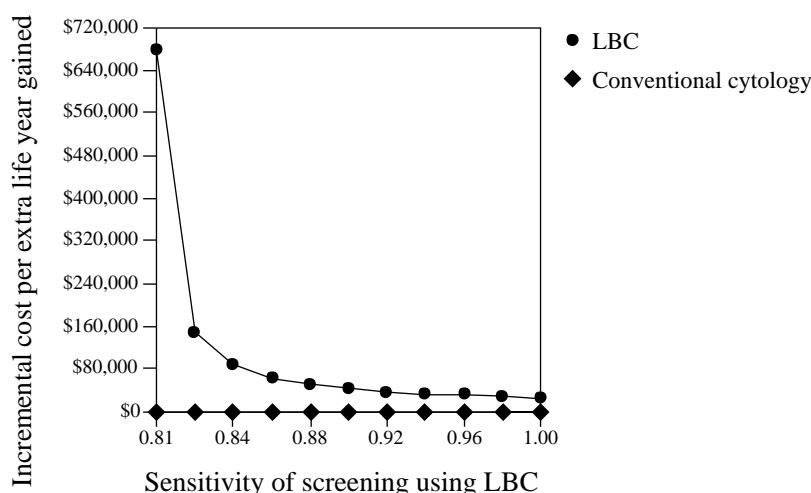


Figure 4 Sensitivity analysis around sensitivity (low-grade abnormality cut-off) of screening using LBC methods.

The estimate that six life-years will be gained by avoidance of an invasive cancer was derived as follows: It can be deduced from data provided in Cervical Screening in Australia 1997-1998 (AIHW 2000) that the average age of diagnosis of cancer is approximately 52 years. From these data, it can also be calculated that the average age of death of a woman with cancer of the cervix is 63 years. If the normal life expectancy of a woman aged 52 years is an additional 33 years (ABS 2000), then the maximum number of life-years a woman could expect to gain by averting cervical cancer are the life-years from age 64 to age 85 (ie 21 years). Discounting these years (which do not occur for another 11 years) at five per cent per annum results in a maximum gain of approximately

eight life years. However, the actual value for life years gained is likely to be lower as detection of a high-grade abnormality is unlikely to result in 100 per cent aversion of cervical cancer, that is some high grade lesions may be cancers that have progressed too far to cure. A gain of six life-years has therefore been used in the indicative analysis.

From data in Figure 4, a threshold analysis can determine the minimum threshold of sensitivity – assuming specificity is constant at 99.4 per cent and sensitivity of screening using conventional slide preparation methods is 80 per cent – at which LBC would produce a cost-effectiveness ratio of \$40,000 or less per life-year saved. This ratio is suggested on the presumption that per capita GDP might provide some basis for a cut-off price to pay per life-year saved. As shown in Fig 4, sensitivity of LBC would need to reach at least 90 per cent before LBC would be considered cost-effective on this basis. Estimates of incremental cost-effectiveness of LBC over conventional cytology for longer time horizons than the two years used in the present calculations may be less favourable to LBC as there may be fewer cases to detect in a given cohort over time, even allowing for the incidence of new lesions.

Figure 5 summarises the results of a sensitivity analysis of total costs for a range of costs of actively treating a lesion. All other variables are assumed to remain constant. This analysis suggests that the results of the model are not particularly sensitive to changes in this variable. This is likely to be because total costs for the current screening program for cervical cancer and the costs for the program proposed in the application vary together.

#### Sensitivity analysis around cost of actively treating a lesion

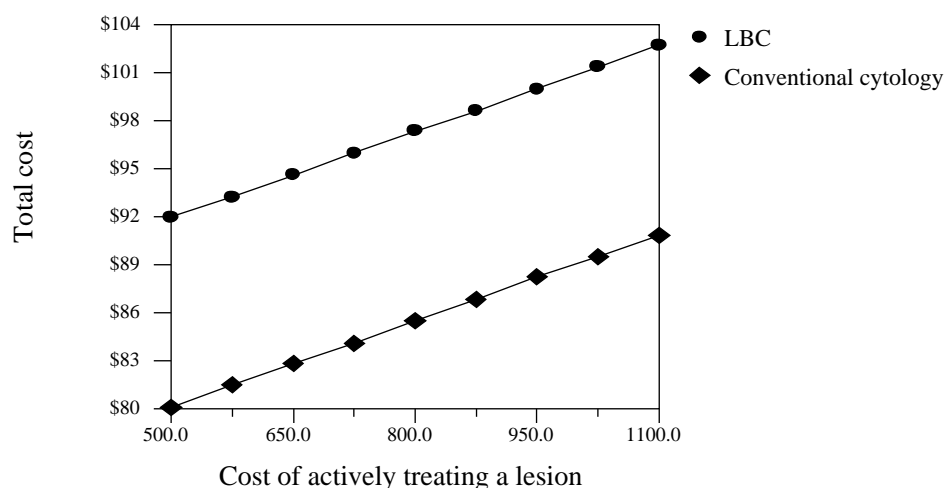


Figure 5 Sensitivity analysis around costs of actively treating a lesion

## Summary

A decision-analytic model was used to simulate the cost-effectiveness of LBC versus conventional cytology. According to this model, LBC is associated with greater costs per woman than conventional cytology. Furthermore, there is insufficient evidence to support any claim that LBC is superior to conventional cytology in detecting high-grade lesions or invasive cancer. It follows that there is no evidence to suggest that LBC would be cost-effective at the proposed price. Given the additional cost associated with LBC, the minimum sensitivity at which LBC would produce a cost-effectiveness ratio of \$40,000 or less per life-year saved is 90 per cent compared to 80 per cent for conventional screening, assuming specificity remains constant at 99.4 per cent. There is no evidence to suggest that a difference in sensitivity of this magnitude is likely.

If the evidence is interpreted as suggesting that LBC is no worse than conventional cytology in the detection of high-grade lesions and if it is accepted that there may be savings through fewer unsatisfactory screens and consequently fewer repeat screens, then the question becomes: At what cost for LBC do potential savings exceed the additional cost of LBC over the Pap smear?

Total costs for a screen using conventional cytology are estimated at \$19.00. If total costs for LBC were less than \$19.53 and the proportion of unsatisfactory slides was reduced from 3.5 per cent to 0.7 per cent, then LBC could be cost-saving compared to conventional screening. The proposed price of LBC, \$30.50, significantly exceeds these figures.

# Conclusions

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## Safety

The safety or risks associated with collection of cervical cells for an LBC test for cervical screening have not been evaluated and reported in the literature. None of the appraised studies reported these outcomes or technical problems arising for women undergoing primary screening using LBC technologies, although any risk is likely to be associated with collection of cervical cells and not the tests themselves.

## Effectiveness

Secondary studies investigating LBC concluded that, to date, there is insufficient high quality data to suggest that LBC is better than the Pap smear for cervical screening. However, Sulik et al (2001) suggest that there may be a role for LBC for women who have had abnormal Pap test results or who are at a high risk of cervical cancer due to infrequent screening.

Bernstein et al (2001) deduced that the LBC test improved sample adequacy and led to improved diagnosis of low-grade and high-grade squamous intraepithelial lesions, however, results comparing LBC and Pap tests were not evaluated against a histological reference test. All authors noted that the most frequent study design was the split-sample method and that many of the clinical studies examined were funded partially or completely by manufacturers of LBC technologies.

The ranges of data calculated from, or reported in, primary studies investigating LBC were similar. From two studies that used different thresholds, the sensitivity of LBC was calculated to range from 41.7 per cent to 82.8 per cent which was similar to that of the Pap test with a range of 39.4 per cent to 89.6 per cent. Specificities for the two tests were also similar, ranging from 47.8 per cent to 98.9 per cent for Pap smears and from 52.2 per cent to 90.2 per cent for LBC.

The relative TPR and FPR of LBC could only be calculated from two and three studies respectively. Relative TPR ranged from 0.91 to 1.52 and relative FPR from 0.82 to 1.73. Overall, LBC had a higher detection rate than Pap smears, but also a correspondingly higher FPR. Guidos (2001) and Tench (2000) reported insufficient data for the calculation of any diagnostic characteristics.

The failure of many studies to meet several validity criteria, and the limitation of studies having applied the reference test only to those who were assessed as positive on either screening test, made interpretation difficult. Diagnostic characteristics could not be calculated from a number of studies due to insufficient data.

Another important issue is that of interpreting overseas data in the Australian context. The difference in cytology classification systems means that data cannot be directly related, bringing into question the relevance of some data. Specifically, the US Bethesda System is not directly comparable to the cytology classifications used in Australia (see Table 2).

Many studies failed to define an upper limit to the period over which the histological outcome was determined. It was therefore unclear whether LBC and conventional cytology were being compared on an equivalent basis.

In summary, there is insufficient evidence to draw meaningful conclusions regarding differences in the diagnostic characteristics of LBC and Pap smears for cervical screening. The lack of high quality evidence on the performance of LBC does not permit evaluation of whether it is inferior, equal or superior in effectiveness to the conventional Pap smear. Further high quality studies using an acceptable reference standard, such as histological confirmation of cytology results, are crucial to allow a valid and reliable judgement concerning the sensitivity and specificity of LBC.

## Cost-effectiveness

### Submitted model

Given the problems identified with the structure of the model submitted to the MSAC, questions relating to the costs of resources and the transition probabilities driving the model, the results are likely to be inaccurate with a bias in favour of the LBC technology. No sensitivity analyses were presented in the MSAC application. However, the model was sensitive to changes in estimates of comparative test sensitivity and specificity.

### Supplementary submission

A supplementary submission provided a re-analysis of the incremental cost-effectiveness of LBC over conventional cytology using the basic model described in the original submission but with minor modifications. Most of the fundamental problems identified with the original model persisted in the modified model. Given the problems identified with the structure of the model, the costs of resources and the transition probabilities driving the model, the results from the re-analysis provided in the supplementary submission are also likely to be inaccurate with a bias in favour of the LBC technology.

### Revised model

As there is no evidence of an increased number of cases of high-grade epithelial abnormalities or invasive cancer detected for LBC versus conventional cytology, listing of LBC on the MBS on a cost-minimisation basis might be appropriate if the evidence could be interpreted as suggesting that LBC was no worse than conventional cytology.

If it is assumed that LBC will reduce the proportion of unsatisfactory slides from 3.5 per cent to 0.7 per cent, as suggested by Roberts et al (1997), the appropriate budget neutral price for a screen using LBC would be \$19.53 or \$0.53 more than the current price for a screen using conventional cytology. If LBC were to reduce the proportion of unsatisfactory slides from 1.9 per cent – the current rate of unsatisfactory slides according to the RCPA Cytopathology Quality Assurance Program – to 0.7 per cent, the appropriate price for a screen using LBC would be \$19.23.

Given the additional cost associated with LBC, the minimum sensitivity at which LBC would produce a cost-effectiveness ratio of \$40,000 or less per life-year saved is 90 per cent compared to 80 per cent for conventional screening assuming specificity remains constant at 99.4 per cent. There is no evidence to suggest that a difference in sensitivity of this magnitude is likely.

Estimates of incremental cost-effectiveness of LBC over conventional cytology for longer time horizons than the two years used in the present calculations may be less favourable to LBC as there may be fewer cases to detect in a given cohort over time, even allowing for the incidence of new lesions.

## Recommendation

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Since there is currently insufficient evidence pertaining to liquid-based cytology for cervical screening, the MSAC recommends that public funding should not be supported at this time for this screening test.

The Minister for Health and Ageing accepted this recommendation on 16 October 2002.

# Acknowledgements

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Several people have assisted in the production of this report, some of who warrant special mention.

The MSAC and the evaluators would particularly like to thank Rob Anderson from the Centre of Health Economics Research and Evaluation, University of Technology, Sydney, for the provision of aggregated cross-tabulations between histology/colposcopy findings and cytological prediction of abnormality according to Pap smears in Australian women in 1999. Rob went out of his way to assist the MSAC and the evaluators with their requests and kindly expressed a willingness to assist the authors in any way possible.

The MSAC and the evaluators would also like to acknowledge the assistance of staff from RCPA Quality Assurance Programs Pty Ltd who were able to provide data to the authors in a timely manner despite other demands and pressures on their time.



# Appendix A MSAC terms of reference and membership

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The MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new and existing medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to the AHMAC.

The membership of the MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

<b>Member</b>	<b>Expertise or Affiliation</b>
Dr Stephen Blamey (Chair)	general surgery
Professor Bruce Barraclough	general surgery
Professor Syd Bell	pathology
Dr Paul Craft	clinical epidemiology and oncology
Professor Ian Fraser	reproductive medicine
Professor Jane Hall	health economics
Dr Terri Jackson	health economics
Ms Rebecca James	consumer health issues
Professor Brendon Kearney	health administration and planning
Mr Alan Keith	Assistant Secretary Diagnostics and Technology Branch Commonwealth Department of Health and Ageing
Associate Professor Richard King	internal medicine
Dr Ray Kirk	health research

<b>Member</b>	<b>Expertise or Affiliation</b>
Dr Michael Kitchener	nuclear medicine
Mr Lou McCallum	consumer health issues
Dr Ewa Piejko	general practice
Professor John Simes	clinical epidemiology and clinical trials
Professor Richard Smallwood	Chief Medical Officer Commonwealth Department of Health and Ageing
Dr Robert Stable	Representing the Australian Health Ministers' Advisory Committee
Professor Bryant Stokes	neurology
Professor Ken Thomson	radiology
Dr Douglas Travis	urology

## Appendix B Supporting committee

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### Supporting committee for MSAC Reference 12a: liquid-based cytology for cervical screening

<b>Professor Brendon Kearney (Chair)</b> MBBS, FRACP, FRACMA Executive Director South Australian Department of Human Services	MSAC member
<b>Professor Sydney Bell</b> MBBS, FRCPA, MD Area Director of Microbiology South East Sydney Area Health Service	Co-opted MSAC member
<b>Dr Paul Craft</b> MBBS, FRACP, MPH Director, Medical Oncology Unit The Canberra Hospital Garran, ACT	Co-opted MSAC member
<b>Dr Dwina Dobriansky</b> MBBS (Hons), FRANZCOG, FRCOG Obstetrician and Gynaecologist	Nominated by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists
<b>Dr Annabelle Farnsworth</b> MBBS (Hons), FRCPA, FIAC, Dip Cytopath (RCPA) Medical Director Douglass Hanly Moir Pathology, Sydney, NSW	Nominated by the Primary Prevention and Early Detection Branch, Department Health and Ageing  Resigned from supporting committee on 7 August 2002
<b>Dr Ray Kirk</b> BSc, PhD Director New Zealand Health Technology Assessment Unit Clinical Senior Lecturer in Public Health Christchurch School of Medicine and Health Sciences University of Otago, New Zealand	Co-opted MSAC member
<b>Dr Alistair Lochhead</b> MBBS, FRCPA, FIAC Staff Specialist, Southern Pathology Staff Specialist in Anatomical Pathology The Wollongong Hospital, NSW	Nominated by the Royal College of Pathologists of Australasia

**Ms Kathleen Mazzella**  
Health Consumers Council WA  
Gynaecological Awareness Info Network

Nominated by the Consumers'  
Health Forum of Australia

**Dr Heather Mitchell**  
MBBS, MD, MSc, FRACP, FAFPHM  
Deputy Director, Victorian Cytology Service

Co-opted Epidemiologist

**Dr Marion Saville**  
MBChB, Am Bd, FIAC, Grad Dip Med (Clin Epi)  
Grad Dip Med  
Director, Victorian Cytology Service

Nominated by the Australian  
Society of Cytology

**Dr Judy Straton**  
MD, MPH, FAFPHM  
Senior Medical Advisor  
Population Health Division  
Department of Health and Ageing

Observer

**Dr Lynnette Wray**  
MBBS, FPA Cert., FACSHP, MMedVen  
General Practitioner  
Coral Lloyd Family Planning Clinic  
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Nominated by the Royal  
Australian College of General  
Practitioners

**MSAC Project Manager**  
Linda Marshall BA, BSc, MBA

Health Technology Section  
Department of Health and  
Ageing

# Appendix C Cytology & histology data: Australian cytology registers

**Table C1 Reporting of cytology results by State and Territory**

State or Territory	CYTOLOGY												
	MNSC	HPV	CIN I	CIN II	CIN III	INCONCLUSIVE	AIS	MICROINVASIVE	INVASIVE	Unsatisfactory	Atypia	HPV possibly present	Reactive or inflammatory changes
ACT													
NSW				***	***		***	***	***				
NT													
Qld													
SA								*					
Tas								*					
Vic													
WA**													

\* Includes invasive disease; \*\* see WA notes, Appendix D; \*\*\* All combined in one category. Shading denotes categories for which figures were supplied.

**Table C2 Reporting of histology results by State and Territory**

State or Territory	HISTOLOGY													
	HPV	CIN I	CIN II	CIN III	AIS	MICROINVASIVE	INVASIVE	N/B	Unsatisfactory	Atypia	HPV possibly present	Endocervical Dysplasia	CIN NOS	N/A
ACT														
NSW			^^	^^										
NT														
Qld														
SA														
TAS														
Vic														
WA														

^^=Combined with CIN III; CIN NOS=CIN Not Otherwise Specified; N/B=Negative/Benign. Shading denotes categories for which figures were supplied.

## Appendix D Additional notes re: Australian cytology registers

State or Territory	Notes and Comments
ACT	None
NSW	70-74 contains 70+
	Unsatisfactory smear results are number of tests, not of women. Unsatisfactory smear results are unable to be reported for women using the first Pap test in the reporting period
	HPV results are included in the minor non-specific changes category. NSW PTR do not report separately for HPV alone
	CIN III includes adenocarcinoma in-situ. NSW Pap test registry do not report adenocarcinoma in-situ separately
	Categories 'Other non-cervical abnormalities' and 'Inconclusive test results' are included in MNSC category
	Invasive and Microinvasive cancers are reported together. Breakdown of these data can be obtained from 'Cervical Cancer Screening in NSW: Annual Statistical Report 1998'
	Full breakdown of Indicator 3 and 4 not provided – cytology combines CIN II, CIN III, AIS, Microinvasive and Invasive Cancers; histology combines CIN II and CIN III
NT	Item 2=first smear for each woman in 1999
	Items 3 and 4 are the number of women who had an abnormal smear in 1999 and a histology result within 183 days (6 months) of the abnormal smear
	Women who had more than one histology result within 6 months of an abnormal smear are counted more than once in items 3 and 4
	For items 2, 3 and 4 there were no women in 1999 who had HPV present with no other abnormality and no cases of adenocarcinoma in-situ
	For items 2, 3 and 4 abnormality classification is based on squamous cell change results
	MNSC = Mild atypia such as parakeratosis or hyperkeratosis, including change of HPV infection without dysplasia + Reactive and inflammatory changes
	Inconclusive; possible HGEA = Cell changes of uncertain significance ie inconclusive; unable to be interpreted with confidence
	Adenocarcinoma in-situ and CIN III combined
Qld	Performance data Feb to Dec 1999; backlog of registering results; if data registered by end of October then Indicator 1 (for 1 yr) and Indicator 2 by late Nov 2000
	Indicators 3 and only if backlog of histology results registered by October
SA	Item 1 – excludes women whose smears are taken post-hysterectomy
	SA does not use the category Microinvasive and minor non-specific changes in squamous cells in reporting on cytology tests
	Provides data for SA only and for interstate and SA women
	Provides population data for SA
	Microinvasive and invasive cancers are combined
Tas	Does not distinguish between microinvasive and invasive in cervical cytology results
Vic	None

State or Territory	Notes and Comments
WA	Only women with an address in WA at the time of the Pap smear have been included
	Vault smears (post-hysterectomy) have been excluded
	Where a cytology test showed one or more abnormalities, the woman was counted only in the most serious category. The categories are arranged from top to bottom in increasing order of seriousness
	Women whose Pap smears showed 'Atypical endocervical cells' as the most serious abnormality have been included in their own category, as they do not fit in any other categories but can still be classed as abnormal (see WA 'Cytology Code for Use by Cervical Cytology Registry')
	Women whose Pap smears showed 'HPV possibly present' as the most serious abnormality have been included in their own category, as they do not fit in any other categories but can still be classed as abnormal (see WA 'Cytology Code for Use by Cervical Cytology Registry')
	WA Cytology codes (see WA 'Cytology Code for Use by Cervical Cytology Registry') included under the 'Micro-invasive cancers' category are as follows: S7 - Suspicious of microinvasion or invasion E5 - Suspicious of adenocarcinoma of the cervix
	WA Cytology codes (see WA 'Cytology Code for Use by Cervical Cytology Registry') included under the 'Invasive cancers' category are as follows: S8 - Squamous carcinoma E6 – Adenocarcinoma
	Where a cytology test showed one or more abnormalities, the woman was counted only in the most serious category. The categories are arranged from top to bottom in increasing order of seriousness

## Appendix E Internet sites searched

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Agencia de Evaluación de Tecnologías Sanitarias (AETS). <http://www.isciii.es/aets/> [Accessed 9 April 2002].

Agencia de Evaluación de Tecnologías Sanitarias de Andalucía. AETSA. <http://www.csalud.junta-andalucia.es/orgdep/AETSA/default.htm> [Accessed 9 April 2002].

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Agency for Health Care Policy and Research (AHCPR). <http://www.ahrq.gov/> [Accessed 9 April 2002].

Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES). <http://www.anaes.fr/ANAES/anaesparametrage.nsf/HomePage?ReadForm> [Accessed 9 April 2002].

L'Agence Nationale pour le Developpement de l'Evaluation Medicale (ANDEM). <http://www.upml.fr/andem/andem.htm> [Accessed 9 April 2002].

Australian Safety and Efficacy Register of New Interventional Procedures-Surgical (ASERNIP-S). <http://www.racs.edu.au/open/asernip-s.htm> [Accessed 9 April 2002].

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Canadian Coordinating Office for Health Technology Assessment (CCOHTA). <http://www.ccohta.ca/> [Accessed 9 April 2002].

Center for Medical Technology Assessment (CMT). <http://www.imt.liu.se/cmt/> [Accessed 9 April 2002].

Agence d'évaluation des technologies et des modes d'intervention en santé (AÉTMIS). <http://www.aetmis.gouv.qc.ca/en/index.htm> [Accessed 9 April 2002].

German Agency for Health Technology Assessment at the German Institute for Medical Documentation and Information (DAHTA@DIMDI). <http://www.dimdi.de/de/hta/index.html> [Accessed 9 April 2002].

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International Network of Agencies for Health Technology Assessment (INAHTA).  
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National Co-ordinating Centre for Health Technology Assessment (NCCHTA).  
<http://www.hta.nhsweb.nhs.uk/> [Accessed 9 April 2002].

National Horizon Scanning Centre (NHSC). <http://www.bham.ac.uk/PublicHealth/horizon/>  
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National Institute for Clinical Excellence (NICE). <http://www.nice.org.uk/>  
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Veterans Affairs Technology Assessment Program (VATAP).  
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# Appendix F      Studies included for critical appraisal

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## Systematic Reviews/Health Technology Assessments

Broadstock, M. (2000). 'Effectiveness and cost-effectiveness of automated and semi-automated cervical screening devices: a systematic review of the literature', *New Zealand Health Technology Assessment*, Christchurch.

Hartmann, K.E., Nanda, K. et al, (2001). 'Technologic advances for evaluation of cervical cytology: is newer better?', *Obstetrical and Gynecological Survey*, 56, 765-774.

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Bernstein, S.J., Sanchez-Ramos, L. & Ndubisi, B. (2001). 'Liquid-based cervical cytologic smear study and conventional Papanicolaou smears: a metaanalysis of prospective studies comparing cytologic diagnosis and sample adequacy', *American Journal of Obstetrics & Gynecology*, 185, 308-317.

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Bergeron, C., Bishop, J. et al, (2001). 'Accuracy of thin-layer cytology in patients undergoing cervical cone biopsy', *Acta Cytologica*, 45, 519-524.

Obwegeser, J.H. & Brack, S. (2001). 'Does liquid-based technology really improve detection of cervical neoplasia? A prospective, randomized trial comparing the ThinPrep Pap Test with the conventional Pap Test, including follow-up of HSIL cases', *Acta Cytologica*, 45, 709-714.

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Park, I.A., Lee, S.N. et al, (2001). 'Comparing the accuracy of ThinPrep Pap tests and conventional Papanicolaou smears on the basis of the histologic diagnosis - A clinical study of women with cervical abnormalities', *Acta Cytologica*, 45, 525-531.

Tench, W. (2000). 'Preliminary assessment of the AutoCyte PREP: Direct-to-vial performance', *Journal of Reproductive Medicine*, 45, 912-916.

## Appendix G Studies excluded from critical appraisal

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### Additional Thin Prep study

Hoerl, H.D., Wagner, J.L. et al, (2001). 'Utility of additional slides from residual PreservCyt material in difficult ThinPrep gynecologic specimens: a prospective study of 58 cases', *Diagnostic Cytopathology*, 25, 141-147.

Massarani-Wafai, R., Bakhos, R. et al, (2000). 'Evaluation of cellular residue in the ThinPrep PreservCyt vial', *Diagnostic Cytopathology*, 23, 208-212.

### Cannot separate results for LBC and Pap

Lee, K.R., Darragh, T.M. et al, (2002). 'Atypical glandular cells of undetermined significance (AGUS): Interobserver reproducibility in cervical smears and corresponding thin-layer preparations', *American Journal of Clinical Pathology*, 117, 96-102.

### Case series of high-grade lesions only

Birner, P., Bachtiry, B. et al, (2001). 'Signal-amplified colorimetric in situ hybridization for assessment of human papillomavirus infection in cervical lesions', *Modern Pathology*, 14, 702-709.

### Case study

Rowe, L.R., Marshall, C.J. & Bentz, J.S. (2001). 'Cell block preparation as an adjunctive diagnostic technique in ThinPrep monolayer preparations: a case report', *Diagnostic Cytopathology*, 24, 142-144.

### Economic data only

Brown, A.D. & Garber, A.M. (1999). 'Cost-effectiveness of 3 methods to enhance the sensitivity of Papanicolaou testing', *Journal of the American Medical Association*, 281, 347-353.

Montz, F.J., Farber, F.L. et al, (2001). 'Impact of increasing Papanicolaou test sensitivity and compliance: A modeled cost and outcomes analysis', *Obstetrics & Gynecology*, 97, 781-788.

### Did not meet inclusion criteria for NZHTA

Johnson, T., Maksem, J.A. et al, (2000). 'Liquid-based cervical-cell collection with brushes and wooden spatulas: a comparison of 100 conventional smears from high-risk women to liquid-fixed cytocentrifuge slides, demonstrating a cost-effective, alternative monolayer slide preparation method', *Diagnostic Cytopathology*, 22, 86-91.

Stevens, M.W., Nespolon, W.W. et al, (1998). 'Evaluation of the CytoRich technique for cervical smears', *Diagnostic Cytopathology*, 18, 236-242.

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Freitas, C., Milanezi, F. et al, (2001). 'Use of cell block preparation for morphological, immunocytochemistry, and ploidy analysis in ThinPrep monolayer preparations', *Diagnostic Cytopathology*, 25, 415-417.

Hatch, K.D. (2000). 'Multisite clinical outcome trial to evaluate performance of the ThinPrep pap test', *Obstetrics & Gynecology*, 95 (4, Supplement 1), 51S.

Jones, H.W., III (2001). 'Endometrial brush biopsy for the diagnosis of endometrial cancer', *Obstetrical & Gynecological Survey September*, 56, 548-549.

Jones, H.W., III (2001). 'Comparison of three management strategies for patients with atypical squamous cells of undetermined significance: baseline results from a randomized trial', *Obstetrical & Gynecological Survey*, 56, 343-345.

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Linder, J. (2000). 'Comparing liquid-based, thin-layer preparation devices', *Journal of Reproductive Medicine*, 45, 966-968.

Payne, N., Chilcott, J. & McGoogan, E. (2000). 'Liquid-based cytology for cervical screening', *Cytopathology*, 11, 469-470.

## Included in NZHTA

Carpenter, A.B. & Davey, D.D. (1999). 'ThinPrep Pap Test: performance and biopsy follow-up in a university hospital', *Cancer*, 87, 105-112.

Hutchinson, M.L., Zahniser, D.J. et al, (1999). 'Utility of liquid-based cytology for cervical carcinoma screening: Results of a population-based study conducted in a region of Costa Rica with a high incidence of cervical carcinoma', *Cancer*, 87, 48-55.

Nanda, K., McCrory, D.C. et al, (2000). 'Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review', *Annals of Internal Medicine*, 132, 810-819.

Payne, N., Chilcott, J. & McGoogan, E. (2000). 'Liquid-based cytology in cervical screening: a rapid and systematic review', *Health Technology Assessment* (Rockville, MD), 4, 1-73.

Sawaya, G.F. & Grimes, D.A. (1999). 'New technologies in cervical cytology screening: a word of caution', *Obstetrics & Gynecology*, 94, 307-310.

Vassilakos, P., Schwartz, D. et al, (2000). 'Biopsy-based comparison of liquid-based, thin-layer preparations to conventional Pap smears', *Journal of Reproductive Medicine*, 45, 11-16.

Weintraub, J. & Morabia, A. (2000). 'Efficacy of a liquid-based thin layer method for cervical cancer screening in a population with a low incidence of cervical cancer', *Diagnostic Cytopathology*, 22, 52-59.

### Narrative reviews

Austin, R.M. & Ramzy, I. (1998). 'Increased detection of epithelial cell abnormalities by liquid-based gynecologic cytology preparations. A review of accumulated data', *Acta Cytologica*, 42, 178-184.

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Khalbuss, W.E., Rudomina, D. et al, (2000). 'SpinThin, a simple, inexpensive technique for preparation of thin-layer cervical cytology from liquid-based specimens - Data on 791 cases', *Cancer Cytopathology*, 90, 135-142.

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## Appendix H Review of submitted models

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### Structure of model provided in the original submission

The population in the model is a cohort of women representative of the population that participates in a cervical screening program. The fundamental structure of the model presented in the submission summarised in Figure H1. This model was used to calculate the incremental cost over conventional cytology of an LBC test per extra abnormality detected.

Several problems with the structure of the model have been identified:

1. While it is acknowledged that for practical purposes it is necessary to simplify clinical practice in a model, the model presented is overly simplistic for the following reasons:
  - the model values all lesions detected on histology equally, regardless of severity. This hampers interpretation of the derived incremental cost per extra abnormality detected with LBC because high-grade lesions are known to have very different clinical consequences compared with a low-grade lesions. If the model had derived the incremental cost per additional high-grade lesion detected, that outcome could have been extrapolated to incremental cost per additional cases of invasive cancer avoided and to incremental cost per additional life-year saved. Such ratios are generally more readily interpretable by decision-makers.
  - the model examines costs and benefits over a one year time horizon. Given the slow rate of progression from pre-cancerous abnormality to invasive cancer of the cervix, women screened regularly at laboratories meeting quality standards will usually have any abnormalities missed at one screen detected at the next screen before invasive cancer develops. An audit of 73 Victorian women who died from cervical cancer in 1994 found that only 10 per cent of the deaths occurred among women who were adequately screened (Mitchell et al 1996). Invasive cervical cancer appears to occur mainly in women who are either unscreened or not screened regularly (Shingelton et al 1995, Mitchell et al 1996). Thus, invasive cancers do not generally arise through failure of screening by conventional cytology.

A one-year time horizon for examination of costs and benefits favours LBC because the number of residual undetected cases is reduced in a cohort over time and thus the incremental benefits of LBC will decline over time. It is important to differentiate incremental cost-effectiveness of a single test from incremental cost-effectiveness of the complete program. A one year time horizon results in comparison of cost-effectiveness of a single test rather than the complete program. However, it is clear that if incremental cost-effectiveness of a single LBC test is not acceptable, the incremental cost-effectiveness of the program will be even less acceptable over a longer time horizon. It is acknowledged that attempting to model incremental cost-effectiveness over a period longer than two years is problematic and would

introduce uncertainties. These would arise from the need for additional health states to be included in the model (eg mortality due to causes other than cancer of the cervix, hysterectomy due to other causes, relapse of treated high grade abnormalities, etc) and the fact that several of the transition probabilities needed in the model are not readily available from the published literature (e.g. likelihood of detecting a previously undetected lesion, likelihood of recurrent lesions after previous lesions have been treated, etc).

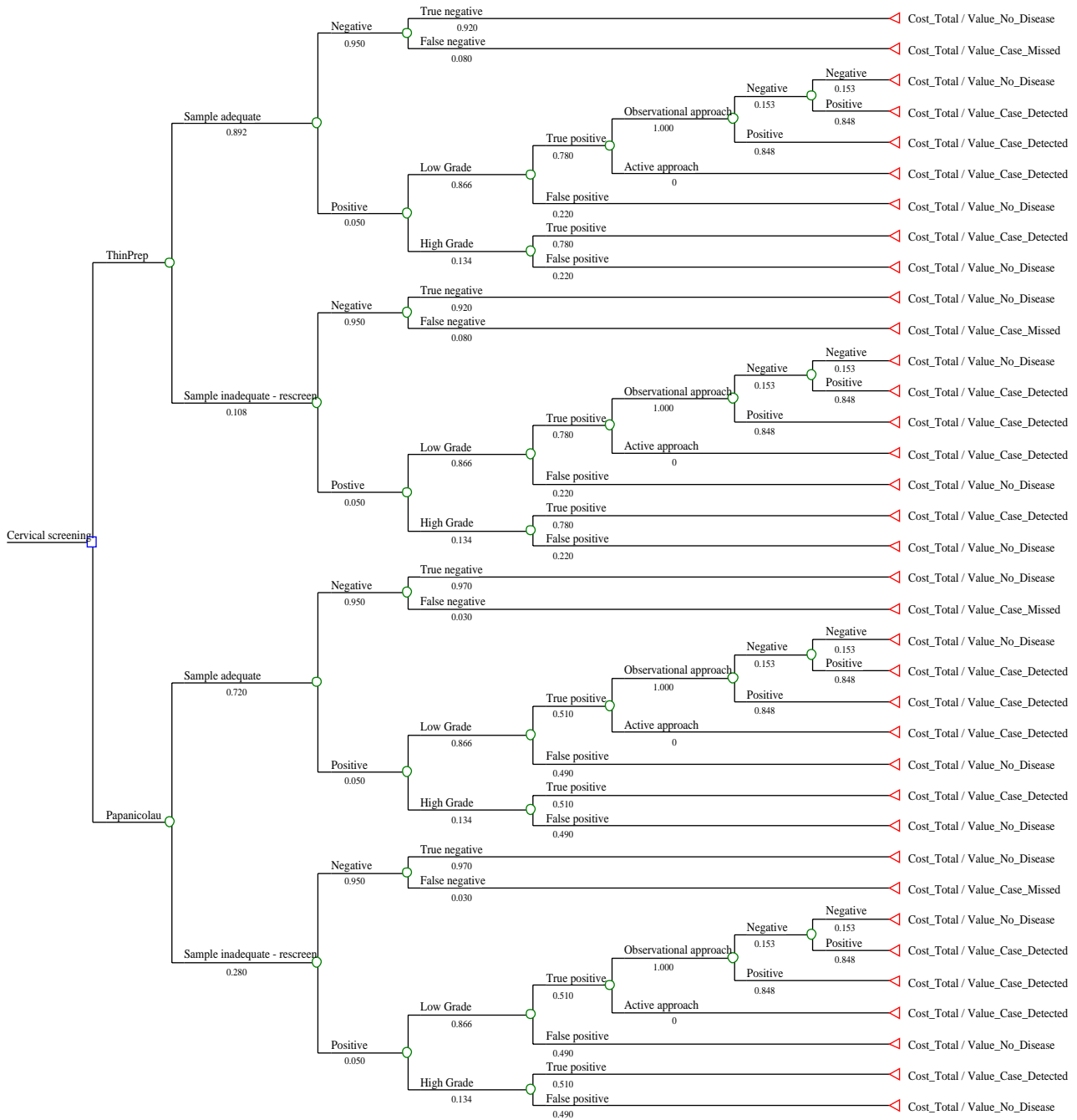


Figure H1 Structure of model presented in submission to the MSAC

2. The node for regression of a low-grade abnormality at 12 months is incorrectly placed after regression has occurred at six months. A lesion cannot regress at six months and regress again at 12 months. The model effectively assumes that 84.75 per cent of women with low-grade lesions that have regressed at six months will relapse by 12 months. It would have been more appropriate for this branch to have been included for women who did not have regression at six months. Alternatively, the model could have included a branch with the probability that a woman will have a repeat negative cytology at 12 months given a negative cytology at six months.
3. The requirement for a re-screen following an inadequate sample could have been dealt with by simply including costs for proportions of women requiring re-screening. It is not necessary to model a separate arm for those women with an inadequate sample as all transition probabilities remain constant.

### Resource variables

The resource variables included in the analysis provided are summarised in Table H1.

**Table H1 Resource variables included in submitted model**

Description (label given in model)	Papanicolaou arm (\$)	LBC arm (\$)
Cost of screening by conventional Papanicolaou test or LBC (Cost_Papanicolaou/LBC/filtration)	18.50	30.00
Cost of re-screening in case of an inadequate sample	47.25	58.75
Cost to investigate an abnormal result on cytology (Cost_Invest))	238.50	238.50
Cost to treat a high-grade abnormality (Cost_Treat)	1,339.10	1,339.10
Cost to treat a low-grade abnormality using an observational approach (Cost_GP_Repeat+Cost_Papanicalou/LBC/filtration)	47.25	58.75
Cost to treat a low-grade abnormality using an active approach (Cost_Treat)	1,339.10	1,339.10

The November 2001 MBS fee for a conventional cytology screen is \$19.00. The fee requested for an LBC cervical screen is \$30.50. It is unclear why the different costs of \$18.50 and \$30.00 for LBC and conventional cytology, respectively were assumed in the model. However, the differences do not have a substantial impact on the final results from the analysis as the incremental cost of an LBC screen over a conventional screen is correct. Costs for the physician or GP visit are not included but this has no effect on the analysis as they are equal for both groups.

Costs for re-screening in the case of an inadequate sample were estimated from the assumed cost for screening as described above. In addition, women were assumed to require a GP visit, assumed to cost \$28.75. This estimate is consistent with the fee for MBS item 23, which is appropriate as it relates to a standard GP visit.

The following assumptions are made in the derivation of costs to investigate an abnormal result on cytology:

1. All women with abnormal results on cytology require a referral to a specialist. This assumption is not consistent with recommendations contained in the NHMRC guidelines for the management of women with screen detected abnormalities (1994). These guidelines suggest that non-specific minor changes be managed by repeat testing at 12-monthly intervals. This assumption has two effects on the analysis of incremental cost-effectiveness. On the cost side, the requirement for referral to a specialist is conservative for LBC as it increases costs in this arm because more women are assumed to be investigated in the LBC arm. However, on the effect side the requirement for referral to a specialist inflates the number of lesions that will be detected. The cost of a specialist visit is estimated at \$67.65, consistent with the fee for MBS item 104, which is appropriate as it relates to an initial visit to a specialist.
  
2. All women will require colposcopy and directed biopsy. The average cost for colposcopy and biopsy is estimated at \$75.85 which, according to the application, assumes:
  - the cost of colposcopy is \$50.50 (this estimate corresponds to the fee for MBS item 35614, which is appropriate as it relates to colposcopy following an abnormal cervical smear);
  - the cost of biopsy is \$50.60 (this estimate corresponds to the fee for MBS item 35608, which is appropriate as it relates to biopsy of the cervix); and
  - the net fee is estimated by applying the multiple procedure rule (ie the fees for two or more operations performed on one patient are calculated by adding 100 per cent of the fee for the item with the greatest schedule fee to 50 per cent of the item with the next greatest schedule fee).

Not all women will require both colposcopy and biopsy. Those with no apparent lesions on colposcopy will not require biopsy. The application appropriately excludes the costs of anaesthesia and facility charges. Colposcopy and biopsy are generally performed in the physician's rooms and anaesthesia is rarely required.

3. Histopathological examination of biopsies will be conducted. The cost of this examination is estimated at \$95.00, which corresponds to the fee for MBS item 72823, and is appropriate as it relates to examination of complexity level 4 biopsy material including cervical samples.

Overall, the assumed costs for investigation of an abnormal result on cytology appear reasonable.

The following assumptions are made in the derivation of costs to treat a high-grade abnormality in the model. The same costs are also assumed for active treatment of a low-grade abnormality:

1. Lesions will be treated by ablative or excisional modalities. The model assumes costs of ablative/excisional therapy to be \$316.10. It is unclear from the application and the model how this figure has been derived. It appears to be the average of a variety of ablative/excisional techniques used to treat cervical lesions.

2. Histopathological examination of biopsy material will be required. The cost of this examination is assumed to be \$160.00. This may be an inappropriate assumption as women have already had a biopsy examined on reaching the stage where ablative/excisional therapy has been decided (see discussion above on costs of investigation of an abnormality). It is not clear that another biopsy would be taken when ablative techniques are being employed to treat a lesion.
3. Women will be hospitalised under DRG N09Z. A hospital cost of \$863 is assumed, which is less than the average cost for this DRG as reported in the National Hospital Cost Data Collection Cost Report for 1999/2000 (\$1,039 for the public sector and \$878 for the private setting). There is an element of double-counting of costs for ablation or excision of lesions as the cost of ablative/excisional therapy is included as part of DRG costs.

Overall, costs of treatment of a high-grade abnormality and cost of active treatment of a low-grade abnormality appear to have been over-estimated.

The following assumption is made in the derivation of costs to treat a cytological prediction of low-grade abnormality using an observational approach:

- All women require a repeat visit to a GP for repeat cervical screening, the cost of which is estimated at \$28.75. This estimate is consistent with the fee for MBS item 23, which is appropriate as it relates to a standard GP visit. The cost of a screen for cervical cancer is estimated at \$18.50. As discussed above, the MBS fee for a Papanicolaou cervical screen is \$19.00. The model is likely to have under-estimated the costs of managing a cytologically-predicted low-grade abnormality by observation as costs are not included for women who will require interventions other than repeat screening over time. The NHMRC guidelines estimate the cost of managing a confirmed low-grade lesion by observation at \$496 (1994).

## Outcome variables

Table H2 summarises the transition probabilities assumed in the submitted model that assumes that 72 per cent of slides prepared using conventional cytology are satisfactory compared with 89.2 per cent for the LBC test. The TreeAge model provided claims that these estimates are based on data from several studies, but this could not be verified as some of these references did not appear to report data on sample adequacy. The estimates included in the model are inconsistent with those provided in the submission, but neither the estimates provided in the model nor those provided in the submission appear appropriate to reflect Australian practice. The 'Performance Standards for Australian Laboratories Reporting Cervical Cytology' (PSALRCC) state that 'between 0.5 per cent and 5 per cent of all smears should be reported as unsatisfactory' (2001). Laboratories are required to return data against this measure. The RCPA Cytopathology Quality Assurance Program reports that the mean percentage of unsatisfactory specimens was 1.9 per cent (range: 0.37-8.99 per cent) in 2000 (PSALRCC, 2001).

An Australian study by Roberts et al (1997) can be used to provide an indication of the maximum improvement in rate of unsatisfactory screens if LBC were used in place of conventional cytology. Roberts et al (1997) reported that 3.5 per cent of conventional smears were found to be unsatisfactory but only 0.7 per cent were unsatisfactory when LBC was used.

**Table H2 Transition probabilities assumed in submitted model**

Description (label given in model)	Papanicolaou arm (%)	LBC arm (%)
Probability that sample will be adequate (Test_Adeq_Pap/TP)	72	89.2
Probability that an abnormality will be detected on cytology (Prob_Abnormality)	5	5
Probability that no abnormality will be detected on cytology <sup>a</sup>	95	95
Probability that a negative result on cytology is a true negative (Test_Spec_Pap/TP <sup>a</sup> )	97	92
Probability that a negative result on cytology is a false negative (ie woman actually has an abnormality in Figure H1) <sup>a</sup>	3	8
Probability that abnormality detected is a high-grade abnormality (Prob_high_given_abnormal)	13.4	13.4
Probability that abnormality detected is a low-grade abnormality <sup>a</sup>	86.6	86.6
Probability that a detected abnormality will be a true abnormality (Test_Sens_Pap/TP <sup>a</sup> )	51	78
Probability that a detected abnormality will not be a true abnormality (ie that woman will have no lesions on histology) <sup>a</sup>	49	22
Probability that a woman with a confirmed low-grade abnormality will be managed using an observational approach (Management -1)	100	100
Probability that a woman with a confirmed low-grade abnormality will be managed using an active approach (Management -0)	0	0
Probability that a confirmed low-grade abnormality (managed by observation) will regress over 6 months (Prob_regress_6)	15.25	15.25
Probability that a confirmed low-grade abnormality will not regress over 6 months <sup>a</sup>	84.75	84.75
Probability that a confirmed low-grade abnormality (managed by observation) will regress over 12 months <sup>b</sup> (Prob_regress_12)	15.25	15.25
Probability that a confirmed low-grade abnormality will not regress over 12 months <sup>a</sup> )	84.75	84.75

<sup>a</sup> As discussed below, the labelling of these transition probabilities in the model as sensitivity and specificity is not correct according to standard definitions. <sup>b</sup> As indicated in discussion on the model structure, this arm has been incorrectly placed in the model provided with the application.

The model assumes that 95 per cent of women will test negative on cytology and that the remainder will have an abnormality predicted. The 'Performance Standards for Australian Laboratories Reporting Cervical Cytology' states that 'not more than 14 per cent of technically satisfactory smears collected by general practitioners and nurses should be reported as abnormal' (PSALRCC, 2001). This standard is intended to refer to smears collected from asymptomatic women taking part in routine screening. To best approximate this, only smears taken by general practitioners and nurses were included. The RCPA Cytopathology Quality Assurance Program states that the mean percentage of satisfactory smears reported as abnormal for laboratories returning data against this measure was 6.01 per cent (range: 1 -50 per cent) in 2000. Thus, the model underestimates the proportion of smears that are reported as abnormal in practice.

There are errors in the derivation of some of the fundamental transition probabilities in the application's model. In particular, the nature of the relationships between sensitivity, specificity, PPV, NPV and true prevalence of abnormality in the population appear to have been disregarded.

Sensitivity is the probability of a positive cytology test result in the presence of an abnormality on histology, whereas the probability in the model is the probability of an abnormality on histology given a positive cytology test result. Specificity is the ability of a screening test to correctly identify a person who is free of abnormality. Positive predictive value is the probability that a positive cytology test will be positive on histology. Negative predictive value is the probability that negative cytology test will be negative on histology. Table H3 summarises the calculation of sensitivity, specificity, PPV, NPV and true prevalence of abnormality.

**Table H3 Relationship between results from cytology screening test and true disease status as determined by histology**

Results predicted by cytology	Results on histology	
	Positive	Negative
Positive	A (true positives)	B (false positives)
Negative	C (false negatives)	D (true negatives)

$$\text{Sensitivity} = \frac{A}{A + C}; \text{ Specificity} = \frac{D}{B + D}; \text{ Positive Predictive Value} = \frac{A}{A + B}; \text{ Negative Predictive Value} = \frac{D}{C + D}$$

$$\text{True prevalence of disease} = \frac{A + C}{A + B + C + D}$$

The NPVs assumed in the model at the node after a negative prediction on cytology are 97 per cent and 92 per cent for conventional and LBC tests, respectively. These probabilities have been inappropriately labelled as Test\_Spec\_Pap/TP. The positive predictive values assumed in the model are 51 per cent and 78 per cent for conventional and LBC tests, respectively. These probabilities have been inappropriately labelled as Test\_Sens\_Pap/TP. The TreeAge model provided reports that these estimates are derived from US Agency for Health Care Policy and Research data for 1999, Cytoc data and literature reviews but does not provide details. It has not been possible to verify that these estimates were appropriately derived.

Tables H4 and H5 show the predictive values used in the model as a 2x2 table, by applying the values to the proportions of women who are assumed to have an abnormality detected or not.

**Table H4 2x2 table for conventional slide preparation**

Results predicted by cytology	Results on histology		
	Positive	Negative	Totals
Positive	51 (51% × 100)	49 (49% × 100)	100 (5%)
Negative	57 (3% × 1,900)	1,843 (97% × 1,900)	1,900 (95%)
Totals	108 (5.4%)	1,892 (94.6%)	2,000 (100%)

**Table H5 2x2 table for LBC slide preparation**

Results predicted by cytology	Results on histology		
	Positive	Negative	Totals
Positive	78 (78% × 100)	22 (22% × 100)	100 (5%)
Negative	152 (8% × 1,900)	1,748 (92% × 1,900)	1,900 (95%)
Totals	230 (11.5%)	1,770 (88.5%)	2,000 (100%)

The true prevalence of abnormality that is implicitly assumed in the two arms of the model can be derived from Tables H4 and H5. The sensitivities and specificities of conventional and LBC implicitly assumed in the model can also be derived.

The probability of a true abnormality (low-grade lesion or worse) in the population assumed in the conventional cytology arm of the model is 5.4 per cent (108/2000). The probability of a true abnormality in the population assumed in the LBC arm of the model is 11.5 per cent (230/2000). It is inappropriate to assume differential rates of abnormality in the two arms of the model. The assumption that there are more women with lesions in the LBC group biases analyses in favour of LBC.

The sensitivity and specificity of conventional screening implicitly assumed in the model are 47.2 per cent (51/108) and 97.4 per cent (1,843/1,892), respectively. The sensitivity and specificity of screening using LBC implicitly assumed in the model are 33.9 per cent (78/230) and 98.8 per cent (1,748/1,770), respectively.

The submitted model assumes a probability of 13.4 per cent that a cytological prediction of an abnormality will be a high-grade lesion. The TreeAge model explains that this estimate is derived by dividing the age-standardised detection rate for histologically-verified high-grade abnormalities (6.7 per 1,000 women screened in 1998; according to Cervical Screening in Australia 1997-1998) by the probability that an abnormality will be detected on cytology. This is inappropriate because the women have had no histological confirmation of disease at this stage of the model.

The submitted model assumes that 100 per cent of women with confirmed low-grade lesions will be managed using an observational rather than an active approach. There is no consensus regarding the requirements for treatment of lesions confirmed as HPV only or CIN I on colposcopy and biopsy. However, historically, a high proportion of CIN I-confirmed lesions has been actively treated in Australia (NHMRC, 1994). Thus, the assumption that no women will be treated using an active approach is likely to be inappropriate.

The submitted model estimates that 15.25 per cent of women with a confirmed low-grade lesion managed by observation will have regression of the lesion over six months. The TreeAge model reports that this estimate has been derived from data reported by Robertson et al (1998). Robertson et al report that 61 per cent of CIN I lesions had regressed at 24 months. By assuming a linear relationship between time and proportion of women with regressed lesions, the model estimates that at six months, 15.25 per cent of lesions would have regressed. At 12 months, another 15.25 per cent of lesions are expected to have regressed. As stated in the discussion of the model's structure, the branch for proportion of women with regressed lesions at 12 months is incorrectly placed.

## Results from the submitted model

Table H6 summarises the results generated by the submitted model. Given the problems identified with the structure of the model, the costs of resources and the transition probabilities driving the model, these results are likely to be inaccurate and biased in favour of LBC. In summary, the results from this model are considered unreliable.

**Table H6 Results of cost-effectiveness analysis presented in submission to the MSAC**

Type of Cytology	Cost per woman	Proportion of women with confirmed lesion	Incremental cost/woman with confirmed lesion
LBC	\$132.92	0.0382	
Conventional cytology	\$156.33	0.0250	
Incremental	\$23.41	0.0132	\$1,769.95

It is also important to recognise that the incorporation into a model of data from clinical studies conducted overseas can be problematic, even if the model has an appropriate structure that reflects the Australian program. The reason is that Australian terminology for reporting cervical cytology is unique and therefore not directly comparable with other systems such as the Bethesda system. In addition, Australian laboratories are required to meet quantifiable performance standards for accreditation to report cervical cytology. This may have a substantial impact on certain parameters published in studies, such as the proportion of specimens reported as unsatisfactory or as abnormal.

## Sensitivity analysis

No sensitivity analyses are presented in the submission. However, the model is sensitive to changes in estimates of comparative test sensitivity and specificity.

## Supplementary submission

Most of the fundamental problems with the original model were also evident in the modified model presented in the supplementary submission. Given the problems with the basic structure of the modified model and the transition probabilities driving it, the results from this model are also considered unreliable.

# Abbreviations

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AGUS	atypical glandular cells of undetermined significance
AHMAC	Australian Health Ministers' Advisory Committee
AHRQ	Agency for Healthcare Research and Quality
AHTAC	Australian Health Technology Advisory Committee
AIHW	Australian Institute of Health and Welfare
AIS	adenocarcinoma <i>in situ</i>
ARTG	Australian Register of Therapeutic Goods
ASCUS	atypical squamous cells of undetermined significance
BMD	borderline mild dyskaryosis
CI	confidence interval
CIN	cervical intraepithelial neoplasia
EUROGIN	European Research Organisation on Genital Infection and Neoplasia
FN	false negative
FP	false positive
FPR	false positive rate
HGEA	high-grade epithelial abnormality
HPV	human papillomavirus
HSIL	high-grade squamous intraepithelial lesion
LEEP	loop electrosurgical excisional procedure
LGEA	low-grade epithelial abnormality
LLETZ	large loop excision of transformation zone
LR	likelihood ratio
LSIL	low-grade squamous intraepithelial lesion
MBS	Medicare Benefits Schedule
MSAC	Medical Services Advisory Committee
NHMRC	National Health and Medical Research Council
NPV	negative predictive value
NR	not reported
NSWCSP	New South Wales Cervical Screening Program
OR	odds ration
Pap smear	Papanicolaou smear
PPV	positive predictive value
QALY	quality adjusted life year
RCPA	Royal College of Pathologists of Australasia
RD	risk difference
RR	relative risk
SIL	squamous intraepithelial lesion
STD	sexually transmitted disease
TGA	Therapeutic Goods Administration
TPR	true positive rate
TN	true negative
TP	true positive
WHO	World Health Organization

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