Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1157 – Cell Enrichment Liquid Based Cytology in Routine Screening for the Prevention of Cervical Cancer

Sponsor/Applicant/s: **Becton Dickinson Pty Ltd**

Date of MSAC consideration: **5 April 2013**

Please note: This item was also discussed by MSAC at its 1 August 2013 meeting.

1. Purpose of application

An application for Medical Benefits Schedule (MBS) listing of liquid-based cytology (LBC) for cervical cancer screening (SurePath™ LBC System), a cell enrichment testing methodology, was received from Becton Dickinson Pty Ltd by the Department of Health and Ageing in April 2011.

Liquid-based cytology uses a different method for preparing cervical cells for cytological examination than the Pap smear test (i.e. conventional cytology or CC). Cells are collected from the cervix using a brush, broom or spatula in the same way as they are collected for a Pap smear, but instead of smearing the cells directly onto a glass slide, the head of the brush or spatula is either rinsed or detached into a vial of LBC preservative fluid to produce a cell suspension which is sent to the laboratory. Under LBC at the laboratory, the cell sample is treated to remove obscuring factors, such as blood, mucus and inflammatory cells, so that a thin layer of cervical cells can be placed on a slide for microscopic examination.

There are currently two marketed LBC preparation systems available in Australia. These systems use different technical methods for storing and preparing the cervical cytology sample, some of which are patented.

The SurePath™ LBC system (Becton Dickinson Pty Ltd) requires that the head of the brush or spatula to be detached into a vial of liquid to produce a cell suspension which undergoes "enrichment" prior to slide preparation via gravity sedimentation. This is known as cell enrichment LBC (CE LBC). This is the application that has been received for consideration by MSAC at its 5 April 2013 meeting.

The ThinPrep® Pap system (Hologic [Australia] Pty Ltd) requires that the head of the brush or spatula be rinsed into a vial of liquid to produce a cell suspension which then undergoes membrane filtration and the cell residue is transferred to the slide. This is known as cell filtration LBC (CF LBC). No current application for MBS listing of this technology has been received by MSAC, accordingly, it is not being considered for MBS listing.

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

The National Cervical Screening Program (NCSP) was established in 1991 and aims to reduce illness and deaths from cervical cancer through an organised approach to screening women for early detection. The NCSP promotes routine cervical cancer screening with Pap smears every two years for women between the ages of 18 (or two years after first sexual intercourse, whichever is later) and 69 years. Women who are detected under the NCSP are managed according to the recommendations of the National Health and Medical Research Council (NHMRC) Screening to Prevent Cervical Cancer: Guidelines for the Management of Asymptomatic Women with Screen Detected Abnormalities (2005). In particular, if the cytology results are suggestive of precancerous cervical intraepithelial neoplasia (CIN), women are referred for specialist histological diagnosis, further follow up and, if necessary, appropriate treatment to reduce progression to invasive cancer.

2. Background

MSAC has reviewed LBC for cervical screening twice before. The finding of the second review (MSAC 1122 assessment report March 2009) was that LBC was "safe, at least as effective, but not cost effective at the price requested". The 2009 review was not based on randomised controlled trial evidence, but rather the best evidence available at the time. The detailed conclusion drawn in the review was that LBC compared with conventional cytology was not statistically significantly different with the exception of reduced specificity for the detection of CIN 2+ at a threshold of possible low-grade squamous intraepithelial lesion (pLSIL), more slides classified as positive for LSIL and reduced rates of unsatisfactory tests. The cost-effectiveness ratio was high and unfavourable at the price requested.

3. Prerequisites to implementation of any funding advice

Becton Dickinson Pty Ltd has advised that all products supplied in Australia for LBC are in accordance with the relevant legislation set out in the new TGA Regulatory Framework (July 2010) for IVD products.

LBC is currently provided by private pathology laboratories for a fee separate from the MBS fee for conventional (Pap smear) cytology (CC). The material is collected for both CC and LBC as part of the same process, and the sample is split, with some applied to a slide for CC and the head of the collector used for LBC.

Training is required for LBC specimen collection, processing and specimen review. Specimen review training is the most intensive, potentially involving training over four days. Appropriate training may also be required for correct usage of the more automated testing methodology.

4. Proposal for public funding

The applicant proposed changes to MBS items 73053, 73055 and 73057 (or alternatively a new item number for each circumstance) under Category 6 – Pathology services (cytology).

In the proposed new MBS item descriptor, the applicant requested 'explicit inclusion' of CE LBC on the MBS such that new methods other than CE LBC (e.g. CF LBC) are excluded from the proposed listing:

Cytology of a smear from cervix or vagina where the smear is prepared by direct application of the specimen to a slide {excluding the use of liquid based slide preparation techniques} or using cell enrichment liquid based techniques utilising centrifugal sedimentation through density reagent and the smear is microscopically examined by or on behalf of a pathologist using manual or automated methods.

Additionally, with the objective of preventing both CC and CE LBC on any single occasion, the applicant has requested the following insertion to the current relevant explanatory notes:

..that on any one occasion only a direct application of the specimen to a slide or a cell enrichment liquid based technique should be used.

Obtaining a specimen for cervical cancer cytology is commonly administered within the context of a medical consultation. It can also be administered by other qualified health professionals or in the context of a specialist appointment. Training would be required for either CE or CF LBC specimen collection, processing and specimen review. Specimen review training is the most intensive, potentially involving training over four days.

5. Consumer Impact Statement

In some areas of far north Queensland, CF LBC (ThinPrep®) is offered as an adjunctive test to CC in women meeting specific criteria (Queensland Cervical Screening Program 2008). Criteria include geographical location and a history of unsatisfactory smears. This program is funded by the Queensland State Government. In 2010, the Queensland Government funded 1,414 CF LBC tests.

Currently, between 250,000 and 400,000 CC tests a year are provided to women, with no out-of-pocket costs or MBS subsidies, through the Victorian Cytology Service (funded by the Commonwealth and Victorian governments), and some Aboriginal Medical Services, women's health centres and sexual health clinics.

6. Proposed intervention's place in clinical management

CE LBC is proposed to be a direct substitute for CC. It is not proposed that CE LBC be used in conjunction with CC. CC would still be available on the MBS; however, the applicant expected the utilisation would decrease with the introduction of CE LBC.

There will be no change to the patients' clinical pathway and follow-up of patients. The only change is the sample preparation in pathology laboratories.

7. Other options for MSAC consideration

The proposed descriptor refers to cell enrichment. However, further details of the methods used in the cell enrichment process may be needed in the item descriptor to ensure that other methods cannot be claimed using the item.

8. Comparator to the proposed intervention

The appropriate main comparator required by the final DAP (May 2012) was CC, i.e. Pap smear testing as funded through the MBS.

Individual laboratories currently make the decision about whether to review slides using manual or automated methods, although only manual review meets requirements for MBS items. Whichever method of review is implemented, laboratories are still required to meet quality standards. Nevertheless, the final Decision Analytic Protocol (DAP) (May 2012) required that a secondary comparison be "undertaken to examine the issue of automated versus manual reading of slides" as in the 2009 MSAC review of LBC.

As recommended in the DAP, CE LBC has also been compared with CF LBC.

CC is reimbursed through MBS item numbers 73053, 73055, and 73057. It is a stand-alone test commonly administered within the context of a medical consultation (MBS Items 3, 23, 36, and 44 for vocationally registered GPs, and MBS Items 52, 53, 54, and 57 attendances with doctors who are not vocationally registered GPs). These items enable the sample to be taken by an appropriately credentialed practice nurse, administered by qualified health professionals or provided in the context of a specialist appointment (MBS Items 104 and 105). A colposcopy and referral to a specialist may be indicated following any abnormal test result from the initial screen.

Table 1 provides a listing of the current MBS item descriptors for CC.

Table 1: Current MBS item descriptors for CC

Category 6—Pathology Services (Cytology)
MBS 73053 Cytology of a smear from cervix where the smear is prepared by direct application of the specimen to a slide, excluding the use of liquid-based slide preparation techniques, and the stained smear is microscopically examined by or on behalf of a pathologist - each examination (a) for the detection of precancerous or cancerous changes in women with no symptoms, signs or recent history suggestive of cervical neoplasia; or (b) if a further specimen is taken due to an unsatisfactory smear taken for the purposes of paragraph; or (c) if there is inadequate information provided to use item 73055; (See para P16.11 of explanatory notes to this Category) Fee: $19.45 Benefit: 75%=$14.60 85%=$16.55
MBS 73055 Cytology of a smear from cervix, not associated with item 73053, where the smear is prepared by direct application of the specimen to a slide, excluding the use of liquid-based slide preparation techniques, and the stained smear is microscopically examined by or on behalf of a pathologist - each test (a) for the management of previously detected abnormalities including precancerous or cancerous conditions; or (b) for the investigation of women with symptoms, signs or recent history suggestive of cervical neoplasia; (see para 16.11 of explanatory notes to this Category) Fee: $19.45 Benefit: 75%=$14.60 85%=$16.55
MBS 73057 Cytology of smears from vagina not associated with item 73053 or 73055 and not to monitor hormone replacement therapy, where the smear is prepared by direct application of the specimen to a slide, excluding the use of liquid-based slide preparation techniques, and the stained smear is microscopically examined by or on behalf of a pathologist - each test. (See para P16.11 of explanatory notes to this Category) Fee: $19.45 Benefit: 75%=$14.60 85%=$16.55
Explanatory notes for above items: P16.11: Item 73053 applies to the cytological examination of cervical smears collected from women with no symptoms, signs or recent history suggestive of cervical neoplasia as part of routine, biennial examination for the detection of pre-cancerous or cancerous changes. This item also applies to smears repeated due to an unsatisfactory routine smear, or if there is inadequate information

provided to use item 73055.

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

(i) an examination interval of two years for women who have no symptoms or history suggestive of abnormal cervical cytology, commencing between the ages of 18 to 20 years, or one to two years after first sexual intercourse, whichever is later; and

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

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

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

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

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

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

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

Related Items: 73053, 73055, 73057

9. Comparative safety

Safety was not specifically addressed in the submission-based assessment (SBA) report from the applicant. This was because both CE and CF LBC, with manual or automated slide reading, used the same procedure for collecting cervical cell samples as the MSAC-accepted comparator CC, and the collection of cervical cells was regarded as safe by MSAC (MSAC 1122 Assessment Report (AR)).

A recent systemic review of Screening for Cervical Cancer for the U.S. Preventive Services Task Force quoted that they, “were unable to identify any studies or data that identified direct harm resulting from collecting the cervical sample for LBC” (Vesco 2011 p.36).

LBC with manual or automated slide reading uses the same procedure for collecting cervical cell samples from a woman as CC and therefore does not introduce any additional risks to the woman (MSAC 1122 AR). Collection of cervical cells is regarded as safe. Some women may experience discomfort or minor bleeding afterwards that resolves spontaneously.

10. Comparative effectiveness

The effectiveness of CE LBC was assessed by reviewing the available literature on diagnostic accuracy outcomes, test yields, unsatisfactory rates, and false positive and negative rates, compared directly with CC and indirectly with CF LBC. The application also indirectly compared automated and manual reading of slides.

Ten studies in cervical cancer screening populations provided the pivotal evidence (Table 2). Two studies compare CE LBC with CC, six studies compare CF LBC with CC and two studies compare manual and automated reading methods. There was no study that directly compared CE LBC and CF LBC, therefore an indirect comparison was provided.

Table 2: Summary of studies presented

Trial ID/ Lead Author	Sample size
Beerman 2009 (Netherlands) July 1997—June 2002	CC=51,154 CE LBC=35,315
RODEO Study (Brazil) May 2010–December 2010	CC=6047 CE LBC=6001
NTCC trial (Ronco 2006a, b) (Italy) 2002–2003	CC=22,547 CF LBC=22,760
NETHCON Trial (Siebers 2008, 2009) (Netherlands) April 2003–July 2006	CC=40,047 CF LBC=48,941
Strander 2007(Sweden) May 2002–Dec 2003	CC=8810 CF LBC=4676
Maccallini 2008 (Italy) 2001–2002	CC=4299 CF LBC=4355
Obwegeser 2001 (Switzerland) July 1998–Sep 1998	CC=1002 CF LBC=997
RHINE-SAAR Study (Germany) August 2007 –October 2008	CC=9296 CF LBC=11,331
MAVARIC Study (Kitchener 2011a, b) (UK) Mar 2006–Feb 2009	Manual=24,668 Auto=48,578
Palmer 2012(Scotland) Oct 2008+	Manual=90,551 Auto=79,366

Across all studies, where reported, colposcopy and/or biopsy were used as the analytical reference standard. The test threshold at which the reference standard was uniformly applied was detection of either atypical squamous cells of undetermined significance (ASCUS+) or high-grade squamous intraepithelial lesion (HSIL+). Generally the outcome assessor, the colposcopist and, where relevant, the histologist, were not blinded to the index/screening test result. In four studies, the outcome assessors were blinded to the cytology test type: Seibers 2008, 2009 (NETHCON); Strander 2007, Maccallini 2008; and Kitchener 2011a, b (MAVARIC).

Beerman 2009 and Strander 2007 were the only studies to follow up all patients by review of any histology results in the relevant national (Beerman 2009) or regional (Strander 2007) database and report the true false negative rates (i.e. “absolute sensitivity and specificity”) and so were given greatest prominence in the SBA report and critique.

The mean age of participants across the trials ranged from 37 to 44 years of age. Similar collection tools were used between the arms within each trial except Obwegeser 2001.

For most trials, the implementation of LBC was new, and so training was reportedly provided to collectors of the LBC specimen and cytology reviewers.

However, there are a number of methodological problems relating to the Beerman 2009 study as the main supporting evidence for CE LBC. Table 3 summarises the key issues that affect the validity of the comparison and thus the applicability of its results to the Australian target

screening population. Similarly Table 4 is provided for the main supporting evidence provided for CF LBC (Strander 2007).

Table 3: Critique of the Beerman 2009 study

Claim of the SBA report	Assessment Group critique
Study design	Study design
A cluster randomised controlled trial with "family practice as the unit of randomisation".	A cohort study rather than a randomised controlled trial (the publication states that cervical samples were taken by general practitioners randomly selected to use either CC or CE LBC using the same brush technique).
Histology outcomes	Historical outcomes
All patients are followed up in the study.	The cytological threshold of referral to colposcopy in the trial is unclear. The follow-up was via a national pathology database (with incidental follow-up of negative test results) rather than a clinically valid and systematic reference standard such as a follow-up smear.
Diagnostic sensitivity	Diagnostic sensitivity
Sensitive for CIN 1+.	Diagnostic accuracy outcomes required to determine effectiveness of cervical cancer screening is that the new test is more sensitive than the conventional test in detecting CIN 3+ (or CIN 2+ as a surrogate).

Table 4: Critique of the Strander 2007 Study

Claim of the SBA report	Assessment Group critique
Study design	Study design
Women were randomised "according to the time of their appointment".	This method is considered pseudo-randomised and there is an uneven distribution of subjects between the groups, both of which indicate that selection bias may be present.
The application of the analytical reference standard used is appropriate.	The methodology used to investigate 'normal' results is not adequate to determine a true/false negative rate. Vesco, 2011 also excluded this study on the basis that it did not systematically apply a reference standard.
Histology outcomes	Histology outcomes
Verification of all subjects (as review of a national pathology database was used) and on this basis the study uses absolute sensitivity as the accuracy measure.	Verification is inadequate (the proportion of subjects undergoing histological verification is not reported or low, respectively) and it is considered that this outcome measure is invalid.
It is assumed that the 'no histology' outcome represents a benign or normal outcome for women with benign or ASCUS+ test result.	The assumption that 'no histology' = normal is not appropriate.
Histological verification of the ASCUS+ or LSIL+ results used for the comparison are available in 46% of women in the CF LBC group and 53% of women in the CC group. In contrast, histological verification of women with HISL is available in 100% of the CF LBC and 98% in the CC group.	Verification in positive patients in this study is inadequate at cytological thresholds lower than HSIL+.
Diagnostic sensitivity	Diagnostic sensitivity
Absolute sensitivity and specificity was able to be calculated. Absolute sensitivity requires verification all of patients, including those with normal cytological outcomes (or at least a random sample of these). This is achieved using national or regional databases (similar to that used in	These absolute sensitivity and specificity measures are not valid. The results do not represent absolute sensitivity as verification of all patients with an appropriate reference standard has not been undertaken. Clinical follow-up with repeat cytology at 1 year provides the most valid reference standard for normal test results.

Australia) to capture the outcome of each cytological and/or histological investigation.	Follow-up of negative results by accessing a national pathology database will only provide incidental (non-systematic) follow-up.
Detection of CIN1+.	Detection of CIN1+ is not a useful outcome measure. No data are available for thresholds of CIN 2+ or CIN 3+, which are the primary diagnostic accuracy outcomes of interest.

The comparative effectiveness of CE LBC versus CC was primarily based on one study conducted in the Netherlands (Beerman 2009). Although presented in the submission as a randomised trial, the authors described their study as a cohort study. Although a randomised design was used, the unit of randomisation was not the study participant, but the general practitioner taking the cervical sample.

The comparative effectiveness of CE LBC versus CF LBC was based on an indirect comparison of the Beerman 2009 study for CE LBC and one study of CF LBC (Strander 2007, which randomised study participants "according to the time of their appointment for smear taking"), using CC as the common reference.

The table below (taken from the SBA report) summarises the comparative effectiveness of CE LBC versus CC, and CE LBC versus CF LBC.

Table 5: Summary of the clinical effectiveness results presented in the SBA report

	Evidence presented in the SBA report				**Claim of the SBA report**
Cell enrichment LBC versus CC (Beerman 2009): comparison based on randomising the GPs taking the cervical sample (not randomising study participants)					
Health outcomes	No data presented				
Diagnostic accuracy outcomes (primary outcome measures) – sensitivity and specificity	For the detection of CIN 1+:				Cell enrichment LBC demonstrates a significantly greater sensitivity and significantly reduced specificity to detect CIN 1+ at a threshold of ASCUS+
		CE LBC	CC	OR (95% CI)	
	Sensitivity: % (95% CI)	96.24 (93.54,97.84)	92.04 (88.87,94.37)	2.23 (1.12, 4.42) p=0.0244	
	Specificity: % (95% CI)	97.75 (97.58,97.90)	98.17 (98.05,98.28)	0.81 (0.73, 0.89) p<0.0001	
PPV RR	Comparative PPV RR (95% CI): ASCUS+: 1.04 (0.91,1.18) LSIL+: 0.98 (0.91,1.07) HSIL+: 1 (0.92,1.07) SCC: 1.33 (0.76,2.35)				No difference in PPV at various test thresholds
Test yield	Cell enrichment LBC vs CC: ASCUS: 2.07% vs 0.87% (p<0.0001) LSIL: 0.27% vs 0.22% (p=0.1284)				Higher detection of ASCUS; no difference in the detection of LSIL
Unsatisfactory rates	0.13% vs 0.85% OR=0.15 (95% CI 0.11 to 0.21, p<0.0001)				Fewer unsatisfactory results with cell enrichment LBC
Cell enrichment vs cell filtration LBC: indirect comparison across Beerman 2009 and Strander 2007 with CC as the common reference					
Diagnostic accuracy outcomes (primary	For detection of CIN 1+: Sensitivity: indirect OR=0.33 (95% CI 0.02 to 6.67, p=0.47) Specificity: Indirect OR=1.26 (95% CI 0.95 to 1.66,				No difference in the detection of CIN 1+

outcome measures) – sensitivity and specificity	*p*=0.10) (An OR >1 indicates performance of cell enrichment LBC is better than cell filtration LBC)	
Unsatisfactory rates	Indirect estimate of effect: OR=0.36 (95% CI 0.19 to 0.69, *p*=0.0022)	Fewer unsatisfactory results with cell enrichment LBC

Abbreviations: ASCUS, atypical squamous cells of undetermined significance; CC, conventional cytology; CIN, cervical intraepithelial neoplasia; CI, confidence interval; HSIL, high-grade squamous intraepithelial lesion; LBC, liquid-based cytology; LSIL, low-grade squamous intraepithelial lesion; OR, odds ratio (cell enrichment LBC versus CC); PPV, positive predictive value; RR, risk ratio; SCC, squamous cell carcinoma; vs, versus

As shown in Table 5, the sensitivity for detection of a histologically proven lesion (CIN 1+) based on an ASCUS+ index test was significantly higher with CE LBC compared to CC (96.24% vs. 92.04%, OR 2.23, 95% CI: 1.12 to 4.42, P=0.0244). Similar results were reported for the detection of CIN 2+ lesions using LBC (97.19%; 95% CI: 94.31 to 98.63 vs 93.46%; 95% CI: 90.21 to 95.68) (Beerman 2009 p.574).

The specificity for the detection of a histological proven lesion (CIN 1+) based on an ASCUS+ index test was significantly lower with CE LBC compared to CC (97.75% vs 98.17%, OR 0.81, 95% CI: 0.73 to 0.89, P<0.0001). Specificity results were not reported by Beerman 2009 for CIN 2+ lesions.

MSAC noted that the estimated absolute increase in sensitivity was 4.2% (P=0.0247), whereas the absolute decrease in specificity was 0.42% (P<0.0001).

Given the above issues and the small volume of evidence presented on CE LBC, MSAC considered there is only weak evidence to support a claim of non-inferiority in terms of sensitivity or a claim of superiority in terms of unsatisfactory rates.

There is no direct evidence on whether substituting CE LBC for CC as a test method for cervical cancer screening has any consequences for subsequent clinical management.

Indirect evidence was documented in only four CF LBC trials. Overall, three trials reported no significant differences in clinical management between CF LBC and CC. However, Maccallini 2008 reported that significantly more patients were referred for colposcopy after CC compared with CF LBC, although the rates of CIN 2+ detection were no different between the arms.

11. Economic evaluation

The economic evaluation presented was a cost-minimisation analysis (CMA). The SBA report also presented a modelled cost-effectiveness analysis (CEA) as a supplement, based on the LBC model considered by MSAC in 2009.

The CMA assumed equal costs across CE LBC and CC for conducting the primary screening test and estimated differences in costs due to differences in unsatisfactory rates and yield rates of low-grade abnormalities (ASCUS, LSIL) as the only differences between CE LBC and CC (manual screening). The only consequence of an unsatisfactory smear or a smear with a low-grade abnormality was to repeat the cytology test – the effect of false positives or false negatives and impact, including on the psychological state of the tested woman, were also not considered. The critique identified that the SBA report had incorrectly calculated the

rates of low-grade abnormalities which was acknowledged by the applicant. Different estimates of unsatisfactory smear rates were examined in the sensitivity analyses.

Table 6: Revised results of CMA after correction of error in the SBA report (base case)

	Cell enrichment LBC	Conventional cytology (CC)	Difference (cell enrichment LBC − CC)
Unit cost of primary screen	$68.42	$68.42	$0.00
Expected cost of repeat screen per unsatisfactory primary screen	$0.78	$1.45	−$0.68
Expected cost of repeat screen per low-grade abnormalities yield in primary screen	$2.56	$1.84	$0.72
Total cost (MBS perspective)	**$71.76**	**$71.71**	**$0.05**
Total patient out-of-pocket costs	$0.00	$8.10	−$8.10
Total societal (MBS + patient) cost	**$71.76**	**$79.81**	**−$8.05**

The applicant proposed the same MBS fee as for CC, which is $19.45. The appropriate rebate, at 85%, is $16.55.

The applicant claimed there would be no co-payment for CE LBC if listed on the MBS.

The applicant also cited Farnsworth 2003 to report that the total number of CC smears read in the laboratory in the calendar year (January 2000–December 2000) was 147,181. Of these, 21,100 were accompanied by CF LBC. Therefore, 14% (21,100/147,181) of women received CC, funded by the MBS, in combination with CF LBC, funded by the patient. Based on internal market research, the applicant updated this estimate to 18% for both CE LBC and CF LBC for the 2011-2012 financial year. This was the basis for the claimed reduction in costs to society from listing CE LBC on the MBS.

There will be minimal impact on the Extended Medicare Safety Net, as the overall cost for any individual patient is considered small.

12. Financial/budgetary impacts

A woman is tested once every two years starting at 18 years of age (or two years after first sexual intercourse, whichever occurs first) and ceasing at 69 years of age.

For the 100% uptake scenario, the revised estimate of MBS utilisation (number of services) of CE LBC, after correcting the error in the rates of low-grade abnormalities is: 1,699,728 in Year 1, rising to 1,717,404 in Year 5 of listing. This represents an increase of 952 services in Year 1, rising slightly to 964 services in Year 5 with the proposed listing. However, 100% uptake is unlikely.

The MBS cost of the overall proposed intervention would be $71.76 per patient, encompassing the cost of the screening test, patient episode initiation fee, consultation to take the sample, and a small percentage of repeat tests for unsatisfactory results or low grade abnormalities. This cost calculation is prior to taking into account CC which will not be done at the same time. Once those costs are taken into account the total net cost to the MBS is proposed to be $0.05 (see Table 6).

The applicant claimed that the total patient out-of-pocket cost per test will be zero, based on multiple assumptions.

Table 7: Summary of arguments presented in the SBA report and critique to support the claim of sustainability of the proposed service at the requested MBS fee – **redacted**

The SBA report provided the internal results of market research conducted by the applicant estimating the charging patterns of eleven pathology practices in Australia when testing with CE LBC or CF LBC in conjunction with MBS-funded CC. Based on this research the estimated weighted average charge per LBC service was $45.

Table 8: Internal Becton Dickinson market research estimating the out-of-pocket costs to patients associated with the use of LBC in conjunction with MBS-funded CC - **redacted**

Table 9 presents the estimated net financial implications to the MBS of adding CE LBC.

Table 9: Estimated net financial implications of adding cell enrichment LBC to the MBS: 100% uptake scenario after correction of error in the SBA report and at 100% benefit

	Year 1	*Year 2*	*Year 3*	*Year 4*	*Year 5*
100% uptake scenario					
Number of services (MBS 73053, 73055)					
Without the proposed listing	*1,698,776*	*1,703,192*	*1,707,608*	*1,712,024*	*1,716,440*
With the proposed listing	*1,699,728*	*1,704,147*	*1,708,566*	*1,712,985*	*1,717,404*
Difference	*952*	*955*	*958*	*961*	*964*
Cost of services (MBS 73053, 73055)					
Without the proposed listing	*$33,296,010*	*$33,382,563*	*$33,469,117*	*$33,555,670*	*$33,642,224*
With the proposed listing	*$33,314,666*	*$33,401,278*	*$33,487,891*	*$33,574,504*	*$33,661,116*
Difference	*$18,656*	*$18,715*	*$18,774*	*$18,833*	*$18,892*
Cost of consultation (MBS 73053, 73055)					
Without the proposed listing	*$68,919,342*	*$69,098,499*	*$69,277,657*	*$69,456,814*	*$69,635,971*
With the proposed listing	*$68,957,959*	*$69,137,238*	*$69,316,517*	*$69,495,796*	*$69,675,076*
Difference	*$38,616*	*$38,738*	*$38,861*	*$38,983*	*$39,105*
Total cost of services and consultation (MBS 73053, 73055)					
Without the proposed listing	*$102,215,352*	*$102,481,063*	*$102,746,773*	*$103,012,484*	*$103,278,195*
With the proposed listing	*$102,272,624*	*$102,538,516*	*$102,804,408*	*$103,070,300*	*$103,336,192*
Difference	*$57,272*	*$57,454*	*$57,635*	*$57,816*	*$57,997*

13. Key issues for MSAC from ESC

- Main issues around the proposed eligible population for public funding and/or the proposed main comparator?

ESC did not agree with the applicant's suggestion of widening the current MBS items for 73053 and 73055 to include vaginal smears and instead advised that consideration be given to varying the existing item 73057 consistent with any other amendments made to the other two items. This item was specifically in place to enable vaginal smears to be taken in the rare instances that it is needed, such as following hysterectomy, cervical cancer or diethylstilboestrol (DES) exposure. The SBA report provided no data on vaginal rather than cervical smears.

ESC agreed that the population eligible for cervical screening with CE LBC, and the comparator being primarily CC, are clear and well defined.

- Main issues around the evidence and conclusions for safety?

ESC accepted that, as found in the previous MSAC considerations, the evidence put forward indicated that the collection of material for LBC (for either CE LBC or CF LBC) is as safe as for CC.

- Main issues around the evidence and conclusions for clinical effectiveness?

The main clinical issue was the claim of non-inferiority between CE LBC and CC in terms of screening accuracy, and superiority in terms of unsatisfactory rates. This was primarily based on one study (Beerman 2009) in which the method of randomisation was suboptimal in minimising bias and confounding. The secondary claim of non-inferiority between CE LBC and CF LBC was primarily based on an indirect comparison of the results of this study and one CF LBC trial, both involving CC as a common reference. Both included studies have major limitations in terms of the quality and applicability of the data used for this comparison.

ESC noted that the Beerman 2009 study is the only reviewable new evidence directly comparing CE LBC and CC since the previous MSAC consideration of LBC (sufficient detail of the RODEO study only became available during the evaluation period). ESC discussed a number of concerns with this study.

ESC noted that, although the study included a large sample of general practitioners (500), the type of general practices was uncertain, and the trial was randomised to general practitioners, not patients, without details as to how general practitioners were randomised (noting also that the SBA report referred to the unit of randomisation being the "family practice", not the general practitioner). Therefore, ESC advised that the risk of material difference in the intervention and control group was not adequately minimised in the results of this study. ESC also noted the evidence of imbalance across the two cohorts receiving the two testing methodologies (N=51,154 for CC and N=35,315 for CE LBC) and advised that confounding also remained an issue to consider when interpreting the results of the study. ESC considered that these issues were not sufficiently taken into account in the subsequent analyses of the data.

ESC also agreed that the threshold used for detecting a precancerous lesion in the evidence presented, CIN1+, as compared to only CIN2 and CIN3, is considered less informative for

comparing accuracy of test methodology because the detection of CIN1 is less confidently prognostic of invasive cervical cancer.

ESC advised that there are problems with interpreting both studies (Beerman 2009 and Strander 2007) in terms of the degree of verification (positive and negative) with the reference standard (based on independent colposcopy and histopathology of colposcopy-guided biopsy). The applicant claimed verification of all subjects (as review of a national or regional pathology database was used) and on this basis used absolute sensitivity as the accuracy measure for the comparison. Consistent with the US evidence synthesis published by Vesco et al in 2011, ESC considered that this verification was inadequate (the proportion of subjects undergoing histological verification is not reported or low, respectively, particularly for individuals who test negative at the screening stage) and so questioned the validity of this outcome measure.

The sensitivity (true positive rate) of CE LBC (96.24%) is 4.2 percentage points greater than that of CC (92.04%) in the detection of CIN1+ (p=0.0247). This suggests more women with CIN1+ will be detected by CE LBC, i.e. CE LBC is better at detecting CIN1+ in women with this abnormality. The specificity (true negative rate) of CE LBC (97.75%) is 0.42 percentage points less than that of CC (98.17%) in the detection of CIN1+ (p<0.0001). This suggests that fewer women who do not have CIN1+ will be detected as being disease negative by CE LBC, i.e. CE LBC will result in more false positive test results in women who do not have this abnormality, leading to more women wrongly being identified as requiring a second verification test. Notwithstanding the much larger absolute difference in sensitivity between CE LBC and CC, the p-value for this difference is higher than that for the difference in specificity because of the much larger population of women whose disease status is CIN1+ negative.

ESC also advised that the evidence provided weak support for the claims regarding the comparative screening performance of CE LBC and CF LBC. This was due to reliance on an indirect comparison, which involved only one study for method, the poor quality of these studies, and the wide confidence intervals in the results reported.

The previous MSAC consideration relied primarily on evidence comparing CF LBC (not CE LBC) to CC. ESC agreed that the DAP's request for a primary comparison of CE LBC with CC and a secondary comparison of CE LBC with CF LBC helped highlight the evidence base for CE LBC as the basis for MSAC considering CE LBC specifically rather than LBC more generally. The indirect comparison of CE LBC and CF LBC presented in the SBA report was insufficient to either support or contradict the previous MSAC consideration.

Overall, ESC advised, in relation to the claims of non-inferiority of CE LBC against CC and against CF LBC in screening performance, that some weak new evidence has emerged, and MSAC needs to consider whether these claims of non-inferiority are adequately supported by the evidence provided.

- Main economic issues and areas of uncertainty?

After correcting the error in the rates of low-grade abnormalities, the economic analysis remained as presented, most sensitive to the test yield data used for CE LBC and CC. The increase in cost was greatest when results from the Beerman (2009) study were used without modification to estimate the comparative test yield in Australian conditions. Given the uncertainty in comparative 'efficacy' of CE LBC and CC, the cost consequences of the proposed listing were uncertain.

Overall, the results of the CMA as presented were uncertain, particularly as equivalence of the yield of high grade cytological abnormalities between CE LBC and CC has not been established.

ESC noted that a pivotal argument of the SBA report was that listing CE LBC at the proposed fee would generate sufficient income for pathology laboratories at the corresponding rebates provided when bulk billed that the current 95% bulk billing rate would be maintained for CE LBC. Given this, ESC considered that the CMA would be more correct if the pathology items in the CMA were costed at the 85% rebate rather than the fee. However, as this applies to both CC and CE LBC in the CMA, this correction would have no effect on the results of the CMA.

However, ESC questioned the SBA report prediction of how behaviour would change if the CE LBC test was listed on the MBS, as it is not clear that everyone would move to the requested arrangements. ESC was particularly concerned that the claimed movement away from carrying out CC at the same time as CE or CF LBC to only carrying out CE LBC, if it was listed on the MBS, may not occur. This concern arose with respect to a perceived need for reinforced certainty of the result, as evidenced by the 18% rate of conducting an LBC test in addition to the MBS listed CC test. This perceived need may be from women being tested or the clinicians ordering the test or a combination of both. (**redacted**)

ESC also questioned how pathology laboratories would charge for CE LBC if it is listed on the MBS. The $45 charge suggested by the applicant's market research is larger than adding the MBS rebate for the initiation of a patient episode ($7.00) to the MBS rebate proposed for CE LBC at the proposed fee ($16.55). This suggests that the rate of bulk billing for CE LBC does not have to drop much below the 95% that it currently is for CC for there to be increased costs to society as a whole and to patients in particular. ESC had reservations that, as the applicant could not control the fees charged by pathology laboratories in the market, patients could be required to pay out-of-pocket costs. Further, given the extent of uncertainty and variability of costs in Table 9, even a small increase in out of pocket costs per patient would outweigh the claimed average $8.10 reduction per patient in the applicant's CMA.

Putting these two issues together, the SBA report indicated that 100%-18% = 82% are *not* tested with both CC and LBC. For this majority of patients, there would need to be only a small decrease in bulk billing rates for CE LBC than CC and/or a small increase in out-of-pocket payments towards $8.10 for those patients who are billed to outweigh the claimed net savings in the SBA report.

ESC considered that the overall impact of listing CE LBC on out-of-pocket expenses will depend on several factors: the extent to which current duplication of testing ceases; the extent to which women switch to using CE LBC rather than CC; and the actual fee charged for CE LBC. While some savings in out-of-pocket expenses might accrue from the removal of duplicate testing, switching to CE LBC will increase out-of-pocket expenses if the actual fee charged exceeds the Medicare rebate. There is a distinct possibility that the net outcome could be a substantial increase in total out-of-pocket expenses to women, especially if the actual fee charged remains at $45 or increases beyond this.

- Any other important areas of uncertainty (e.g. budget impact, translation of clinical evidence into the economic evaluation, linkage between an investigative intervention and a subsequent therapeutic intervention and outcomes?

ESC discussed the issue of whether automated versus manual screening should be referred to in any item descriptor, and advised against this.

ESC was also concerned by the placement of the applicant's suggested insertion to the wording of the relevant explanatory notes because this could imply that the listed professional bodies support CE LBC as a particular technique. As currently written, it is clear that these bodies support the National Policy on Screening for the Prevention of Cervical Cancer rather than any particular test methodology. So although ESC agreed with the objective of the suggested insertion to prevent both CC and CE LBC being rendered on any single occasion, ESC advised that the placement of the proposed insertion should be reconsidered to avoid any inadvertent endorsements. Consideration might be given to reinforcing this message that CC and CE LBC would be alternatives on any one occasion in the item descriptor rather than the explanatory notes.

14. Other significant factors

Not applicable.

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

MSAC noted that there were three previous applications requesting the MBS listing of liquid-based cytology (LBC), with the most recent consideration concluding that LBC was "safe, at least as effective but not as cost effective as conventional Pap smears at the price requested". The fee requested in this application is now the same as that of conventional cytology (CC).

This application for CE LBC is specifically for a BD SurePath™ LBC system, a cell technology which involves the use of a brand specific Density Reagent™ and Prep Stain™.

MSAC accepted some advantages of CE LBC versus conventional cytology (CC). These include the reduction in the number of blood cells, inflammatory cells and non-diagnostic cellular debris in the sample. CE LBC also improves quality and viability of the cells for examination and captures more cells taken at the procedure. It also potentially enables testing for human papilloma virus (HPV), *Neisseria gonorrhoeae*, and chlamydia.

MSAC accepted that, as found by MSAC in 2009 for application 1122, the technique is as safe as CC and there is no basis to conclude a significant clinical difference between CE LBC and cell filtration (CF) LBC and CC.

MSAC understood that the proposed item descriptor excluded CF LBC (ThinPrep™), an alternative LBC method. However, the submission did not provide clinical evidence of the comparative screening performance of CE and CF LBC to justify this mutual exclusiveness.

The submission also requested an amendment of the relevant MBS items to allow for vaginal as well as cervical smears. MSAC concluded that, in the absence of evidence for CE LBC for vaginal smears, there was insufficient basis to support this request.

MSAC agreed that the nominated population eligible for cervical screening with CE LBC, and the nominated primary comparator were both appropriate. The nominated population was as defined for the existing cervical cancer screening program, and the nominated comparator was CC.

MSAC noted that Beerman et al. (2009) was the only new evidence that directly compared CE LBC and CC since the previous MSAC consideration of LBC. MSAC discussed the validity of this study and concluded that there was insufficient information about the methodology of randomisation in this clustered randomised controlled trial, and the methods of analysis were on a per patient basis without adjusting for the clustering effect. In addition, this study provided training to GPs randomised to use CE LBC, but not to GPs randomised to continue with CC, which may explain some of the observed better results for CE LBC. These uncertainties limit the quality and applicability of the data from this new study.

MSAC noted that there is no increase from CC to CE LBC in the detection of cervical intraepithelial neoplasia CIN 2+ and CIN 3+, the high grade cervical squamous intraepithelial lesions (HSIL), which are the clinically significant lesions. MSAC also noted CE LBC has a higher rate of detection of CIN 1+, which is a form that rarely progresses to high grade lesions. In the Australian clinical model, detection of CIN 1+ or atypical squamous cells of undetermined significance (ASCUS) will be subjected to re-test in 12 months, but not to further investigation, such as colposcopy. Therefore, there is little adverse impact on costs. MSAC considered this high rate was of little clinical significance in the Australian context. However, MSAC noted that the higher rate of detection of CIN 1+ could potentially and unnecessarily impact on patient anxiety.

MSAC considered the validity of the economic evaluation from the full health care system perspective (including costs to patients) and concluded that the cost-minimisation analysis (CMA) proposed in the submission was not valid, as the assumption by the applicant that there will be no patient co-payment is not plausible. The submission assumed zero out-of-pocket costs with CE LBC. However, the proposed fee of $19.45 was considered an unrealistic estimate of the fees likely to be charged by laboratories for CE LBC, because the corresponding rebate, together with the patient episode initiation (PEI) rebate, is significantly less than the $25-$50 currently charged. It is likely that the fees charged for MBS-listed CE LBC by laboratories will increase beyond current fees charged for CC. MSAC considered that this is likely to result in increased out-of-pocket payments that will outweigh the claimed offsets leading to the conclusion that the cost-minimisation analysis presented for CE LBC is therefore unlikely. Rather, an increase in overall costs is much more likely, which means that convincing evidence of superiority of CE LBC versus conventional cytology (CC) would need to be presented to inform a cost-effectiveness analysis (CEA).

MSAC raised further concerns regarding the listing of CE LBC due to the increased likelihood of a patient co-payment. The Committee noted that the likely additional charge for CE LBC over CC would be expected to discourage participation in the National Cervical Screening Program (NCSP), particularly in disadvantaged population groups with a lower socioeconomic status, for example the indigenous community. This potential impact is also evidenced by the market research of the use of LBC in different states supplied by the applicant showing a range of costs much higher than the projected rebates for CE LBC. In that research, Victoria had the lowest percentage of the states using LBC, whilst having the highest participation rate in screening nationwide.

MSAC noted the renewal of the NCSP is currently underway through MSAC (Application 1276), and uses CC as the comparator. MSAC noted the uncertainty associated with this as the renewal is considering the entire screening pathway. A further source of uncertainty arises from the unknown effectiveness of HPV vaccination on the rate of cervical cancer and the spectrum of cytological changes. MSAC noted that more extensive data will be available in five years and would likely impact on the NCSP.

For future consideration of LBC listing on the MBS, MSAC advised that further clinical data are needed to directly support the clinical advantages of CE LBC versus CC. A direct comparison between CE LBC and CF LBC is also needed. Evidence of the advantages of HPV DNA testing associated with both approaches to LBC would also be important. MSAC also noted that little evidence is available comparing manual and automated slide reading.

Overall, MSAC noted that the place of LBC (including CE LBC) is in a state of flux, and relevant information from the renewal is not yet available. CE LBC performs similarly to CC according to Beerman et al, the best evidence available. CE LBC and CF LBC are also likely similar, based on a less convincing indirect comparison across randomised trials involving CC as the common reference. From a health care perspective, the likely increased charge by laboratories beyond current bulk billing practice would result in a cost shift to patients. This in turn may result in reduced screening participation rates.

16. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of cell enrichment liquid based cytology (BD SurePath™) for cervical cancer screening, MSAC does not support public funding at this time.

17. Applicant's comments on MSAC's Public Summary Document

BD is pleased that MSAC has reaffirmed its March 2009 conclusion that CE LBC is safe and at least as effective as CC. As BD has now requested public funding of CE LBC at the same price as CC, questions remain as to the MSAC decision not to reimburse.

Note: The applicant has noted and agreed to release this public summary document noting that the Minister is yet to note the MSACs advice. This public summary document is not indicative of any Government decision regarding this MSAC application.

18. Context for decision

This advice was made under the MSAC Terms of Reference.

MSAC is to:

Advise the Minister for Health and Ageing on medical services that involve new or emerging technologies and procedures and, where relevant, amendment to existing MBS items, in relation to:

- the strength of evidence in relation to the comparative safety, effectiveness, cost-effectiveness and total cost of the medical service;
- whether public funding should be supported for the medical service and, if so, the circumstances under which public funding should be supported;
- the proposed Medicare Benefits Schedule (MBS) item descriptor and fee for the service where funding through the MBS is supported;
- the circumstances, where there is uncertainty in relation to the clinical or cost-effectiveness of a service, under which interim public funding of a service should be supported for a specified period, during which defined data collections under agreed clinical protocols would be collected to inform a re-assessment of the service by MSAC at the conclusion of that period;
- other matters related to the public funding of health services referred by the Minister.

Advise the Australian Health Ministers' Advisory Council (AHMAC) on health technology assessments referred under AHMAC arrangements.

MSAC may also establish sub-committees to assist MSAC to effectively undertake its role. MSAC may delegate some of its functions to its Executive sub-committee.

19. Linkages to other documents

MSAC's processes are detailed on the MSAC Website at: www.msac.gov.au.