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Original Article

An alternative cost effectiveness analysis of ThinPrep in the Australian setting

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Abstract

Objective: To assess the clinical and economic impacts of the use of liquid based cytology (LBC) in the Australian average risk population from the perspective of the public health care budget.

Background: Concerns over the evaluation of medical technologies in Australia, which are assessed by the Medicare Services Advisory Committee (MSAC), have been raised recently. We report on the evaluation of LBC, which although being widely adopted in other parts of the world, has, despite substantial uptake in the private sector in Australia, been rejected for public funding by MSAC.

Methods: We used the health economic model developed by MSAC, but populated the model with the best available international data, sourced from a published review article. The economic model considered the clinical benefits and the costs arising from a biennial cervical screening programme. Net costs divided by life years saved is the cost per life year saved and this is reported as the incremental cost effectiveness.

Results: Populating the MSAC model with data on test performance showed that one type of LBC (ThinPrep) 'dominates' the conventional Pap smear in the screening of average risk women in the Australian setting.

Conclusion: The health economic model created by MSAC predicts that ThinPrep dominates the conventional Pap as a screening test for cervical cancer. An additional 2240 high-grade lesions could be detected, resulting in 480 life years gained and delivering an expected saving to the health care system of $5 536 000 per annum if liquid based cytology replaced the conventional Pap.

Key words: cervical histology, cost-benefit analysis, cytology, Pap smear, ThinPrep.

Introduction

Concerns over the transparency of the evaluation of pharmaceuticals by the Pharmaceutical Benefits Advisory Committee (PBAC) and related processes have been raised and addressed as part of the Free Trade Agreement with the USA.[1] Recently, the practices of a similar government body, the Medicare Services Advisory Committee (MSAC), have been criticised for failing to meet its terms of reference for poor science, poor process and unique decision-making benchmarks in its evaluation of positron emission tomography (PET).[2] Ware *et al.* concluded that evaluation of evidence by MSAC of PET was fundamentally compromised and the use of inferior-quality information for decision-making was likely to harm rather than enhance healthcare outcomes. The free trade agreement (FTA) will not address these latter concerns and, without changes to the processes followed, perceived problems with MSAC will continue to arise. We report on the MSAC evaluation of another health care technology – liquid based cytology (LBC) – that has been widely adopted in other parts of the world, but which, despite substantial uptake privately, has not been accepted for public funding in Australia.

In 2002, MSAC undertook their evaluation of LBC for cervical screening, which included the development of a decision analytic model to determine the cost effectiveness of LBC in the Australian setting. In their evaluation, MSAC concluded from their review of the literature[3] that:

> 'There is insufficient evidence to enable us to draw conclusions regarding the diagnostic characteristics of LBC and Pap smears for cervical screening'.

This is a conclusion that was and is still contested by Cytyc (manufacturers of one LBC technology, ThinPrep) and others, as there is substantial evidence of ThinPrep test's superiority compared with the conventional Pap.[4–6]

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However in their evaluation, MSAC go on to state that:

> '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'.

MSAC also pointed out that they considered that there were a number of limitations of the studies of LBC, including:

> 'Limitation of having applied the reference test only to those who tested positive on either screening test made interpretation difficult' and 'many of the clinical studies examined were funded partially or completely by manufacturers of LBC technologies'.

These comments and suggestions by MSAC indicate that the level of evidence required for public funding of LBC exceeds that which is usually available in such circumstances and could be sufficiently excessive to preclude public funding of LBC in Australia. Furthermore, such stringent requirements around the introduction of new pharmaceuticals into Australia would preclude any new drugs becoming available to the Australian public. Because of these flaws, we believe that data on test performance were either ignored or not accepted and that, if the *modus operandi* of the evaluation process is unchanged, there is little chance of reversing the original decision.

We contend that the requirements of MSAC are unrealistic, and indeed even unethical, particularly if there continues to be a requirement for histological verification of negative smears (which would imply taking a biopsy from a normal cervix). Given earlier criticisms of MSAC, delay or avoidance of funding could be the desired goal of Government.[2]

Thus, we aimed to assess the clinical and economic impacts of the use of one form of LBC, ThinPrep, in the Australian average risk population eligible for screening using the best available data and according to requirements stipulated in the MSAC guidelines.

Methods

Since the MSAC evaluation, additional data has been released on the effectiveness of LBC and one such LBC method in particular, ThinPrep (Cytyc Corporation, Boxburgh, USA). In the UK, the National Institute for Clinical Excellence (NICE, a sister body to Australia's MSAC) sponsored a large scale clinical trial in the NHS of LBC and released its findings on 24 September, 2003 which has resulted in LBC being recommended as the primary means of processing samples in the England and Wales cervical screening program.[7] In addition to the National Health Service (NHS) trial in the UK, others have published results of new primary and secondary research. Limaye *et al.* reported on a retrospective analysis of conventional and ThinPrep Pap tests and concluded that ThinPrep is a superior screening test in the detection of precancerous changes of the cervix.[5] Abulafia *et al.* undertook an evaluation of 24 English-language articles (from a total of 47 identified in their Medline search).[8] This

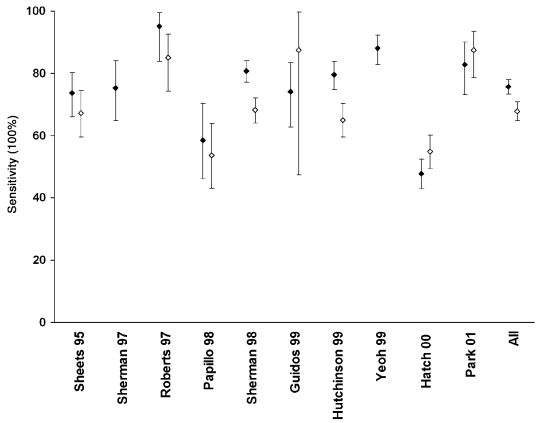

Figure 1 Sensitivity of ThinPrep and conventionally prepared Papanicolaou smears, each versus a gold standard. (◆) ThinPrep; (◇) Conventional.

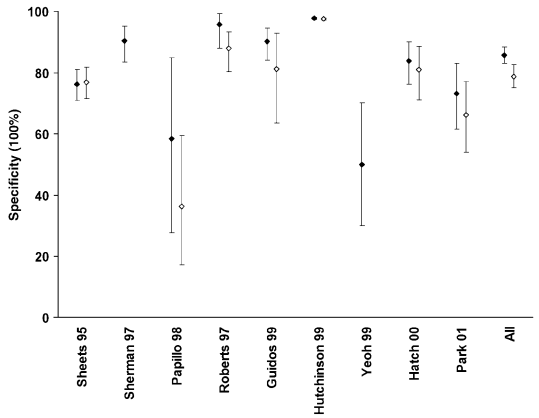

Figure 2 Specificity of ThinPrep and conventionally prepared Papanicolaou smears, each versus a gold standard. (◆) ThinPrep; (◇) Conventional.

report relates well to MSAC's key concerns with ThinPrep – the Pap and ThinPrep tests' sensitivity and specificity (Figs 1 & 2), as 10 of the articles compared cytology with histology or other gold standard diagnoses for 21 752 patients.

Thus, the results from the quantitative survey by Abulafia, Pezzullo and Sherer were incorporated into the health economic model produced by MSAC as part of their 2002 evaluation of LBC (Fig. 3). Two key assumptions made by the MSAC evaluators in creating their model were the tests' sensitivity and specificity and these assumptions were replaced with data derived from the Abulafia study. Modelling was undertaken using the standard decision analytic techniques and software (DATA PRO, TreeAge Inc, Mass) that the MSAC evaluators used in their earlier work. Despite shortcomings in the model developed by the MSAC to evaluate LBC, we used the same model structure in our revised evaluation, as we considered that this would be the least contentious approach for the Government in displaying the benefits of LBC. Given the comments by the MSAC regarding company involvement in the clinical trials of LBC, we sought to minimise any further bias that government decision makers

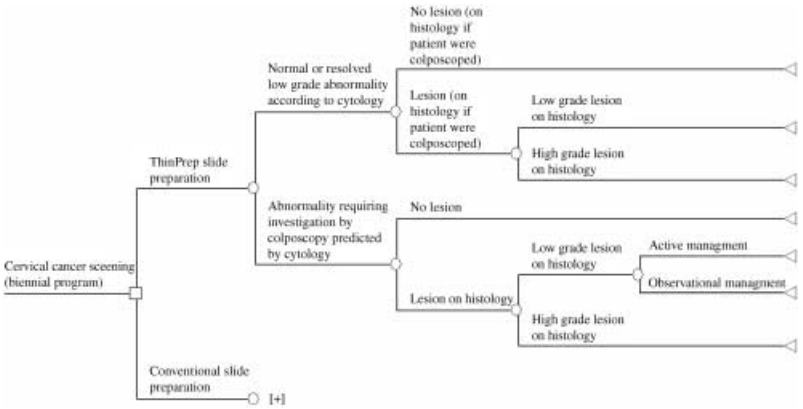

Figure 3 Medical Services Advisory Committee (MSAC) health economic model.

might have in the results of this revised evaluation. Thus the model used in this evaluation was the Government-sponsored one and not a company-sponsored one.

The primary endpoints adopted by MSAC were used in our evaluation, viz cost per high-grade lesion detected and cost per woman screened. The secondary endpoints used by MSAC (cost per extra case of cancer avoided and cost per additional life-year saved) were also assessed. To derive the latter two outcomes, MSAC used simple extensions of the model to derive indicative values. The assumption used was that 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 2-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. MSAC assumed that 4% of high grade lesions would progress to cancer over the 2-year cycle of the screening program and that a high-grade lesion detected would result in a discounted gain of 6 life-years.

The MSAC estimate that 4% of high grade lesions would be, or would progress to, cancer over 2 years was obtained by considering that between 2 and 3% of high grade lesions detected would be invasive cancer (MSAC, Tables 3 and 4[3]) 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%.[9]

The estimate that 6 life-years will be gained by avoidance of an invasive cancer was deduced by the MSAC from data provided in Cervical Screening in Australia 1997–1998 that the average age of diagnosis of cancer was approximately 52 years. From these data, MSAC also calculated that the average age of death of a woman with cancer of the cervix was 63 years. If the normal life expectancy of a woman aged 52 years is an additional 33 years (taken from life expectancy tables), 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 (i.e. 21 years). Discounting these years (which do not occur for another 11 years) at 5% per annum results in a maximum gain of approximately 8 life years. However, the MSAC stated that actual value for life years gained is likely to be lower as detection of a high-grade abnormality was unlikely to result in 100% aversion of cervical cancer, so a gain of 6 life-years was used by MSAC in the analysis.[3]

In the model, the mean values of sensitivity and specificity stated in the Abulafia study were used. The cost of ThinPrep used in the model was $30.50, which is consistent with the price used and explained in Cytyc's application to the MSAC – the approach adopted a conservative cost plus approach, where the approximate average laboratory cost per Pap test was estimated from financial accounts of the Victorian Cytology Service, a government-run institution, to which the cost of LBC consumables were added. The resource variables included in the analysis are summarised in Table 1, taken directly from the MSAC report. Other than those related to test sensitivity and specificity, all other variables in the model remain unchanged from the MSAC values (tables 21–28 of MSAC report[3]).

The incremental cost effectiveness ratio (ICER) of ThinPrep compared with the conventional Pap was determined, where the ICER is where the incremental benefits are compared with the incremental costs, according to the following equation:

$$\text{ICER} = (\text{Cost of ThinPrep} - \text{Cost of Pap})/(\text{Benefit of ThinPrep} - \text{Benefit of Pap}) \quad (1)$$

Table 1 Resource variables included in model

Description	Conventional cytology arm ($)	Liquid-based cytology arm ($)
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	1021.25	1055.75

To test the robustness of the model's results, we undertook a sensitivity analysis (a Montecarlo analysis) using the approximate 95% confidence intervals for sensitivity and specificity for each test from figures in the Abulafia paper. For the conventional Pap test, we used the values mean 68% ± 2.6% for test sensitivity and mean 79% ± 2.8% for test specificity. For the ThinPrep test, we used the values mean 76% ± 1.4% for test sensitivity and mean 86% ± 2.4% for test specificity. These values were then defined as distributions within the TreeAge model and a Montecarlo analysis undertaken, to demonstrate the confidence with which the ICER of ThinPrep can be assumed to be correct. In their analysis, MSAC implied that the maximum ICER acceptable for public funding decisions would be $40 000 per life year gained (LYG).[3] In our sensitivity analysis, we used this same maximum ICER.

Results

Updating the MSAC model's assumptions with new data showed that ThinPrep 'dominated' the conventional Pap smear in the screening of average risk women in the Australian setting (Table 2). Domination is the term used in health economic evaluations when a test, procedure or intervention is both more effective and less expensive than the comparator.

When the assumptions regarding test sensitivity and specificity are replaced with the data from the Abulafia review, the MSAC model predicts that an additional 0.0014 high-grade lesions would be detected per woman screened per 2-year screening cycle, which would result on average in 0.0003 life years gained. If 1.6 million women were to participate in the biennial screening program per annum (i.e. a total of 3.2 million participants every 2 years – in line with Australian Institute of Health and Welfare data[10]), then this translates into an incremental 2240 high-grade lesions detected and 480 life-years gained. The MSAC model also predicts a cost saving to the health care system from the use of ThinPrep of $3.46 per high-grade lesion detected, which could amount to $5 536 000 per annum.

As we did not change the fundamental structure of the MSAC model (like MSAC, we assigned no value to detecting a low grade lesion and the perspective adopted was that of the health care system rather than a societal one), it is likely that the model will underestimate the true benefits, and thus the ICER, of ThinPrep.

The results of the Montecarlo analysis are displayed in Figures 4 and 5. Each dot represents one outcome from the analysis, the oval represents the 95% CI for the ICER and the dashed line is the $40 000 per life-year gained threshold, or willingness to pay line (WTP). From the model, it can be predicted that ThinPrep would dominate the conventional Pap on almost 74% of occasions, and would provide an acceptable ICER in another 25% of occasions. The use of ThinPrep would not be cost effective in less than 1% of occasions, which are represented by the dots that lie above the dotted WTP line.

Table 2 Medical Services Advisory Committee (MSAC) Health Economic Model output with revised test sensitivities and specificities – cost per high-grade lesion detected and cost per life year gained (LYG)

Strategy	Cost	Incremental Cost	Effectiveness (cases detected)	Incremental Effectiveness (cases detected)	Cost/ Effectivenes ($ per case detected)	Incremental Cost/ Effectiveness	Effectiveness (cases detected)	Incremental Effectiveness (life years gained)	Cost/ Effectiveness ($ per LYG)	Incremental Cost/ Effectiveness
ThinPrep slide preparation	$143.80		0.0131 cases detected		$10 940		0.0032 LYG		$A45 583	
Conventional slide preparation	$147.27	$3.46	0.0118 cases detected	0.0014 cases detected	$A12 521	(Dominated)	0.0028 LYG	(0.0003 LYG)	$52 172	(Dominated)

LYG, life year gained.

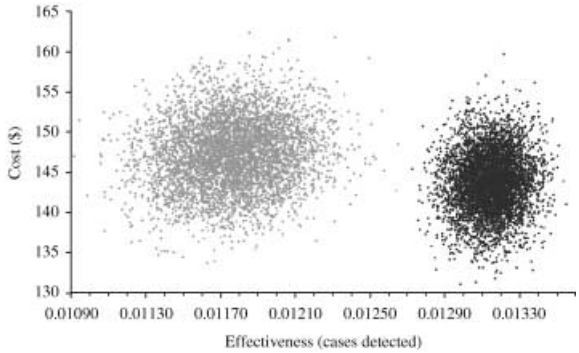

Figure 4 Cost effectiveness scatterplot for the conventional Pap and ThinPrep, cost per high grade lesion detected. (●) ThinPrep slide preparation; (●) Conventional slide preparation.

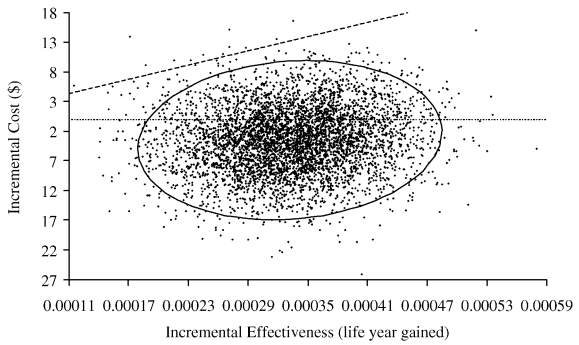

Figure 5 Incremental cost effectiveness scatterplot for the conventional Pap and ThinPrep, cost per life year gained.

Discussion

When the health economic model created by MSAC includes test sensitivities and specificities derived from a review article comparing cytology with histology or other gold standard diagnoses, ThinPrep dominates the conventional Pap as a screening test for cervical cancer. Health care outcomes from the cervical cancer screening programme (lesions detected and deaths averted) would be substantially improved with large financial savings to the health care budget. However, the MSAC model (and hence, our modelled evaluation) is likely to underestimate the true benefits of LBC, as it ignores the benefits from detecting low grade lesions and does not take a societal perspective.

In their health economic evaluation of LBC, MSAC implicitly assumed that there was no value in detecting low grade cervical lesions, as these lesions have no cost implications to the health care system – the rationale being that such lesions would resolve spontaneously or be picked up at subsequent screening episodes should they progress to higher grade lesions. This is contested on two counts.

First, a societal perspective is better adopted in an economic evaluation of health technologies. This is acknowledged in the MSAC Guidelines,[11] which state that:

> 'For the purpose of these guidelines, a societal perspective should be adopted'.

The majority of women who are currently paying 'at least $30'[12] for ThinPrep in Australia are women participating in the national screening programme, the majority having no abnormality. Of those with an abnormality, the prevalence of low grade lesions is eight times more than high grade lesions.[3] Ignoring the benefits and valuation of the product to the majority of the population (i.e. those women who participate in the screening programme but have either no lesions or a low grade lesion) cannot reflect a true societal perspective in an economic evaluation. Second, data supplied by the State and Territory Cervical Screening Registries to MSAC showed that 26% of women with a cytological diagnosis of CIN I (one type of low grade lesion) actually have a diagnosis of CIN II or higher by histology, representing a high-grade rather than a low-grade lesion.[3]

Furthermore, the recent controversies that surround the forthcoming National Health and Medical Research Council Guidelines for Cervical Cancer Screening suggests that many in the medical community at large believe there is value in detecting low grade lesions.[13] In an article, the president of the Australian Society for Colposcopy and Cervical Pathology is quoted as saying that these concerns reflected a 'widespread concern by well-informed clinicians and colposcopists'.

However, the new data used in the revised model, including the data generated from the NICE study, would still be criticised by MSAC, as they constitute level 3 evidence with cohort controls, have not applied the reference test to all screening participants, and funding in many was partially or completely provided by manufacturers of LBC technologies. Thus, although MSAC's own model predicts superior health outcomes and cost savings to the health care budget, the processes required by the MSAC evaluation make public funding of LBC unlikely. Action is required to change the evaluation of health technologies, which should provide access to cost effective health care for Australians. Although the Chair of the MSAC recently announced an examination of 'the way it responds to its terms of reference' was to take place, and that the MSAC would report to the Federal Minister for Health and Ageing sometime in 2005, it is unlikely that an internal review of MSAC would be sufficiently robust to correctly identify the issues to be addressed.

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