Medical Services Advisory Committee Public Summary Document

Application No. 1122 – Liquid Based Cytology (LBC)

Sponsors: Cytyc (Australia) Pty Ltd and Becton Dickinson Pty Limited Australia
Date of MSAC consideration: 44th MSAC meeting, 20 March 2009, Canberra

1. Purpose of Application

Liquid-based cytology (LBC) involves collection of cervical cells in a similar way as for conventional Pap, but the head of the brush, broom or spatula is rinsed into a vial of liquid to produce a cell suspension. The cell sample is treated to remove other material, such as blood and mucus, so that a thin layer of cervical cells can be placed on a slide for microscopic examination. Automated cytology refers to the use of a computer imager to scan slides prepared using LBC or conventional techniques. Two systems of automated LBC slide reading are marketed in Australia, the ThinPrep® Imager [Cytyc Pty Ltd] and the FocalPoint Imaging System [Becton Dickinson Pty Ltd]. These systems are used to direct cytologists to the areas on the slide most likely to contain abnormal cells.

2. Background

Applications to MSAC undergo an eligibility step that includes an assessment of the application's compliance with any required Therapeutic Goods Administration (TGA) listing, conformity with MSAC's Terms of Reference and consistency with Government policy.

MSAC receives a report from expert independent evaluators on the strength of the evidence of the safety, effectiveness and cost-effectiveness of the requested procedure and related technology, which is produced under the guidance of an Advisory Panel consisting of MSAC members, clinical experts, and consumer representatives. The applicant is consulted at the initial research protocol stage and at the final draft report stage of the production of this report.

At its 44th MSAC meeting, MSAC considered the strength of the evidence for the safety, effectiveness and cost-effectiveness for LBC compared with manual screening of conventional Pap smear cytology. Members considered the final report of the evaluation of the evidence (as endorsed by the Advisory Panel), the applicant's response and evaluator's rejoinder, as well as presentations/input from the 1st discussant (independent MSAC member), 2nd discussant (MSAC Advisory Panel Chair), and the MSAC Economics Sub-Committee.

The evidence on the use of LBC is available mainly through overseas research and its use in the United Kingdom, Europe, Canada and the United States. Assessment of international research needs to take into account the effectiveness of Australia's cervical cancer screening program, which has halved rates of cervical cancer, and the likely preventive impact of the recently introduced human papilloma virus (HPV) vaccination program.

MSAC agreed to combine consideration of LBC and automated LBC compared to Pap testing with the reference 39 HPV triage for Pap smears.

3. Safety

Liquid based cytology with manual or automation-assisted slide reading uses the same procedure for collecting cervical cell samples as conventional Pap cytology tests and is considered a safe procedure.

4. Clinical effectiveness

No studies have assessed the impact of LBC with manual or automated slide reading on incidence or mortality rates of invasive cervical cancer compared to conventional cytology. The review therefore relied on evidence about the relative accuracy of manual or automated LBC to detect precancerous cervical lesions to draw conclusions about its relative effectiveness. This 'linked evidence' approach is justified by existing evidence that early detection and treatment of precancerous cervical lesions leads to a reduction in the incidence and mortality of cervical cancer.

Manual LBC

High quality systematic reviews and a large randomised trial have indicated that liquid based cytology compared to conventional cytology:

- provides no statistically significant increase in sensitivity or specificity;
- provides no statistically significant difference in sensitivity for high-grade squamous intraepithelial lesions, low-grade squamous intraepithelial lesions or possible low-grade squamous intraepithelial lesions (HSIL, LSIL or pLSIL thresholds) or specificity (HSIL or LSIL thresholds) for the detection of cervical intraepithelial neoplasia (CIN2+);
- reduces the specificity for the detection of CIN2+ at a test threshold of pLSIL;
- classifies more slides as positive for low-grade lesions;
- reduces the rate of unsatisfactory smears; and
- has a high cost-effectiveness ratio which appears to be unfavourable in the current Australian setting.

Automated LBC

There is no evidence of an advantage, disadvantage or equivalence of the accuracy of the Focal Point system compared to conventional cytology. The ThinPrep Imager system compared to manual reading of conventional cytology:

- significantly decreases slide reading time;
- reduces the rate of unsatisfactory smears;
- detects at least as many CIN2+ lesions as conventional cytology, and may detect more; (it is unclear whether any increase in detection of high grade lesions with the ThinPrep Imager system is attributable to LBC alone, to the automation-assisted reading system, or a combination of both); and
- classifies more slides as positive for low-grade lesions.

However, it has a high cost-effectiveness ratio which appears to be unfavourable in the current Australian setting.

Following discussions regarding the sensitivity versus specificity of LBC, equity and the patient pathway and the likelihood of decreasing HPV incidence in the population with the uptake of the HPV vaccine, MSAC members agreed that LBC was as effective as Pap testing.

5. Cost effectiveness

The economic considerations of LBC are also considered in MSAC Reference 39 Human Papilloma Virus Testing (HPV).

The main findings of the economic evaluation are that neither of the technologies under consideration - automated LBC (ThinPrep Imager) and LBC with manual reading - would be cost-effective in the Australian setting at the currently requested level of reimbursement.

Automated LBC was associated with a cost of $194,835 per life year saved. The cost associated with manual LBC varied depending on the level of reimbursement, but ranged from $126,315 per life year saved ($2.40 incremental cost) to $385,982 per life year saved ($10.90 incremental cost).

The findings are sensitive to assumed relative test accuracy, differences in the unsatisfactory smear rate, assumptions about disease natural history (particularly for regression and progression to high grade) and the recommended screening interval. Favourable assumptions were made about the accuracy of the new technologies. Based on these favourable assumptions, both technologies would result in a marginal improvement in life years saved, but this would come at a substantially higher cost, due mainly to direct cytology test costs but also due to follow up costs for an increased number of positive tests.

Net annual costs for manual LBC screening (including management and follow-up) are estimated to range from $173.4 million (when reimbursed at an incremental cost of $2.40) to $189.7 million (when reimbursed at an incremental cost of $10.90). This represents an annual increase of $7.3 million to $23.6 million (or 4 – 14%). Net annual costs for automated LBC (ThinPrep Imager) are estimated as $203.5 million, which represents an annual incremental cost of $37.4 million (or 22.5%).

The economists on MSAC queried the use of a “willingness to pay” threshold for cost per life-year saved in the report and advised that there was no established basis for the use of such a threshold.

MSAC agreed that reference to a “willingness to pay” threshold should be removed from the report as reference to such a value could be misconstrued as Australian Government policy (noting also that the Applicant 2’s response and the Evaluator’s rejoinder mentioned the threshold).

MSAC discussion and formulation of advice on cost effectiveness proceeded on the basis of advice from the Advisory Panel Chair that removal of the reference to a “willingness to pay” threshold would be agreed by the Panel. After the MSAC meeting the Secretariat sought the Advisory Panel’s agreement to remove the reference to a willingness-to-pay threshold from the report, before providing MSAC’s advice and final report to the Minister.

6. Rationale for MSAC’s Advice

The collection of cervical cytology samples into an LBC medium provides the opportunity for reflex testing of a range of pathogens, including Human Papilloma Virus (HPV), *Chlamydia trachomatis* or *Neisseria gonorrhoeae* which is discussed in MSAC Reference 39 - HPV testing.

There is an increasing shortage of trained cytotechnologists in Australia. Technologies which decrease cytology slide screening time and increase productivity may aid in addressing workforce shortages by decreasing staff requirements. With the recent introduction of the HPV vaccine in Australia, the expected impact is a decrease in the prevalence of HPV and pre-cancerous cytological abnormalities and also alteration of the distribution of cytological abnormalities, further increasing technical difficulties for cytotechnologists manually screening slides.

It was noted that evidence on the use of LBC is available mainly through overseas research, noting its use in the United Kingdom, Europe, Canada and the United States. Assessment of international

research needs to take into account the effectiveness of Australia's cervical cancer screening program which has halved rates of cervical cancer, and the likely preventive impact of the recently introduced Human Papilloma Virus (HPV) vaccination program.

With respect to Liquid Based Cytology (LBC), MSAC finds that in comparison to the Papanicolaou (Pap) test that LBC:

- is safe,
- is at least as effective,
- is not cost effective at the price requested.

MSAC advises that LBC not be supported for public funding.

With respect to automated (computerised) testing of LBC specimens, MSAC finds that in comparison to the Papanicolaou (Pap) test Automated LBC testing:

- is safe,
- is at least as effective,
- is not cost effective at the price requested.

MSAC advises that automated testing of LBC specimens not be supported for public funding.

MSAC notes that this technology is used in several laboratories for reasons such as quality assurance, recruitment and retention and occupational health and safety. MSAC supports the use of these technologies for these reasons but does not support additional public funding at this time.

7. Context for Decision

This advice was made under the MSAC Terms of Reference:

- 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 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.
- Undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to the AHMAC.

8. Linkages to Other Documents

The MSAC Advisory Panel Report is available at
http://www.msac.gov.au/internet/msac/publishing.nsf/Content/MSACCompletedAssessments1121-1143