Health Technology Assessment 2004; Vol. 8: No. 20

Liquid-based cytology in cervical screening: an updated rapid and systematic review and economic analysis

J Karnon, J Peters, J Platt, J Chilcott,
E McGoogan and N Brewer

May 2004

Health Technology Assessment
NHS R&D HTA Programme

How to obtain copies of this and other HTA Programme reports.
An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (http://www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

– fax (with **credit card** or **official purchase order**)
– post (with **credit card** or **official purchase order** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you **either** to pay securely by credit card **or** to print out your order and then post or fax it.

Contact details are as follows:

HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK

Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can only be purchased for the current or forthcoming volume.

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *Direct Mail Works Ltd* and drawn on a bank with a UK address.

Paying by credit card
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of *HTA on CD*?

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. *HTA on CD* is currently free of charge worldwide.

The website also provides information about the HTA Programme and lists the membership of the various committees.

Liquid-based cytology in cervical screening: an updated rapid and systematic review and economic analysis

J Karnon,[1*] J Peters,[1] J Platt,[2] J Chilcott,[1] E McGoogan[3] and N Brewer[1]

[1] The School of Health and Related Research (ScHARR), The University of Sheffield, Sheffield, UK

[2] The Royal Hallamshire Hospital, Sheffield, UK

[3] University of Edinburgh and Patient Services Director Pathology, Lothian University Hospitals NHS Trust, UK

* Corresponding author

Declared competing interests of authors: none of the authors has any financial interest in any of the companies producing products for liquid-based cytology. Dr McGoogan has received research funding from AutoCyte Inc. and Cytyc Corporation for studying the properties of their products.

Published May 2004

This report should be referenced as follows:

Karnon J, Peters J, Platt J, Chilcott J, McGoogan E, Brewer N. Liquid-based cytology in cervical screening: an updated rapid and systematic review and economic analysis. *Health Technol Assess* 2004;**8**(20).

Health Technology Assessment is indexed in *Index Medicus*/MEDLINE and *Excerpta Medica*/EMBASE.

NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The HTA programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, consumer groups and professional bodies such as Royal Colleges and NHS Trusts.

Research suggestions are carefully considered by panels of independent experts (including consumers) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or designing a trial to produce new evidence where none currently exists.

Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a limited time period.

Criteria for inclusion in the HTA monograph series
Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this monograph was commissioned and funded by the HTA Programme on behalf of NICE as project number 02/27/01. The authors have been wholly responsible for all data collection, analysis and interpretation and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme, NICE or the Department of Health.

ISSN 1366-5278

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.

T

Abstract

Liquid-based cytology in cervical screening: an updated rapid and systematic review and economic analysis

J Karnon,[1*] J Peters,[1] J Platt,[2] J Chilcott,[1] E McGoogan[3] and N Brewer[1]

[1] The School of Health and Related Research (ScHARR), The University of Sheffield, Sheffield, UK

[2] The Royal Hallamshire Hospital, Sheffield, UK

[3] University of Edinburgh and Patient Services Director Pathology, Lothian University Hospitals NHS Trust, UK

* Corresponding author

Objectives: To update an earlier published report reviewing the effectiveness and cost-effectiveness of liquid-based cytology (LBC).

Data sources: Electronic bibliographic databases, relevant articles, sponsor submissions and various health services research-related resources.

Review methods: The selected data were reviewed and assessed with respect to the quality of the evidence. Pooled estimates of the parameters of interest were derived from the original and the updated studies. Meta-analyses were undertaken where appropriate. The mathematical model developed for the original rapid review of LBC was adapted to synthesise the updated data to estimate costs, survival and quality-adjusted survival of patients tested using LBC and using Papanicolaou (Pap) smear testing. Cost data from published sources were incorporated into the above model to allow economic, as well as clinical, implications of treatment to be assessed. The primary incremental cost-effectiveness ratio is the cost per life year gained (LYG), although estimates of the cost per quality-adjusted life-year (QALY) gained are also presented. A sensitivity analysis was undertaken to identify the key parameters that determine the cost-effectiveness of the treatments, with the objective of identifying how robust the results of the economic analysis are, given the current level of evidence.

Results: From the evidence available, it is likely that the LBC technique will reduce the number of false-negative test results. Modelling analyses undertaken as part of this study indicate that this would reduce the incidence of invasive cancer. There is now more evidence to support improvements emanating from the use of LBC screening in terms of a reduced number of unsatisfactory specimens and a decrease in the time needed to obtain the smear samples. The estimated annual gross cost of consumables and operating equipment, and other one-off conversion costs associated with introducing the new technique, will be between £17 and £38 million in England and Wales, depending on the LBC system and the configuration of the service. Analyses based on models of disease natural history, conducted in this study, showed that conventional Pap smear screening was extendedly dominated by LBC (LBC was always more cost-effective than conventional Pap smear testing over the same screening interval). Comparing LBC across alternative screening intervals gave a cost-effectiveness of under £10,000 per LYG when screening was undertaken every 3 years. The cost-effectiveness results were relatively stable under most conditions, although if screening outcomes such as borderline results and colposcopy are assumed to induce even small amounts of disutility then LBC screening at 5-yearly intervals may be the most cost-effective option.

Conclusions: This updated analysis provides more certainty with regard to the potential cost-effectiveness of LBC compared with conventional Pap smear testing. However, there is uncertainty regarding the relative effectiveness (and cost-effectiveness) of the two main LBC techniques. Further research in the area of utility assessment may be worthwhile and possibly a full cost-effectiveness study of LBC based on a trial of its introduction in a low-prevalence population, although the results of the modelling analysis provide a robust argument that LBC is a cost-effective alternative to conventional cervical cancer screening. A randomised comparison of the two main techniques may also be useful.

Contents

List of abbreviations

AGUS	atypical glandular cells of uncertain significance
AHCPR	Agency for Health Care Policy and Research, USA
ASCUS	atypical squamous cells of uncertain significance
CCTR	Cochrane Controlled Trials Register
CDSR	Cochrane Research of Systematic Reviews
CI	confidence interval
CIN	cervical intraepithelial neoplasia
CIS	carcinoma *in situ*
DARE	Database of Assessments of Reviews of Effectiveness
Ext. dom.	extendedly dominant
FDA	Food and Drug Administration
FIGO	International Federation of Obstetrics and Gynaecology
FNR	false-negative rate
HGIL	high-grade glandular intraepithelial lesion
HPV	human papilloma virus
HRG	Health Resource Group
HSIL	high-grade squamous intraepithelial lesion
HSIL+	high-grade squamous intraepithelial lesion and carcinoma
IC	invasive cancer
ICER	incremental cost-effectiveness ratio
LBC	liquid-based cytology
LSIL	low-grade squamous intraepithelial lesion
LSIL+	low-grade squamous intraepithelial lesion as well as higher grade lesions
LYG	life-year gained
NHSCSP	NHS Cervical Screening Programme
NHS EED	NHS Economic Evaluations Database
NICE	National Institute for Clinical Excellence
NRR	National Research Register
Pap	Papanicolaou
PCT	Primary Care Trust
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RR	relative risk
SIL	squamous intraepithelial lesions

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

This report presents the results of a review of effectiveness and cost-effectiveness that updates an earlier published report with the same objectives, published in January 2000.

Epidemiology and background

Around 4 million women per annum in England have a cervical screening test. Currently the age-standardised incidence of cervical cancer is around 9 per 100,000 per annum. The mortality rate in 1997 was 3.7 per 100,000 per annum.

Liquid-based cytology (LBC) is a new method of preparing cervical samples for cytological examination. Unlike the conventional 'smear' preparation, it involves making a suspension of cells from the sample and this is used to produce a thin layer of cells on a slide. The new intervention would thus form part of the process of population screening to reduce the incidence of invasive cervical cancer.

Methods

This review updates the original HTA rapid review of LBC (Payne *et al. Health Technol Assess* 2000;**4**(18):1–73) to reflect any new evidence, including the results of the pilot studies implemented as a result of the previous review. The data extracted from the relevant literature searches were reviewed and assessed with respect to the quality of the evidence. Pooled estimates of the parameters of interest were derived from the original and the updated studies. Meta-analyses were undertaken where appropriate.

The mathematical model developed for the original rapid review of LBC was adapted to synthesise the updated data to estimate costs, survival and quality-adjusted survival of patients tested using LBC and using Papanicolaou (Pap) smear testing.

Cost data from published sources, if available, or derived from published or other sources of resource and cost data were incorporated into the above model to allow economic, as well as clinical, implications of treatment to be assessed. The primary incremental cost-effectiveness ratio is the cost per life year gained (LYG), although estimates of the cost per quality-adjusted life-year (QALY) gained are also presented.

A sensitivity analysis was undertaken to identify the key parameters that determine the cost-effectiveness of the treatments, with the objective of identifying how robust the results of the economic analysis are, given the current level of evidence.

Results

There were no randomised trials using an outcome such as invasive cancer or mortality as outcome measures. A few studies attempted to compare the sensitivity and specificity of the existing technique with LBC by using a histological examination gold standard. Most comparisons were split-sample studies comparing cytological results.

From the evidence available, it is likely that the LBC technique will reduce the number of false-negative test results. Modelling analyses undertaken as part of this study indicate that this would reduce the incidence of invasive cancer. There is now more evidence to support improvements emanating from the use of LBC screening in terms of a reduced number of unsatisfactory specimens and a decrease in the time needed to obtain the smear samples.

The estimated annual gross cost of consumables and operating equipment, and other one-off conversion costs associated with introducing the new technique, will be between £17 and £38 million in England and Wales, depending on the LBC system and the configuration of the service.

No UK-based studies providing direct evidence regarding the cost-effectiveness of LBC screening were identified. Analyses based on models of disease natural history, conducted in this study, showed that conventional Pap smear screening was extendedly dominated by LBC (LBC was always

more cost-effective than conventional Pap smear testing over the same screening interval). Comparing LBC across alternative screening intervals gave a cost-effectiveness of under £10,000 per LYG when screening was undertaken every 3 years. The cost-effectiveness results were relatively stable under most conditions, although if screening outcomes such as borderline results and colposcopy are assumed to induce even small amounts of disutility then LBC screening at 5-yearly intervals may be the most cost-effective option.

Recommendations for research

The sensitivity analyses undertaken around hypothesised utility values in order to generate preliminary estimates of cost-effectiveness with respect to QALYs gained showed that such factors could influence the choice of screening programme. Therefore, further research may be worthwhile in the area of utility assessment, particularly with respect to the short-term impact of false-positive screen results.

This updated analysis provides more certainty with regard to the potential cost-effectiveness of LBC compared with conventional Pap smear testing. A full cost-effectiveness study of LBC based on a trial of its introduction in a low-prevalence population would provide more definitive information than is possible by modelling studies, although the results of the modelling analysis provide a robust argument that LBC is a cost-effective alternative to conventional cervical cancer screening, such that the large expenditure required to fund a trial is probably not justified. However, there is uncertainty regarding the relative effectiveness (and cost-effectiveness) of the two main LBC techniques, ThinPrep® and PrepStain®, and a randomised comparison of these two techniques may be worthwhile.

Other important issues regarding implementation

It is clear that increasing coverage of the cervical screening programme is also an important way of reducing the burden of invasive cervical cancer. Given the low cost-effectiveness ratios for moving from no screening to any form of screening, it is likely that any effective intervention aimed at increasing coverage will be a cost-effective use of resources. Such interventions will also be equitable, as non-uptake of a screening programme is likely to be due to inequities in access to healthcare (whether they be defined as differences in the relative costs of screening, or through inequities in education or health information).

In addition, a range of economic evaluations was identified in the updated systematic search (1999–2002) that assessed the economic impact of cervical screening approaches other than conventional Pap smear testing and LBC techniques, including semi-automated slide analysis, human papilloma virus testing as an adjunct or alternative to Pap smear testing, and protocols for the management of atypical screening results.

The aggregate analysis of the cost-effectiveness of potential combinations of these approaches to screening for cervical cancer is outside the scope of this review, although it is noted that the relative cost-effectiveness of all relevant screening programme configurations should be analysed simultaneously.

Chapter 1

Aim of the review

Liquid-based cytology (LBC) is one of a number of current developments in screening technology, and has been described as the one most likely to have an early impact on the NHS. Potentially the technique should improve the quality and readability of the slides, thus reducing the number of false negatives and inadequate slides. It would, however, involve significant capital investment, reorganisation of the service and significant running costs.

The current report is intended to update an earlier HTA report, published in January 2000,[1] which addressed the following question: 'What is the effectiveness and cost-effectiveness of liquid-based cytology for cervical screening compared with conventional smear testing?'

Guidance from the National Institute for Clinical Excellence (NICE) published on the basis of the earlier report concluded that, although LBC "could provide significant and important benefits … [The] quality of the evidence is variable and … there is insufficient evidence to justify the nationwide introduction of LBC technology at this time". Instead, the NICE Appraisal Committee recommended the undertaking of a series of pilot implementation projects to investigate the feasibility of LBC in terms of workload, productivity and detection rates. The evaluation of the introduction of LBC at these pilot sites updates important sections of the modelling analysis used to inform the cost-effectiveness of LBC.[2] In addition, an independent evaluation of a similar series of pilot studies, completed in Scotland,[3] and an updated systematic review of the literature, are used to update the analysis of effectiveness and cost-effectiveness.

Chapter 2
Background

Description of the underlying health problem

The incidence of and mortality from cervical cancer have fallen by more than 40% since the NHS Cervical Screening Programme was implemented in 1988. It has been suggested that the observed changes in incidence and mortality may, in part, be attributable to a cohort effect, with cohorts born before 1935 and those born in the 1980s onwards having a lower underlying risk than those born in the 1960s.[4] The age-standardised incidence of invasive cervical cancer in England in 1997 was estimated to be 9.3 per 100,000 per annum[5] and recent trends are shown in *Table 1*. There has been a reduction in incidence during the 1990s since the peak incidence of the mid to late 1980s.

Mortality from cervical cancer has been falling in England by 1–2% each year from the mid-1950s. Following the introduction of the organised screening programme in 1987/88 the fall has accelerated and is now about 7% per annum (*Table 1*). In 1997, therefore, the age-standardised mortality rate was 3.7 per 100,000 per annum.[5]

Significance in terms of ill-health

For an average primary care trust (PCT) of 100,000 population there are around six incident cases of invasive cervical cancer each year and about three deaths each year. There will, however, be large numbers of women needing to be screened, and substantial numbers of these would need further examination and treatment for premalignant disease. Some indication of these numbers will be given in the following section.

Current service provision

Currently a nationwide cervical screening programme is in place. Women aged 20–64 years are invited to be screened (although coverage figures are usually estimated from the 25–64-year age group)[6] and the national policy is that eligible women should be screened every 3–5 years. In 2000/01 in England 3.6 million women were screened, the majority (2.4 million) after a formal invitation from the screening programme. Coverage was relatively high, at 83% of women (i.e. the proportion less than 5 years since their last test). In that time, laboratories examined an estimated 4.1 million smears.[6] Coverage has increased substantially in the past decade, from a figure of only 22% in 1987/88.[6]

Screening at present involves taking a sample of cells from the cervix uteri obtained under direct vision using a vaginal speculum. Usually a spatula broom-type device or a cyto-brush is used to sweep around the cervix and take a sample of cells. After the sample has been taken, the method in current use is to 'smear' the material onto a glass slide, which is then rapidly sprayed with or immersed in a fixative solution to preserve the cells. This slide is sent to the laboratory where it is stained and then examined by a cytologist. The microscopic examination of these smears takes around 4–10 minutes (to screen one slide) and is often repeated by a second cytologist. The staining using the Papanicolaou method, has resulted in the technique being known as the 'Pap' test. It is important to emphasise the need for a high degree of training for all staff involved.[5] A quality-assurance programme has been introduced with guidelines for clinical practice and programme management.[7]

TABLE 1 *Age-standardised incidence and mortality from cervical cancer, England*

Year	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997
Mortality	7.0	6.9	6.7	6.4	6.4	6.1	6.2	6.5	6.1	6.1	5.6	5.5	5.0	4.9	4.7	4.1	4.1	4.0	3.7
Incidence	14.5	15.0	15.1	14.7	14.6	15.0	16.2	15.9	15.6	15.9	14.6	15.2	12.7	12.2	11.1	10.9	10.3	–[a]	9.3[a]

Rates per 100,000 per annum, directly age standardised using the European standard population.
[a] Incidence was not given for 1996 and the 1997 value is an estimate.[5]

Women who have negative smears and no signs of abnormality will be invited for rescreening in 3–5 years. Those in whom abnormalities are detected are managed according to the degree of cellular abnormality detected. This can range from a repeat smear in a reduced period to referral for colposcopy and biopsy. Treatment is then in accordance with the result of the colposcopy examination and biopsy.

Currently (data for England, 2000/01) about 8–9% of smears are considered 'abnormal' (any grade). Some 2.4% show mild dyskaryosis, but 0.91% show moderate dyskaryosis, and 0.73% show severe dyskaryosis or worse.[6] Women with changes in these latter two categories are referred for immediate colposcopy.[8] Women with changes in the first category are referred if the abnormality persists on a repeat smear. Although the proportion of smears showing any abnormality has been increasing during the 1990s, the proportion of those with severe dyskaryosis has remained fairly steady during this period.[5]

An increasing proportion of smears are reported as 'inadequate', that is unable to be interpreted. They may be too thick or too thin; obscured by inflammatory cells or blood, incorrectly labelled; or fail to contain sufficient numbers of the right type of cells. In these cases the woman is recalled so that the smear can be repeated. Around 9% of smears are reported as inadequate.[8]

Some indication of the scale of the cervical screening programme is given in *Table 2*.

Patients having repeat smears fall into two groups: those whose first smear was technically inadequate, and those whose smears are repeated after a shorter interval because of concerns about possible abnormalities (borderline and mild dyskaryosis). These women are asked to attend for repeat smears at reduced time intervals and only when two are consecutively negative do they return to the normal screening interval.[7]

Limitations of cervical screening testing methods

Like all screening tests, the cervical smear or any new cytological methods are not perfect tests. Thus, in considering a new screening methodology it is important to consider its limitations alongside those of existing methods.

Sensitivity is the proportion of truly diseased persons in the screened population who are identified by the screening test.[9] In other words, sensitivity assesses the propensity of a test to avoid false negatives; that is, giving a negative result when disease is actually present in the woman. These false negatives can arise in a variety of ways:

- when there are no abnormal cells on the specimen because of failure in collecting cells from lesions or transferring such cells to the slide
- when there are abnormal cells present in the sample that have not been detected or have been misinterpreted in the laboratory
- when the disease is rapidly progressing and the lesion itself was not present at the time of sampling. This situation is considered to be quite uncommon.[10]

Specificity is the proportion of truly non-diseased persons who are so identified by the screening test.[9] In other words, specificity assesses the propensity of a test to avoid false positives; that is, giving a positive result when the true result is negative. In assessing the performance of a new test compared with the current screening methods it is important to consider whether sensitivity is only increased at the expense of a loss of specificity and hence an increase in the women referred for unnecessary further investigation and intervention.

With most screening tests there is to some extent a trade-off between sensitivity and specificity. If the threshold of the test is set to give higher sensitivity then this will be at the expense of reduced

TABLE 2 *Scale of the cervical screening programme and associated further treatment in an average health authority*

	Approximate numbers per annum in an average PCT (100,000 population)[a]
Number of cervical smears taken	7286
Number of repeat cervical smears	670
Total number of referrals for colposcopy	104
Number of referrals for colposcopy for higher grade lesions	47

[a] Based on NHS Cancer Screening Programmes. *NHS Cervical Screening 2002 Review*.[8]

specificity; similarly, increasing the specificity will tend to reduce the sensitivity. As with other screening methods, the relationship between sensitivity and specificity in cervical screening can be formally assessed by plotting a receiver operating characteristic curve (see e.g. Fahey and colleagues[11]).

A wide range of performance has been reported by Fahey and co-workers for sensitivity and specificity with current cervical smear tests.[11] In part this is due to differences between studies in respect of what is considered a positive result. If low thresholds are set, a newer test may be able to improve on the detection of abnormalities of lesser severity, but may be no different in respect of its sensitivity for detecting high-grade lesions or in influencing the incidence of invasive cancer. As a broad approximation, Fahey and colleagues' review concluded that the sensitivity for conventional smears was on average about 55–65% and the specificity 65–70%. As the reference test itself may not be perfect, Boyko has suggested that the sensitivity and specificity are prevalence dependent and that the sensitivity may be underestimated.[12] Moreover, estimates of sensitivity and specificity require a reference diagnosis to be defined for positive and negative results. However, in cervical cytology screening no consistently used reference exists. Ideally one would compare against biopsy diagnosis, but this raises the ethical implications of carrying out an invasive procedure on women with negative cytology. This may be justified in high-risk women, but this would be a biased assessment of the sensitivity of the test in the general population.

Finally, and most importantly, the sensitivity of any one test still does not fully represent the sensitivity of the programme as a whole. One false-negative test may be of no significance if the abnormality is picked up before the development of invasive or symptomatic disease when the woman is next screened. Thus, the programme sensitivity will be a function of the screening interval and it may, for example, be a better policy to reduce the screening interval or to ensure that women do not miss a screening round, or both, than to improve on the sensitivity of individual tests. This introduces the concept that will be discussed later of the sensitivity of the whole screening programme rather than of individual screening tests within it.

Current service cost

Cervical screening, including the cost of treating precancerous lesions, has been estimated to cost about £135 million each year in England,[13] although it is unclear whether this includes all the relevant costs.

Variation in services: coverage and screening interval

Coverage of the cervical screening programme in England varies quite widely. For 5-year (or more frequent) testing, some 12 out of 100 health authorities in 1998/99 had coverage below the national target of 80%, while ten health authorities had coverage of over 90%. Three-year testing coverage was more variable, with only three health authorities having a coverage of 80% or more, while 12 had coverage of under 60%.[5] This reflected the fact that about 60% of health authorities invited women every 3 years and 15% had a mixed policy, inviting women every 3–5 years depending on their age.[14] Whether the demise of the health authorities and the uptake of this responsibility by PCTs in England will have any impact on coverage remains to be seen.

The new intervention in cervical screening

Intervention

LBC for cervical screening aims to improve the quality of the conventional cervical smear through an improved slide preparation technique following collection of the sample in the standard way. This is designed to produce a more representative sample of the specimen, with reduced obscuring background material. This should allow faster and more reliable screening by laboratory staff.

It is perhaps worth noting that suggestions for methods to improve cervical specimen cytology have also been made in the past. For example, Steven and co-workers suggested chemical depolymerisation of cervical mucin to help to produce monolayers.[15] Neugebauer and co-workers in 1981 described a sedimentation velocity separation method,[16] and a pulse wash method was suggested by Näslund and colleagues.[17,18]

The LBC technique that is the subject of the present report involves not making a smear of the material obtained on the spatula or collection device, but rinsing it in a preservative fluid, so generating a suspension of cells that is subsequently used to deposit a monolayer of cells on the slide. Almost all of the cells collected from the cervix should thus be present in the fluid. The subsequent stages of the procedure result in a smaller, but more representative cell sample from the cervical specimen than is obtained in a

conventional smear. Cellular preservation is said to be enhanced, the preparation is more of a monolayer and contamination (blood cells, pus and mucus) is reduced.[19] Moreover, improved fixation allows more consistent staining.

Thus, preparation techniques are claimed to reduce the proportion of specimens classified as technically unsatisfactory for evaluation. A further advantage is that the cell suspension in preservative can be retained and used for later testing such as for human papilloma virus (HPV), chlamydia and other molecular biological tests.[20] Testing for HPV is not precluded by a screening system that uses conventional smear tests. However, since a recommendation of management is part of the cytology result, the HPV result needs to be taken into consideration by the laboratory before release. This would be facilitated by specimens having the same or clearly linked identifiers. Furthermore, it is well recognised that the leftover material after conventional smears is not a random sample of the different cellular populations and this may lead to discrepancies.[21–23]

The products currently available that use this liquid-based methodology are summarised below (full details are not intended to be given here, merely the main points of the process). Products are listed alphabetically.

CytoScreen® (Altrix Healthcare, Leeds, UK)

A proprietary plastic collection device (CytoPrep®) is used to collect a cervical sample and the head is detached into a vial of proprietary transport fluid (CytEasy™). In the laboratory the vials are placed on a shaker before a photometric reading is taken to assess cellularity. An appropriate aliquot of the sample is centrifuged onto a glass slide. Staining follows using normal laboratory staining procedures. Samples are said to be "processed with the CytoScreen® method using standard laboratory equipment, readily available in the market and in most labs". The only innovations are the plastic collection device (CytoPrep), the composition of the preservative and the method of establishing the volume of sample necessary to produce a fully CytoPrep representative sample and an adequate quantity of cells (Altrix Healthcare's submission to NICE, October 1999).

Labonord Easy Prep® (Surgipath Europe, Peterborough, UK)

Samples are taken using a plastic collection device and transferred to proprietary fixative fluid. An aliquot of the fluid is placed in a separation chamber with a strip of absorbent paper punched to produce a 250 mm hole; eight chambers are placed together in a clamping unit. The plastic chamber retains the cell suspension in place during sedimentation while the absorbent paper gently removes the fluid, resulting in a dry, thin layer of cells. "This is a method for producing a liquid-based preparation that is said to have the advantages of the methodology, but does not rely on the use of additional expensive instrumentation and uses standard laboratory equipment" (Surgipath Europe's submission to NICE, January 2000).

PrepStain™ slide processor and SurePath® test pack (previously known as AutoCytePrep®, CytoRich™, Pathlore, Nottingham, UK)

A sample from the cervix is collected using a plastic collection device. The head of the collection device is detached into a vial containing a proprietary transport fluid (PrepStain). In the laboratory the vials are vortex mixed and the cell suspension is treated through a density gradient centrifugation process to remove red blood cells and other clinically non-significant material and to enrich the cell suspension. The centrifuge tubes are loaded onto a PrepStain slide processor, SurePath, which handles 48 samples at a time. The cell pellet is resuspended and an aliquot transferred to a settling chamber mounted on a microscope slide. The cells are allowed to sediment under gravity to form a thin layer on the slide. Excess fluid and cells are removed and the slide is then stained automatically as part of the process. If the preparation is considered inadequate or unsatisfactory it is possible to revert to the original cell pellet and prepare another slide using a larger aliquot of suspension. In the USA, Food and Drug Administration (FDA) approval has been given to the PrepStain SurePath system.

ThinPrep® (Cytyc UK, Crawley, UK)

This was approved by the FDA in 1996 and is currently available as the ThinPrep3000 System. A plastic collection device is rinsed thoroughly into a vial containing a proprietary transport fluid (PreservCyt®). In the laboratory, each vial is placed in the ThinPrep3000 Processor. There are three key phases to the process:

1. Dispersion: a randomised cell suspension is produced, breaking up cell clumps and mucus.
2. Cell collection: a negative pressure pulse is produced which draws the fluid through a filter trapping a layer of cellular material; the flow of fluid through the filter is monitored and controlled to optimise cell collection.

3. Cell transfer: the cellular material on the filter is transferred to a glass slide, which is then deposited into a vial of fixative.

Subsequent staining and microscopic evaluation of the slides proceeds in a similar manner to a conventional smear. The ThinPrep3000 process system provides automated batch processing.

Identification of patients and important subgroups

It is assumed for the purpose of this review that, if introduced, the methodology would be to replace the existing fixed cervical smear specimens that are currently used in the cervical screening programme. In other words, that there are no subgroups for whom it would be introduced preferentially.

Criteria for the introduction of the technology

If the LBC methodology were introduced, the criteria for the introduction of the technology would be the same as for those for the existing cervical screening programme. That is, that women between the ages of 20 and 64 years are invited to have a free cervical screening test every 3–5 years.

Personnel

Those carrying out the speculum examination and collection of the cervical material need training in respect of the new method of handling the specimen thus obtained. Instead of making a smear onto a glass slide the material is transferred into a vial of preservative fluid. Arguably this is no more complex a process and may be regarded as simpler.

In the laboratory, an additional resource is required to produce the new slide preparations. Training will be required for those staff involved in these new processes. In addition, cytologists need to be trained to interpret these new slide preparations. It is said that the slides are quicker to assess, but also that more concentration is required, making them more tiring to read (this will be discussed later).

Setting

The setting for this intervention is in two main sites. The cervical specimen is usually taken in a primary care setting by the GP or practice nurse, at a community clinic such as a family planning or well-woman clinic, or at a colposcopy clinic. Using the LBC method would not change these arrangements, although some of the equipment required would be different.

Transport of specimens to the laboratory may need different arrangements. Many trusts and health authorities have pathology collection vans and thus do not use the postal service. However, the vials are bulkier, and this may need greater capacity in the collection vehicles. In addition, it may not be possible to use the Royal Mail (as occurs in some areas) if fluids containing alcohols are used in the transport medium. However, in the ongoing pilot in England, LBC vials are being collected using the same Trust van system as is used for the conventional smears in all pilot sites.

The cervical samples are currently sent to a pathology laboratory, usually based in a hospital and under the overall responsibility of a consultant pathologist. Again, using the LBC method, there would be no substantial change to these arrangements, but rather more substantial changes would be needed in the staff and equipment required.

Equipment required

The equipment required to take the cervical sample is different with LBC to that required for conventional smears. Instead of making smears on glass slides, applying a fixative and leaving the slide for drying and labelling, the smear taker obtains a sample using a broom-like device. The broom is then placed in a plastic vial (for SurePath and CytoScreen) containing a cell preservative solution and labelled. Thus, instead of a smear being produced and fixed at the time of obtaining the specimen, a cell suspension is sent to the laboratory.

At the laboratory, processing devices are used to prepare the cell suspension and transfer a sample of cells to microscope slides. These are perhaps the main items of capital expenditure involved in the new methodology. Although the staining and slide preparation procedures are broadly similar to conventional smears there may be different equipment involved at this stage.

Although the use of automated analysis equipment is outside the scope of this report, it is important to consider that these new preparation techniques may greatly facilitate the introduction of such automated analytical methods and are being tested in a number of centres.

In the laboratory extra storage space is needed for the vials, and disposal of the cell suspension may also require additional arrangements and resources.

Degree of diffusion

At present, apart from use in research studies and the ongoing pilot in England, LBC has not been introduced for cervical screening in England, although a decision to implement LBC techniques in Scotland has been made. Conversely, in the light of the report by the New Zealand Health Technology Assessment,[24] the New Zealand National Cancer Screening Programme has decided not to purchase or endorse LBC for its population-based screening programme at present. LBC is, however, being used routinely in at least some laboratories in most developed countries.

Anticipated costs

The marginal gross cost of the preparation capital equipment associated with introducing the new technique would be £45,000 for PrepStain and £95,000 for the ThinPrep3000 system for each slide preparation centre. The national cost of investing in the new preparation equipment, assuming 4.4 million smears taken per year, would be between £3.3 and £6.6 million for PrepStain (for centre capacity of 30,000 and 60,000 smears per year, respectively), and £7 and £14 million for ThinPrep3000.

Assuming a 7.4% decrease in the number of smears taken (owing to improved inadequacy rates), the additional non-capital resources (consumables and staff costs) required to collect and prepare smears nationally will be around £14.7 million for the ThinPrep3000 system and £5.4 million for the PrepStain system.

In the laboratory, one-off conversion costs are estimated as £10.3 million nationally, or £72,800 for a laboratory reporting 30,000 smears annually. These costs include training of both smear takers and smear readers, as well as resources required to analyse the backlog of conventional smears, which could be viewed as a cost of the current system.

However, some cost savings may be expected in the laboratory owing to the reduced time required to read smears and the reduced number of inadequate smears. It is assumed that the recognition of a smear as being inadequate takes half the normal reading time. The combined annual saving nationally is estimated at around £1.5 million (£10,000 per 30,000 capacity laboratory).

The total year 1 conversion cost to LBC is, therefore, estimated to be between £17.5 and £20.8 for the PrepStain system and £30.5 and £37.5 for the ThinPrep3000 system. These cost estimates give a general idea of the cost impact of introducing LBC, although individual products may be introduced at lower costs than these.

Chapter 3

Effectiveness of LBC in cervical screening

The search aimed to identify all literature relating to the update of 'Liquid-based cytology in cervical screening: a rapid and systematic review'.[1] The main searches were conducted in October 2002.

Sources searched

Eleven electronic bibliographic databases were searched, covering biomedical science, social science, health economics and grey literature. A list of databases is provided in Appendix 1.

In addition, the reference lists of relevant articles and sponsor submissions were handsearched and various health services research-related resources were consulted via the Internet. These included health technology assessment organisations, guideline-producing agencies and generic research sites. A list of these additional sources is given in Appendix 2. Citation searches were conducted on key papers and authors using the Science and Social Science Citation Index facilities.

Search terms

A combination of free-text and thesaurus terms was used. 'Population' search terms (e.g. cervix, cervical, vaginal, neoplasm, cytology) were combined with 'intervention' terms (e.g. liquid, fluid based, thinlayer, cytorich, autocyte). Three searches were performed in MEDLINE, the first was the main sensitivity/specificity MEDLINE search, the second was for the economics of cervical screening, and the third search was performed to identify further references specifically related to modelling cervical screening. Two searches were performed in EMBASE and the Science and Social Science Citation Indexes; the first were the main cervical screening searches, and the second were performed to identify articles specifically for the modelling of cervical screening. Two searches were also performed in the Cochrane Library, the first being the main cervical screening search, and the second to identify only systematic reviews about Pap smears. Copies of the search strategies used in the major databases are included in Appendix 3.

Search restrictions

No language restrictions were applied to the searches; however, the searches were limited by date to 1999–2002 in order to reflect the timing of the searches performed for the previous study. The search performed in the Cochrane Library for the Pap smear systematic reviews was not limited to 1999 to the present to ensure that all data were available for review. No study or publication type restrictions were applied to the main searches.

Data extraction strategy

All abstracts and papers were double read. For both reports, data for relevant articles were extracted by one of the authors and checked by the second. Key tabulations and calculations for summary tables were checked by entering the published study data (where available) into a spreadsheet and recalculating the relevant percentages.

Quality assessment strategy

Studies varied in study design quality and presentation of results. Only those with a clear tabulation of the numerical data were used in the conventional smear versus LBC assessments. Other comments on the quality of studies and study design are made later in the text in relation to specific study types. For the review update, the methodological quality of the primary studies was assessed using the Cochrane model,[10] modified as described by Broadstock for the New Zealand Health Technology Assessment review.[24]

Results

Quantity and quality of research available

In considering what literature should be looked for, the following principles were kept in mind in terms of both study design and outcome measures examined.

The gold standard outcome measure for evaluation of a new screening methodology is whether it can reduce the incidence, morbidity and/or mortality from cervical cancer. Other patient-based objectives may be important, such as reducing the need for repeat smears because these are likely to cause inconvenience and anxiety and hence impact on a patient's quality of life.

If these outcome measures are not available then other measures may provide helpful proxies. Thus, if the sensitivity of the test is improved then more precancerous lesions should be detected. This, however, will only lead to a reduction in incidence, morbidity and/or mortality if the abnormalities detected do progress rather than spontaneously regress, and if the additional detection results in earlier treatment by an interval that reduces incidence, morbidity and/or mortality. It should not be assumed that the detection of additional abnormalities will automatically lead to a reduction in these outcome measures.[10]

Improvements in specificity may be a proxy for reductions in unnecessary repeat screening examinations and indeed more invasive investigations and treatment.

Other outcome measures such as the proportion of inadequate or unsatisfactory smears may be important in reducing both unnecessary anxiety and costs of repeat smears. Time taken to carry out the examination of smears, and other factors associated with the costs and organisation of the screening programme are also important outcomes.

The literature search results are divided into two types:

- secondary research: health technology assessment reviews
- primary research.

Secondary research literature: health technology assessment reviews

For the original report a small number of reviews from other health technology assessment centres was found in the literature search:

- Australian Health Technology Advisory Committee Report
- Canadian Co-ordinating Office for Health Technology Assessment
- Agency for Health Care Policy and Research (AHCPR).

For the update report, one additional review was identified:

- New Zealand Health Technology Assessment Report.[24]

Australian Health Technology Advisory Committee Report, April 1998[10]

This report examined both the ThinPrep and SurePath technologies. Literature available from 1990 to July 1997 was examined. Problems with the available evaluative studies were summarised as:

- low numbers of studies
- difficulty in assessing degree of independence as many are supported by the manufacturers
- lack of randomised controlled trials (RCTs) of technologies
- lack of community-based studies
- lack of consistent cytological threshold for positive and negative results
- variety of definitions as to what constitutes a 'positive smear'
- few studies with biopsy confirmation of positive results
- no definition of gold standard for negative results (e.g. subsequent negative smear)
- reviewers not always blinded to outcome when assessing smears
- lack of consistent comparator
- non-random selection of samples
- samples do not reflect usual practice (e.g. high proportion of positive smears)
- review process does not reflect usual practice (e.g. repeated examination of particular slides)
- information concerning the comparability of cases and controls not always reported
- sensitivity and specificity generally not reported
- tests of statistical significance often not undertaken or not reported
- lack of recognition that most technologies require a period of familiarisation before specimens can be evaluated appropriately.

The main points concluded by the Australian Health Technology Advisory Committee review in respect of the SurePath and ThinPrep were as follows:

- There were few peer-reviewed studies of SurePath found for evaluation. To date, all comparative studies of SurePath and conventional smears have been prospective and have used the split-sample technique. There is one study comparing ThinPrep and SurePath.
- SurePath has been less well studied than has ThinPrep. It probably has similar benefits, but there are insufficient data to demonstrate comparable improvements in sensitivity.
- There is a reduction in the proportion of smears rated unsatisfactory for evaluation when SurePath is used.
- A high level of concurrence between SurePath and conventional smears has been found.
- There is evidence that this technique leads to lower rates of missed diagnoses (i.e. greater sensitivity) compared with conventional smears,

but there are insufficient data reliably to estimate the magnitude of relative improvement.
- There is evidence that screening time is shorter with SurePath.
- To date, comparative studies of ThinPrep and conventional smears have been prospective and have used the split-sample technique. No data are available on the performance of ThinPrep as a sole preparatory method for cervical cytology.
- Some reports of sensitivity and specificity in literature of ThinPrep are limited, as comparison was not made with the gold standard of biopsy confirmation.
- There is a reduction in the proportion of smears rated unsatisfactory (by Bethesda criteria) for evaluation when ThinPrep is used.
- There is evidence that ThinPrep has a higher sensitivity than conventional smears, and results in a greater number of low-grade lesions being diagnosed. Adjunct use of ThinPrep leads to the recognition of both screening and subsampling errors.
- Use of ThinPrep results in a significant increase in the detection of minor, non-specific changes.
- In recent studies, a high level of concurrence between ThinPrep and conventional smears was found.
- There is evidence that the adjunctive use of ThinPrep with conventional smears may increase the detection of biopsy-proven high-grade abnormalities by between 5 and 6%, and increase the detection by between 6 and 11% for all cervical abnormalities
- The sampling device used seems to have an impact on the performance of ThinPrep.
- There is evidence that screening time is shorter with ThinPrep, but that additional preparatory staffing is required.
- There is a significant learning period to become competent in assessing monolayer samples.

In summary, the Australian Health Technology Advisory Committee report concluded that liquid-based slide preparation techniques may increase the detection of biopsy-proven high-grade cervical abnormalities by between 5 and 6%. In addition, it concluded that current studies are finding that these slide preparation techniques reduce the number of slides rated as unsatisfactory (exceptions of this reduction not specified) and improve the reading of slides. This, in the Australian setting, would mean that the sensitivity increase would result in an increase in slides reported as high-grade abnormalities from about 1% of smears to 1.05%.

It was estimated that the use of liquid-based cytology would add at least 70 million Australian dollars (Aus$) (~£29 million) per 2-year screening cycle (in a population just over one quarter the size of England and Wales, with a lower coverage rate). If this replaced conventional practice there would be offset savings of Aus$25 million (~£10 million). It was estimated that the costs per additional cancer prevented would be Aus$1 million (~£400,000) if the technology were used in addition to the current technology. (The year on which these costs are based is not clear, but it is probably no later than 1997.)

It was recommended that population-based trials should be carried out comparing this technology with conventional smears. At present, the relative improvement in sensitivity was not considered sufficient to mandate their universal introduction. Until there are data demonstrating the cost-effectiveness of the new technologies from a population basis, their increased uptake cannot be justified from a public health perspective.

Australian practice is for a 2-year screening cycle, so the improvement in sensitivity would have a smaller potential increase in prevention of invasive disease than in a setting where the screening interval was longer. The coverage is, however, lower in Australia than in England and Wales (the assumption for the economic model in the Australian Health Technology Advisory Committee report was that only 63% of eligible women are screened).

Canadian Co-ordinating Office for Health Technology Assessment, May 1997[20]

Like the Australian report, this report also considered new slide preparation (and automated analytical) methods. The report found that agreement between liquid-based thin-layer preparations and conventional cervical smear is high (in the range of 88–99%). The newer method gives enhanced preservation and distribution of the cells, making slides easier and quicker to view, although fatigue sets in more quickly. The report states that "reduced total number of cells can increase the number of unacceptable slides", although this is not quantified. Many studies were found reporting that monolayer preparation slightly improves detection of low- and high-grade disease, perhaps owing to superior cell preservation and distribution. However, substantial training for cytotechnologists and pathologists was thought to be required and the high cost of these preparation systems was noted. It was stressed that newer techniques should not divert resources and effort

from increasing recruitment, information systems, training and quality control for laboratories and programmes. Again, the coverage may be lower in Canada than in England and Wales.

AHCPR, January 1999[26]

This report carried out a very full and systematic search of the literature and applied quality filters to select papers to review. Only one study was found on LBC that met the full criteria of colposcopy/histology reference standards and sufficient data to calculate sensitivity and specificity. Criteria had thus to be modified to include studies that used a cytology reference standard and allowed estimation of sensitivity and specificity. This resulted in the inclusion of eight studies of ThinPrep. The main conclusions from the report are set out below.

Despite the demonstrated ability of cervical cytological screening in reducing cervical cancer mortality, the conventional smear test is less sensitive than it is generally believed to be. Studies unaffected by work-up bias provided estimates of the specificity of conventional smear screening of 0.98 [95% confidence interval (CI) 0.97 to 0.99] and sensitivity of 0.51 (95% CI 0.37 to 0.66). The smear test is more accurate when a higher cytological threshold is used with the goal of detecting a high-grade lesion. Lower test thresholds or use of the smear test for detecting low-grade dysplasia results in poorer discrimination.

Existing information fails to provide accurate estimates for specificity of thin-layer cytology technology. The initial requirement for verification of test negatives with colposcopy or histology led to the exclusion of all but one study of ThinPrep. The values reported for sensitivity and specificity using histological or colposcopic reference standards are well within the range of sensitivity and specificity reported for the conventional smear test. However, including studies that directly compare ThinPrep with conventional smear testing (screening or rescreening) using a cytological reference standard results in significant improvements in sensitivity.

The cost-effectiveness of a technology that improves primary screening sensitivity (e.g. thin-layer cytology) is directly related to the frequency of screening: longer intervals result in lower estimates of cost per life-year saved.

These findings were relatively insensitive to assumptions about cervical cancer incidence, the cost of technologies, diagnostic strategies for abnormal screening results, age at onset of screening or most other variables tested.

There is substantial uncertainty about the estimates of sensitivity and specificity of thin-layer cytology. The uncertainty is not reflected in the point estimates for effectiveness or cost-effectiveness. Although it is clear that both thin-layer cytology technologies provide an improvement in effectiveness at higher cost, the imprecision in estimates of effectiveness makes drawing conclusions about the relative cost-effectiveness of thin-layer cytology and computerised rescreening technologies problematic.

Using a modelling approach, however, the AHCPR report concludes that the increased sensitivity would result in moderate improvements in life expectancy at much higher costs than conventional screening methods. When screening intervals are 3 years (or longer), the new method was estimated to have an incremental cost-effectiveness ratio (ICER) that is "within the range of accepted health care practices"[24] [i.e. below US$50,000 (~ £30,000) per life-year].

New Zealand Health Technology Report, October 2000

This report examined the evidence for clinical effectiveness (primarily sensitivity and specificity) and cost-effectiveness of introducing automated and semi-automated devices for cervical screening into New Zealand's population-based screening programme. It aimed to update the Australian Health Technology Advisory Committee Report (1998).[10] The two LBC techniques considered were ThinPrep and SurePath plus the semi-automated imaging device Autopap. The literature considered included English language material available from January 1997 to 31 May 2000. Only 15 studies were identified on clinical effectiveness of LBC compared with conventional screening, of which nine were at least partially funded by industry involved with the production of the devices under consideration, and most were severely limited by poor design, inadequate reference standards and incomplete verification of cytological diagnoses. Studies comparing different LBC preparation techniques were also of limited quality and the author concluded that the clinical effectiveness of ThinPrep and SurePath for detection of high-grade abnormalities could not be reliably determined from the existing evidence base. It was also not clear whether one device had any advantages over the other with respect to

given outcomes. In terms of semi-automated devices for primary screening and rescreening, there was some limited evidence of potentially increased detection of low-grade abnormalities for AutoPap compared with conventional screening, but no increased detection of high-grade abnormalities and a lack of evidence on specificity. All cost-effective models were severely limited by the uncertainty surrounding estimates for improved sensitivity and the lack of information on changes to specification, which may occur with the introduction of new devices into a screening programme.

The main conclusions of the report were as follows:

- Estimates of test sensitivity and test specification for the new devices could not be reliably determined.
- Estimates of test sensitivity and specification were the main source of uncertainty in the economic models investigating clinical effectiveness of new devices.
- Any increases in sensitivity resulting from the introduction of new devices may come at the cost of decreased specification.
- High quality is required to generate valid estimates of test sensitivity and specification.

Several other systematic reviews were published between 1999 and 2002, but irrespective of review quality, the evidence cited duplicated that already reported in the original HTA report. Therefore, these were all excluded from this update report.

Primary research literature

Figure 1 presents a summary of the papers excluded at different stages of the review process for primary research on LBC. There were no trials identified which randomised patients to have their cervical samples analysed by either conventional smears or liquid-based slide preparations and then used an outcome measure such as mortality or invasive cancer incidence. For the update report, in one study, a prospective, randomised controlled design was used to compare ThinPrep with conventional smear taking with all those screening high-grade squamous intraepithelial lesion and carcinoma (HSIL+) being followed up for 12–15 months with histology or cytology.[27] Unfortunately, the study focused on the method of sampling and the collection device and did not measure sensitivity. In a second study, two separate smears were taken from the same person, each to be analysed by one of the two methods (conventional and liquid based), and the order of smear taking was randomised.[28]

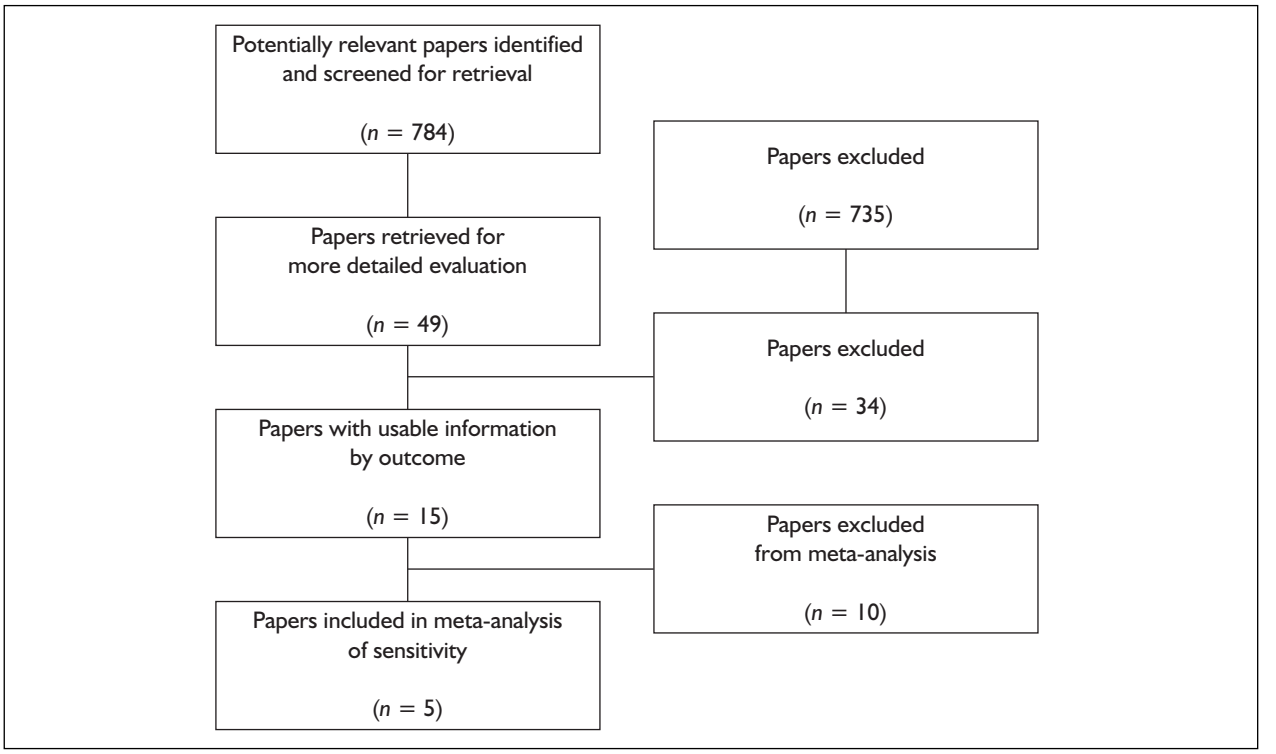

FIGURE 1 *Summary of results of the literature search and inclusion of primary research for LBC update*

Thus, any attempt to determine the effect of the LBC on outcome measures of mortality or invasive cancer incidence can only be arrived at by attempts at modelling with, therefore, all the assumptions and subsequent uncertainties about the conclusions.

For the update report, four research studies were identified from the national research register. Contact with research leads was made. However, results were not available for any of the studies, although two had been completed.

Sensitivity and specificity studies

The original report identified ten studies, plus one confidential document, with information on sensitivity and specificity on LBC techniques compared with conventional smear taking. From the 15 papers that were identified as published since the original HTA report, five provided additional information on sensitivity and specificity and their details have been added to the original table (*Table 3*). For three of these five,[10,26,27] details on ages of the subjects studied were not given. In another study, insufficient biopsy data were available for the conventional Pap smear slides.[29] Sensitivity and specificity could only be calculated therefore for the LBC slides.

Sensitivity is the proportion of true positives identified as such, and specificity is the proportion of true negatives correctly identified. To determine sensitivity and specificity, a gold standard diagnostic measure is needed. This implies that all those having the screening test should also have the gold standard test administered. No studies were identified, in either the original or the update literature, that carried this out for a population of average risk, and indeed there are doubts about whether this would be a practicable study to undertake as it would mean subjecting large numbers of women to a more invasive test in addition to the screening procedure. Two alternative sorts of sensitivity and specificity study were found, however; those that used a proxy gold standard by carefully reviewing all the available cervical cytology results by additional specialists, and those that did carry out additional examinations (such as colposcopy and biopsy) in high-risk women.

In all the studies in the original report, in these two categories, the sensitivity was higher (or the same) in the LBC group. In several cases the numbers were very small and the differences were often small and/or not statistically significant. Of the additional five studies identified in the update of this report, in some cases sensitivity was higher in the conventional than in the LBC group, but again, where tested and reported, no statistically significant differences were found between the two groups. Of the 15 papers cited in the initial review and the update, only five of them covered 'ordinary' populations[22,29,34,42,43] and four of the five reported on ThinPrep, while Bishop and colleagues[43] were the only researchers who compared SurePath with conventional methodology. Ten studies contained 'high-risk' populations,[28,30,35,36,38,40,41,44–46] again with proportionally more (70%) reporting on ThinPrep than on SurePath (30%).

Figure 2 differentiates between studies that compared the alternative screening techniques in ordinary populations and in high-risk populations. The proportions represent false negatives on the basis of low-grade squamous intraepithelial lesion (LSIL) test results or worse being defined as positive. In the four studies based on screening ordinary populations a statistically significant relative risk (RR) for false negatives of 0.55 was found, whereas the analysis of the high-risk populations resulted in an insignificant RR of 0.88. The aggregate RR is 0.75, where the sensitivity rates for conventional Pap smear testing and LBC are 0.715 and 0.801, respectively. Thus, LBC is associated with a 12% improvement in sensitivity. Insufficient biopsy data in one study[29] meant that it could not be included in this analysis.

The estimation of sensitivity on the basis of LSIL or worse is not directly comparable to the UK cervical screening programme, as LSIL corresponds to a mild dyskaryosis screen result, and covers histologically defined results less than cervical intraepithelial neoplasia 2 (CIN2). However, the aggregate estimate of an improvement in sensitivity of 12% is taken as the best estimate for the aggregate sensitivity rate.

The majority of the identified studies examined ThinPrep, with a few looking at SurePath. Indirect comparisons of the alternative LBC techniques found no differences between the results, so the modelling analysis does not differentiate between alternative techniques.

Meta-analysis of the six studies that compared specificity between conventional Pap smear testing

TABLE 3 *Summary of results of studies attempting to assess sensitivity and specificity*

Study/population	Methodology	Smear sensitivity	Smear specificity	LBC sensitivity	LBC specificity	Definition of positives and of reference standard
Sheets *et al.*, 1995[30] Colposcopy clinic referrals, USA	ThinPrep	67.3% (107/159)	76.9% (220/286)	73.6% (117/159)	76.2% (218/286)	Colposcopic biopsy
Ferenczy *et al.*, 1996[23] Colposcopy clinic referrals, USA	ThinPrep	70.1% (*n* not stated)	74.7% (*n* not stated)	78.0% (*n* not stated)	73.6% (*n* not stated)	LSIL+ based on histology in women referred for colposcopy; no significant difference detected between methods
Corkill *et al.*, 1998[31] Planned parenthood clinic referrals, USA	ThinPrep	34.5% (29/84)		71.4% (60/84)		LSIL+ based on an independent pathologist's review of cytology slides
Sherman *et al.*, 1998[32] Diverse population groups, USA	ThinPrep	68.1% (374/549)		80.7% (443/549)		LSIL+ based on independent pathologist's masked review of slides; hospital and screening centres
Bishop *et al.*, 1998[33] Mixed hospital and health maintenance organisation-served population, USA	SurePath	78.5% (73/93)		89.2% (83/93)		LSIL+ based on positive biopsy patients (part of a larger study)
Bolick and Henman, 1998[34] Routine clinical practice, USA	ThinPrep	85.1% (57/67)	36.4% (8/22)	95.2% (40/42)	58.3% (7/12)	LSIL+ based on biopsy results (part of a larger study), numbers are very small
Inhorn *et al.*, 1998[35] Known cases of cervical cancer, USA	ThinPrep	93.6% (44/47)		95.7% (45/47)		Invasive cervical cancer based on biopsy confirmation; involves only 47 cases
Ashfaq *et al.*, 1999[36] Population with high glandular abnormality rates	ThinPrep	56.4% (22/39)		84.6% (22/26)		Glandular lesions based on biopsy confirmation; numbers are small
Hutchinson *et al.*, 1999[37] Population with high incidence of cervical cancer, Costa Rica	ThinPrep	68.7% (222/323)		87.9% (284/323)		LSIL+ based on a final diagnosis that was made by a combination of cytology, histology and cervicography

continued

TABLE 3 *Summary of results of studies attempting to assess sensitivity and specificity (cont'd)*

Study/population	Methodology	Smear sensitivity	Smear specificity	LBC sensitivity	LBC specificity	Definition of positives and of reference standard
Data on file, CellPath, 1999 Three USA sites	SurePath	77.2% (363/470)		76.8% (361/470)		LSIL+ graded as such by three reference pathologists
Vassilakos *et al.*, 2000[25] London sample from large Swiss population	SurePath	88.6% (124/140)		91.0% (690/758)		HSIL+ confirmed by histology after colposcopy, but includes only ASCUS+ smears so may overestimate sensitivity
Yeoh and Chan, 1999[29] 171 general practices, screening for cervical cancer, ages unknown, Hong Kong	ThinPrep	Insufficient biopsy data		87% (175/201)	53% (10/19)	LSIL+ based on biopsy follow-up data; only 220 biopsy records available in part of a larger group studied
Ferris *et al.*, 2000[39] Routine screening 79%, colposcopy following abnormal Pap smear 21%, USA, aged 18+ years	ThinPrep	63% (95% CI: 49–76%) (36/57)	99.7% (99.4–99.9%) (1846/1851)	53% (43–62%) (61/116)	99.5% (98.8–99.9%) (825/829)	LSIL+ confirmed by pathologist's evaluation of histology and cytology
Minge *et al.*, 2000[40] Obstetric and gynaecology high-risk population, aged 15–57 years, USA	SurePath	62% (numbers not given)	89% (numbers not given)	53% (numbers not given)	79% (numbers not given)	ASCUS and LSIL+ based on biopsy follow-up data; only 134 biopsy records available as part of a larger group studied
Bergeron *et al.*, 2001[28] Patients with previous abnormal cytology, no ages given, USA	SurePath	69% (249/362)	83% (66/80)	67% (273/405)	73% (66/91)	LSIL+ confirmed with biopsy by blinded cytopathologist. Note: sensitivity and specificity calculated with 'unsatisfactory' slides omitted
Park *et al.*, 2001[41] Patients with known or suspected cervical abnormality, no ages given, South Korea	ThinPrep	90% (78/87)	70% (37/53)	83% (72/87)	83% (44/53)	ASCUS+, confirmed by histology, but 18 cases excluded for calculation of specificity, even though they showed a lesion more severe than LSIL in both methods

ASCUS+, atypical squamous cells of uncertain significance (as defined in the Bethesda system; for further explanation see *Table 4*); HSIL+: diagnosis of high-grade intraepithelial lesions or higher; LSIL+, diagnosis of low-grade squamous intraepithelial lesions or higher.

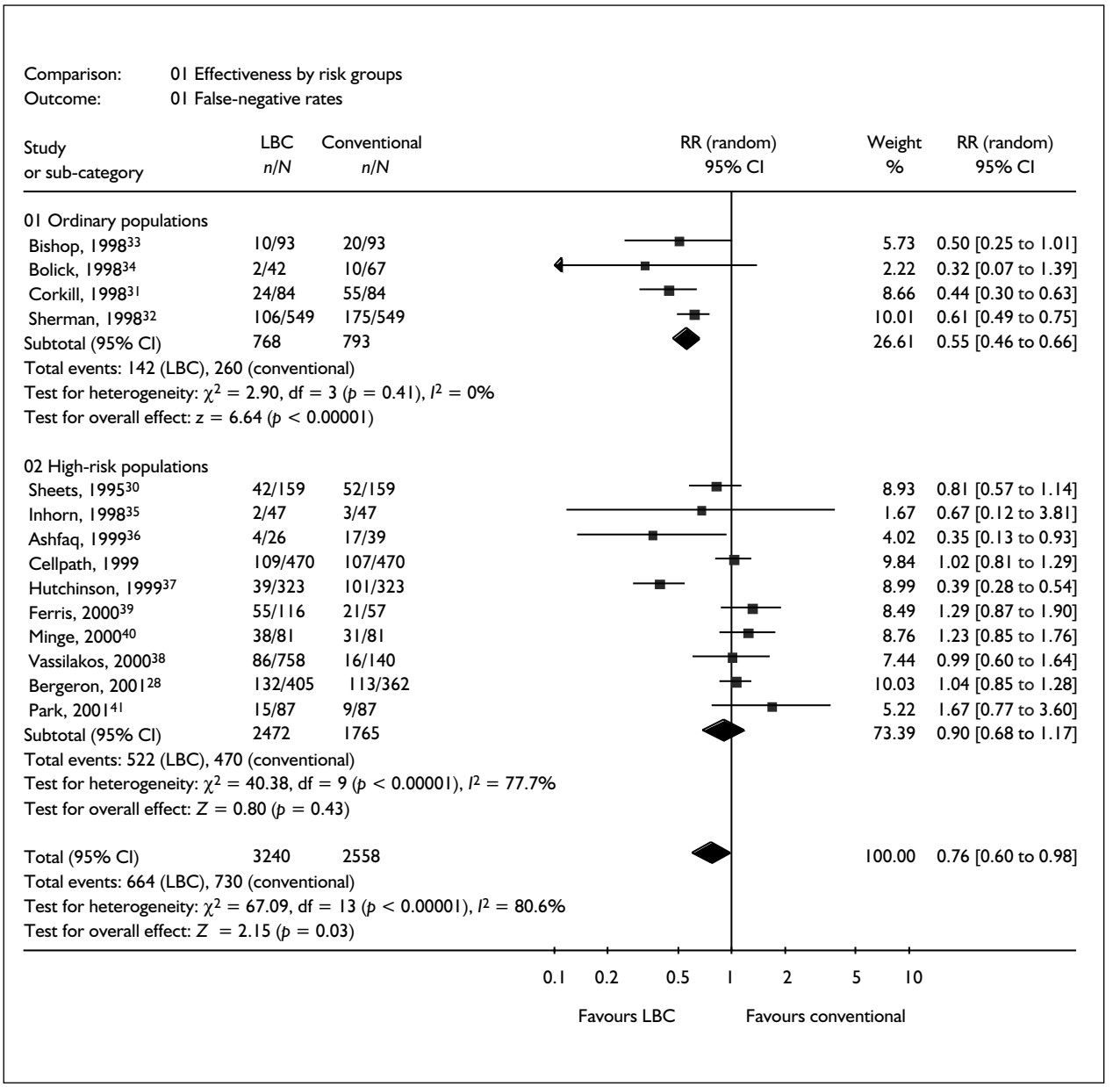

FIGURE 2 *False-negative rates in studies comparing LBC with conventional Pap smear screening*

and LBC showed no difference, and the specificity of the LBC techniques is assumed to remain unchanged from the conventional specificity. Overall, the findings from the additional five studies on sensitivity and specificity of LBC techniques compared with conventional smear methodology do not change the overall conclusions of the original report.

Split-sample studies

The most frequent study design was the split-sample method. Many of these studies are funded in part or wholly by the manufacturers of the liquid-based preparation technique. With this study design, the cervical specimen, obtained using a variety of collection devices, is used first to make a smear in the conventional manner. Next the remaining cervical cell specimen is used for LBC. Two specimens are produced for each patient screened, a conventional smear and a liquid-based preparation. In one study, two specimens were taken and allocated in random order to conventional and liquid-based analysis.[28] Thus, the agreement or difference between the two methods can be compared. As slides can be classified into a number of different diagnostic categories (*Table 4*) many different comparisons are possible. However, the main outcome comparison in these studies seems to be patients with a diagnosis of LSIL+ (as defined in the Bethesda system; also known as

TABLE 4 *Comparison of UK and Bethesda classification systems*

UK	Result code	Bethesda
Inadequate	1	Unsatisfactory
Negative	2	Negative
Borderline changes (HPV is borderline in UK but LSIL in Bethesda system)	8	ASCUS, AGUS
Mild dyskaryosis	3	LSIL
Moderate dyskaryosis	7	HSIL
Severe dyskaryosis	4	HSIL
Severe dyskaryosis, ?invasive	5	Carcinoma
Glandular neoplasia	6	HGIL

AGUS, atypical glandular cells of uncertain significance; ASCUS, a typical squamous cells of uncertain significance; HGIL, high-grade glandular intraepithelial lesion; LSIL, diagnosis of llow-grade squamous intraepithelial lesions.

TABLE 5 *An example of tabulation of split-sample results*

		Conventional smear					
		Negative	**ASCUS**	**LSIL**	**HSIL**	**Cancer**	**Total**
Liquid-based method	Negative	**7264**	122	137	18	0	7541
	ASCUS	569	**20**	43	15	3	650
	LSIL	177	12	**64**	41	1	295
	HSIL	46	5	17	**56**	15	139
	Cancer	1	0	1	3	**6**	11
	Total	8057	159	262	133	25	8636

From Hutchinson *et al.*[37]
Numbers where the two methods agree exactly are shown in bold.
ASCUS, a typical squamous cells of uncertain significance; HGIL, high-grade glandular intraepithelial lesion; LSIL, diagnosis of llow-grade squamous intraepithelial lesions.

mild dyskaryosis in the UK classification system). The use of this outcome threshold for comparing these slide preparation methods is justified because it seems to be the most consistently available across a large number of studies. In addition, there have been increases in the proportion of specimens reported as borderline (or ASCUS) during recent years. This reflects changing practice rather than a change in the underlying prevalence of the relevant cervical changes. Moreover, the proportion of liquid-based specimens classified as borderline or ASCUS tends to be higher at first, but then reduces as cytologists become used to and gain experience with the new slide preparation method. Finally, the AHCPR report[26] implies that the LSIL+ threshold is frequently used in the USA as an indication for colposcopy (and indeed sometimes a lower threshold is advocated).[47]

In the review of new evidence for the update of the original HTA report, the reporting of evidence as a diagnosis of LSIL+ has been maintained, but in addition, where possible, the HSIL+ detection rate has also been calculated from the available new evidence.

It should be further emphasised that split-sample studies are not the ideal study design. To assess the key test characteristics of sensitivity, specificity and positive/comparison one needs a gold standard comparison and, as stated earlier, few of these studies exist. However, the split-sample studies provide some proxy indication of how the sensitivity might compare between conventional and liquid-based methods.

Even within the UK there are some classification differences; thus, in Scotland any grade of dyskaryotic glandular cells may be classified as 'glandular abnormality', whereas 'adenocarcinoma' is reserved for changes suggesting invasive cancer.[48] It is also important to add that many would regard these sorts of conversion tables as being too simplistic.

Studies were included if they gave a clear tabulation of the results that showed the numbers in each possible classification status combination with respect to conventional smear and LBC. An example of the sort of tabulation that was used to provide these results is shown in *Table 5*.[37]

It should be stressed again that *Table 5* is shown to provide an example of how the data are handled in this sort of study. These data cannot be used to calculate sensitivity, specificity or positive/negative predictive values as gold standard comparisons are not available. The reasons for choosing to report the LSIL+ cut-off in summarising the results from other studies were explained earlier.

In the above example, in 2.8% [(177 + 12 + 46 + 5 + 1 + 0)/8636] of cases the liquid-based method resulted in a classification of LSIL+, while the conventional smear result was only negative or ASCUS. Conversely, there were 2.5% [(137 + 43 + 18 + 15 + 0 + 3)/8636] where the conventional smear result was LSIL+ but the liquid-based method result was negative or ASCUS. Both methods agreed that the sample was LSIL+ in 2.4% [(64 + 17 + 1 + 41 + 56 + 3 + 1 + 15 + 6)/8636] of cases.

Tables 6–8 summarise the results from the studies examined in the original review. Those identified through the update have been added to each table where appropriate. Overall, the liquid-based method seemed to result in more slides being classified as LSIL+, which were classified as a lower diagnosis (e.g. negative or ASCUS) by conventional smears than the reverse situation (i.e. slides considered below LSIL+ by LBC being considered LSIL+ by conventional smear). This pattern of results was also seen for seven of the eight studies identified for the update of the review. Studies were of variable size and variable quality (e.g. in the blinding of cytologists to the results from the other specimen obtained). The statistical significance of the difference in proportions was also variably reported. Some, albeit a minority, of these split-specimen studies found that LBC classified more slides as below LSIL+ than conventional smears more often than the converse. Although it is tempting to seek to combine the data from studies in these tables, they are from heterogeneous populations at differing risk (as shown in the final column). The meta-analytical techniques for combining studies such as these (which are not clinical trials) are beyond the scope of this review.

It is important also to note that there is a considerable variation between studies in respect of the prevalence of significant abnormality and hence the type of population that was studied. The final column of *Tables 6–8* gives an indication of this: the proportion of LSIL+ (by both methods) varied from only just over 1% to over 50% in the original report, and this remained unchanged following the addition of more recently published evidence. In the UK-screened population one would only expect about 4% to be in this LSIL+ category (i.e. mild dyskaryosis or more).[6]

An earlier review of split-sample studies was carried out by Austin and Ramzy in 1998.[73] These authors also used the LSIL+ detection as a summary measure and concluded that the liquid-based methods showed overall increased detection of epithelial cell abnormalities. Results varied considerably from study to study and appeared to be influenced by collection devices' different delivery of cellular material in the split-sample studied, first to the conventional smear and second to the liquid-based medium. Newer liquid-based preparatory methodologies seemed to be associated with enhanced detection.

The authors of most of these split-sample studies claim that their results include that the liquid-based method has a greater sensitivity.

Both the preparation techniques in common use, ThinPrep and SurePath (AutoCytePrep) have been studied in this way and both seem to give similar results from these sorts of split-sample study. A detailed review of the potential differences between these two techniques in this respect is beyond the scope of this assessment report.

Since low-grade squamous epithelial lesions may regress, for the studies identified for the update, detection rates for HSIL or higher have been calculated and compared between conventional and liquid-based methods. The results for the HSIL+ show a similar pattern of results to those seen for LSIL+. In four of the six recent studies comparing ThinPrep with conventional smear taking,[59,60,62,63] and one of the two that used SurePath,[28] the liquid-based method resulted in more slides being classified as HSIL+, which were classified as LSIL or lower by conventional smears.

Further discussion of the interpretation of split-sample studies is provided in the assessment of effectiveness, below.

Two-cohort studies

The next type of study identified is called a two-cohort analysis in this review. This examines two groups of women, usually from two different periods, whose cervical cytology specimens have been examined by one or other (but not both) slide preparation technique. The outcome used is most often the proportion of specimens classified as at or above a certain diagnostic level of severity (usually LSIL+). The assumption is that, if the women come

TABLE 6 *ThinPrep split-sample studies*

Study/country	No. of samples/ women	Conv > Liq LSIL+ (HSIL+) (%)	Liq > Conv LSIL+ (HSIL+) (%)	Both LSIL+ (HSIL+) (%)
Hutchinson *et al.*, 1991,[49] USA	443	0.45	1.13	18.7
Hutchinson *et al.*, 1992,[45] USA	2,655	0.68	2.64	12.3
Awen *et al.*, 1994,[50] USA	1,000	0.0	0.5	1.3
Wilbur *et al.*, 1994,[52] USA	3,218	0.8	3.1	17.0
Laverty *et al.*, 1995,[51] Australia	1,872	2.4	3.3	7.5
Aponte-Cipriani *et al.*, 1995,[53] USA	665	0.5	0.8	3.0
Sheets, 1995,[30] USA	782	1.5	3.3	29.4
Bur *et al.*, 1995,[55] USA	128	1.6	1.6	19.5
Tezuka *et al.*, 1996,[54] Japan	215	2.3	0.0	54.4
Ferenczy *et al.*, 1996,[44] Canada/USA	364	7.7	8.8	33.5
Wilbur *et al.*, 1996,[56] USA	259	3.1	1.9	13.5
Lee *et al.*, 1997,[57] USA	6,747	1.9	3.3	6.1
Roberts *et al.*, 1997,[58] Australia	35,560	0.3	0.5	1.7
Corkill *et al.*, 1998,[31] USA	1,583	0.8	3.7	1.9
Hutchinson *et al.*, 1999,[37] Costa Rica	8,636	2.5	2.8	2.4
Wang *et al.*, 1999,[59] Taiwan	990	0.1 (0)	1.7 (1.1)	3.6 (3.2)
Monsonego *et al.*, 2001,[60] France	5,428	0.4 (0.1)	1.1 (0.2)	1.4 (0.4)
Park *et al.*, 2001,[41] South Korea	478	2.9 (1.4)	1.0 (0.6)	18.2 (13.7)
Biscotti *et al.*, 2002,[61] USA	400	1.0 (0.8)	3.0 (0.3)	8.8 (4.0)
Luthra *et al.*, 2002,[62] Kuwait	1,024	0.1 (0)	0.6 (0.1)	2.4 (0.8)
Ring *et al.*, 2002,[63] Ireland	1,300	2.5 (1.7)	6.2 (2.0)	27.8 (10.1)

Conv > Liq LSIL+, proportion where the conventional smear result was LSIL+ but the liquid-based method result was negative or ASCUS.
Liq > Conv LSIL+ , proportion where the liquid-based method result was LSIL+ but the conventional smear result was negative or ASCUS.
For more explanation see *Table 5* and text.

TABLE 7 *SurePath split-sample studies*

Study/country	No. of samples/ women	Conv > Liq LSIL+ (HSIL+) (%)	Liq > Conv LSIL+ (HSIL+) (%)	Both LSIL+ (HSIL+) (%)
Vassilakos *et al.*, 1996,[64] Switzerland	560	0.5	1.3	3.2
Takahashi and Naito, 1997,[65] Japan	2,000	0.4	0.3	3.2
Howell *et al.*, 1998,[66] USA	852	0.8	1.1	2.5
Geyer *et al.*, 1993,[67] USA	551	0.0	0.7	12.5
Sprenger *et al.*, 1996,[68] Germany	2,863	2.0	5.1	36.2
Bishop, 1997,[43] USA	2,032	1.1	3.1	3.1
Laverty *et al.*, 1997,[69] Australia	2,064	3.9	1.6	5.0
Wilbur *et al.*, 1997,[70] USA	277	1.1	6.1	2.9
Data on file, CellPath, 1997, USA	8,983	1.6	2.2	5.7
Stevens *et al.*, 1998,[71] Australia	1,325	1.3	0.2	3.9
Minge *et al.*, 2000,[40] USA	2,156	1.5 (0.8)	3.0 (0.6)	2.8 (0.5)
Bergeron *et al.*, 2001,[28] USA	500	9.8 (12.2)	12.6 (15.6)	46.6 (20.2)

For more explanation see *Tables 5* and *6* and text.

TABLE 8 *ThinPrep and SurePath combined: split-sample study*

Study/country	No. of samples/ women	Conv > Liq LSIL+ (HSIL+) (%)	Liq > Conv LSIL+ (HSIL+) (%)	Both LSIL+ (HSIL+) (%)
McGoogan and Reith, 1996,[72] Scotland	3,091	1.0	0.3	3.6

For more explanation see *Tables 5* and *6* and text.

TABLE 9 *Two-cohort studies*

Study/country	No. conventional smear	No. LBC	Conventional smears LSIL+ (HSIL+) (%)	LBC LSIL+ (HSIL+) (%)
Weintraub, 1997,[74] Switzerland	35,000	18,000	0.70	2.27
Bolick and Hellman, 1998,[34] USA	39,408	10,694	1.12	2.92
Dupree *et al.*, 1998,[75] USA	22,323	19,351	1.19	1.67
Papillo *et al.*, 1998,[76] USA	18,569	8,541	1.63	2.48
Vassilakos *et al.*, 1998,[77] Switzerland	15,402	32,655	1.1	3.6
Vassilakos *et al.*, 1999,[38] Switzerland and France	88,569	111,358	1.58 (0.38)	2.52 (0.68)
Carpenter and Davey, 1999,[78] USA	5,000	2,727	7.7	10.5
Diaz-Rosario and Kabawat, 1999,[79] USA	74,573	56,095	1.85 (0.27)	3.24 (0.53)
Guidos and Selvaggi, 1999,[80] USA	5,423	9,583	1.11	3.70
Tench *et al.*, 2000,[81] USA	10,367	2,231	1.02 (0.46)	1.7 (0.67)
Weintraub and Morabia, 2000,[82] Switzerland	130,381	39,864	0.6 (0.1)	2.3 (0.5)
Ferris *et al.*, 2000,[39] USA	2,110	1,004	3.6 (1.7)	11.4 (3.7)
Marino and Fremont-Smith, 2001,[83] USA	41,871	15,534	1.4, 1.3[a] (0.38) (0.53)	2.0 (0.8)
Day *et al.*, 2002,[84] USA	53,835	18,819	0.9 (0.25)	1.6 (0.29)
Baker, 2002,[85] USA	4,872	3,286	3.5 (0.7)	5.1 (1.0)

[a] Two conventional data sets: current, 2000; and historic, 1999.

from the same underlying population, with similar levels of cervical cancer and precancerous changes, then any change in the detection of significant diagnostic changes will be a proxy measure of increased sensitivity. Once again, of the studies identified both in the original reports and for the update review, an increase in the classification of specimens as LSIL+ was found. The authors often suggest that this is an indication of increased sensitivity. Studies in this category are shown in *Table 9*. Not all the studies in this table provide full details of the proportions of specimens graded as HSIL+, but the two largest studies included in the original report and a further six from the update do (*Table 9*). Vassilakos and co-workers[38] found that this increased from 0.38 to 0.68% with the use of the SurePath LBC method, and Diaz-Rosario and Kabawat[79] found a similar increase of 0.27 to 0.53% using ThinPrep. Both of these two large studies also found a decrease in specimens graded as ASCUS. Subsequently published studies are more likely to report results for HSIL+ graded specimens. In all five papers included in this update, an increased number of HSIL+ specimens was found with the LBC methodology.

However, as has been discussed earlier in respect of split-sample studies, these cohort studies can only provide a proxy guide to improvements in key test characteristics such as sensitivity.

Other outcome measures

Inadequate specimens

Other outcome measures were found in a number of studies. The rate of inadequate specimens was mentioned in a large number of studies. There was considerable variation among studies in both the definition of an inadequate (sometimes referred to as an unsatisfactory) specimen and the proportion of slides classified as such. The majority of studies reported that liquid-based methods had a larger proportion of specimens classed as totally satisfactory. However, as what will really influence the need to recall women is the proportion of inadequate or unsatisfactory specimens, this outcome is described in more detail here from the studies in which the data were available for comparison between liquid-based and conventional smear methods; that is, the 20 studies covered in the original systematic review and the 15 papers included in the update. These

TABLE 10 *Specimens classed as inadequate or unsatisfactory*

	Inadequate or unsatisfactory specimens		
Study	**Conventional smear**	**LBC**	**System**
Hutchinson *et al.*, 1991[49]	0.67% (3/446)	0.67% (3/446)	ThinPrep
Aponte-Cipriani *et al.*, 1995[53]	2.7% (of 854)	8.5% (of 854)	ThinPrep
Bolick and Hellman, 1998[33]	1.1% (427/39,408)	0.29% (31/10,694)	ThinPrep
Laverty *et al.*, 1995[51]	1.5% (of 2,026)	5.2% (of 2,026)	ThinPrep
Lee *et al.*, 1997[57]	1.6% (114/7,223)	1.9% (136/7,223)	ThinPrep
Roberts *et al.*, 1997[58]	3.5% (1,258/35,560)	0.66% (235/35,560)	ThinPrep
Dupree *et al.*, 1998[75]	2.0% (447/22,323)	3.8% (731/19,351)	ThinPrep
Carpenter and Davey, 1999[78]	0.6% (of 5,000)	0.3% (of 2,727)	ThinPrep
Diaz-Rosario and Kabawat, 1999[79]	0.22% (163/74,573)	0.67% (374/56,095)	ThinPrep
Guidos and Selvaggi, 1999[80]	1.2% (65/5,423)	0.45% (43/9,583)	ThinPrep
Shield *et al.*, 19998[86]	17.3% (of 300)	6.3% (of 300)	ThinPrep
Weintraub, 1997[74]	0.70% (of 13,163)	0.26% (of 18,294)	ThinPrep
Vassilakos *et al.*, 1996[64]	5.2% (29/560)	3.8% (21/560)	PrepStain
Data on file, CellPath, 1997	1.0% (89/9,212)	0.6% (54/9,212)	PrepStain
Laverty *et al.*, 1997[69]	2.6% (56/2125)	0.28% (6/2125)	PrepStain
Wilbur *et al.*, 1997[70]	3.6% (10/280)	1.1% (3/280)	PrepStain
Bishop *et al.*, 1998[33]	1.0% (89/9,212)	0.6% (54/9,212)	SurePath
Cheuvront *et al.*, 1998[87]	0.67% (141/21,000)	0.73% (15/2,047)	SurePath
Howell *et al.*, 1998[66]	0.35% (3/853)	0.0% (0/853)	SurePath
Data on file, CellPath, 1999	0.33% (8/2,438)	0.78% (19/2,438)	PrepStain
McGoogan, 1999[88]	8% (40/500)	2.4% (12/500)	ThinPrep
Vassilakos *et al.*, 1999[38] (Swiss results)	13.4% (2070/15,402)	2.7% (890/32,655)	SurePath
Vassilakos *et al.*, 1999[38] (French results)	2.5% (1615/63,853)	0.54% (383/71,017)	SurePath
Bergeron *et al.*, 2001[28]	11.6% (58/500)	0.8% (4/500)	SurePath
Day *et al.*, 2001[84]	4.04% (2,177/53,835)	0.13% (25/18,819)	SurePath
Marino and Fremont-Smith, 2001[83]	0.26% (91/35,496) 0.33% (21/6,375)	0.1% (15/15,534)	SurePath
Minge *et al.*, 2000[40]	0.89% (19/2,156)	0.09% (2/2,156)	SurePath
Tench, 2000[81]	2.94% (305/10,367)	0.4% (9/2231)	SurePath
Baker[85]	0.7% (44/6,576)	0.8% (37/4,719)	ThinPrep
Biscotti *et al.*, 2002[61]	0% (0/400)	0.25% (1/400)	ThinPrep
Ferris *et al.*, 2000[39]	2.4% (76/3,114)	0.4% (12/3,114)	ThinPrep
Luthra *et al.*, 2002[60]	3.5% (36/1,024)	4.9% (50/1,024)	ThinPrep
Monsonego *et al.*, 2001[60]	0.48% (26/5428)	0.53% (29/5,428)	ThinPrep
Park *et al.*, 2001[41]	1.0% (5/478)	1.0% (5/478)	ThinPrep
Ring *et al.*, 2002[63]	2.7% (35/1300)	0.8% (11/1,300)	ThinPrep
Wang *et al.*, 1999[59]	1.1% (11/990)	1.1% (11/990)	ThinPrep
Weintraub and Morabia, 2000[82]	27.5% (of 130,050)	8.1% (of 39,790)	ThinPrep
Yeoh and Chan, 1999[29]	1.36% (99/7,258)	0.56% (93/16,541)	ThinPrep

results are summarised in *Table 10*. More studies from the original systematic review show a higher inadequate specimen rate with conventional smears than with the liquid-based method, and a similar pattern of results was found in the later evidence from the further 15 studies. It should, however, be noted that these proportions, even for conventional smears, mostly tend to be substantially lower than those seen in the NHS programme, where around 9% of smears are regarded as inadequate. Indeed, with a higher inadequate specimen rate in the UK it may be that there is no more to gain in this aspect from the introduction of LBC. (There are, however, some differences between the Bethesda/USA and UK definitions of 'inadequate' in terms of the proportion of the slide that has to have squamous cells.)

As the studies in *Table 10* are from heterogeneous populations, it is uncertain whether it is appropriate to combine these data.

Finally, with respect to specimen adequacy, the introduction of LBC is likely to need a definition of the minimum number of cells for each preparation technique so that standards for adequacy can be clearly and uniformly defined.

Specimen interpretation time

Specimen interpretation times were mentioned in a very few studies.[23,72] Liquid-based methods seem to be associated with shorter times (around 3 minutes compared with 4–6 minutes for conventional smears). Cytologists in Edinburgh found that screening monolayers required more intense concentration and was more tiring. Individual members of staff reported that they suffered from fatigue more quickly and needed to take more frequent breaks than for conventional microscopy.[72] Papillo and co-workers found that there are potential savings of 60% in slide evaluation time for liquid-based methods over conventional preparations, although as slide preparation time is longer, the actual savings are reduced slightly.[89] Papillo concluded that the use of thin-layer liquid-based technologies may decrease the need for cytotechnologists, but only if this technique were "the sole change we were to expect in cytopathology in the next decade".[90]

The need for continuous major adjustments in focus is eliminated as the cells are mainly in one focal plane when using a 10 × screening objective.

Staff training

The need for adequate staff training in the use of the new method has been commented on by several authors reviewing this new technique. Cytotechnologists initially overinterpreted enhanced cytological features observed in thin-layer preparations.[45] Iverson reported that a short educational intervention (over 4.5 hours) did not improve the test scores between a control and an experimental group of cytotechnologists.[91] These authors concluded that it is important that more training opportunities be made available to provide cytologists with information regarding the cytological features unique to thin-layer preparations necessary to ensure accurate interpretation. Spitzer, reviewing recent advances in cervical screening, also drew attention to the training required, particularly in relation to differences in cellular appearance in these preparations.[92] However, Marino and Fremont-Smith[83] found that once they had organised the laboratory workflow, using the LBC process improved efficiency and accurate sample handling and identification and did not necessitate the addition of any new employees in the laboratory. The learning curve for the staff for screening and interpreting ThinPrep slides was minimal.[83] A laboratory guidance document and training log has been agreed for use in Scotland for the demonstration projects set up there.[3]

Homogeneity of specimens

Hutchinson and colleagues[93] showed that the liquid-based method had greater specimen homogeneity than conventional smears and suggested that this accounted for increased diagnostic accuracy.

Assessment of effectiveness

In general, there appears to be evidence suggesting that LBC methods offer the following advantages over traditional smear techniques:

- a decrease in the proportion of inadequate specimens, although the literature reveals a wide and overlapping range in this proportion with both conventional smears and liquid-based methods
- an improvement in sensitivity (seen in the earlier studies but not necessarily maintained subsequently), although this is hard to quantify with the data available in the published literature; this has the potential to help to avoid missing a diagnosis of a lesion requiring further treatment
- a probable decrease in specimen interpretation times, although this is reported in relatively few studies; if confirmed, this may imply that a reduction in primary screener hours is possible

- the potential to use more easily other tests such as HPV on the liquid-based specimen collected; in this context the National Screening Committee is currently conducting a pilot of using HPV status to triage women with mild and borderline abnormalities
- the potential to use the liquid-based technique in automated cytological scanning systems; this was the original impetus for developing LBC, but is outside the remit of this systematic review update.

There are, however, disadvantages, uncertainties and reservations associated with the liquid-based methodology. These have already been listed by the other HTA reviews described earlier, but perhaps the most important are included here:

- There are still no RCT studies comparing important outcomes such as invasive cancer incidence or mortality.
- There are increased costs (mainly laboratory costs) associated with the technique. The magnitude of any savings, such as in reduced repeat tests or in the treatment costs of invasive disease, are hard to quantify from the literature available.
- Considerable retraining is required for cytological laboratory staff and, to a lesser extent, those taking the cervical specimens.
- There are few sensitivity studies using a gold standard comparator. The specificity of the liquid-based method is largely unknown and may be worsened.

The American College of Obstetricians and Gynecologists gave a Committee Opinion Statement on new screening techniques in 1998.[94] This too concluded that there was no large, population-based prospective study to determine whether any of these techniques (including LBC) lowers the incidence of invasive cervical cancer or improves the survival rate. Efforts to reduce the false-negative rate should not detract from encouraging greater participation in the screening programme. Their statement ended: "The appropriate use of these new techniques requires further investigation. They are currently not the standard of care".

In an editorial, Wain argues that it is not clear how LBC techniques compare with other methods of quality improvement, such as random rescreening of a mandated proportion of smears, directed rescreening of 'high-risk' groups and 'rapid rescreening'.[95]

The New Zealand HTA report[24] concluded that estimates of sensitivity and specificity for liquid-based devices could not be reliably determined. Existing research does not provide evidence for improved detection of high-grade abnormalities using liquid-based technologies. The vast majority of missed abnormalities should be detected at subsequent screens and therefore a robust cervical screening programme, using conventional screening, would do this.

Before reaching a conclusion about LBC, however, a number of other important issues should also be considered; these will be described and discussed below.

Assessment of sensitivity

Although the available evidence suggests that test sensitivity is likely to be improved, one needs to ask whether this is a sufficient measure. The aim is to reduce the mortality and morbidity from invasive cervical cancer. To this end there is a cervical screening programme and it is arguable that the sensitivity of the programme as a whole needs to be considered. This can be influenced by a number of factors beyond the issue of the individual test itself.

- The screening coverage of the population: many cancers occur in individuals who have never been screened or who have been only infrequently screened. Increasing the uptake of screening may be much more effective in reducing invasive disease in a population, compared with increasing the sensitivity of individual tests. In the UK as a whole, uptake is fairly high, so it may be hard and expensive to increase it still further. However, uptake is also quite variable (e.g. geographically) and further efforts to target an improvement in uptake may be more effective and cost-effective than an improvement in test sensitivity.
- The frequency of screening: if the premalignant phase has a long duration compared with the frequency of screening then a single false-negative result is likely to be diagnosed correctly at the next screen before the disease has progressed. The sensitivity of the programme is thus a function not only of individual tests but also of the screening interval. To make best use of resources to increase the programme sensitivity a balance may have to be struck between investment in more sensitive but more costly tests and investment in more frequent testing. In this context, it is important to note that coverage is already relatively high in England and Wales. However, the potential to increase it still further in some groups, particularly those in which uptake is low, should be considered.

Assessment of LBC using split-sample studies

Much of the evidence cited in support of LBC is based on results from split-specimen studies. Here the cervical specimen is split between making a conventional smear and being used for a liquid-based method. This may be an unfair assessment of both techniques because clearly less of the specimen is available for either method. Indeed, because the liquid-based sample is usually the residual specimen after the smear is made there may be a substantial loss in the smear preparation of cellular material that would otherwise be included in the liquid-based sample. To this extent, this study methodology may underestimate the improved performance of the liquid-based method. This drawback has been studied and attempts have been made to quantify it.[42] Although the two-cohort study methodology does not have the in-built comparison mechanism, it may be a fairer assessment of the improvements in sensitivity provided that the two cohorts are both large enough and genuinely comparable. It is also argued that, in split-sample studies, the liquid-based method is clearly the 'research' technique, in contrast to the conventional smear as the 'standard', and this in itself may introduce bias.

Sawaya and Grimes, in considering new technologies in cervical cytology screening, also discuss the reasons that split-sample study designs are suboptimal.[97] First, an increase in the absolute percentage of women with abnormal results may not mean that these women have abnormal histology. Second, sensitivity cannot be calculated if investigators do not apply the same reference standards to all the women in the study. In the split-sample studies, the reference standard was not applied to all the women in the study, so the number of women in the study with disease was unknown. Third, replacement techniques are bidirectional. Compared with conventional smears, they may reclassify some relatively low-grade smears as higher grade or reclassify some relatively high-grade smears as low grade. Although additional higher grade smears may be uncovered, some may be hidden. Therefore, the net benefit is unclear. Although liquid-based methods usually detected more abnormalities than conventional smears, Sawaya and Grimes argue that replacement techniques should be expected to identify at least the abnormalities identified by conventional tests.[96]

Specimen collection devices and the effectiveness of specimen collection

In comparing conventional cervical smears with LBC and examining the associated literature it became clear that it is important also to consider the specimen collection device. Although a full systematic review of this issue was not within the terms of the previous report or this update, the previous report considered the published systematic review and meta-analysis by Martin-Hirsch and colleagues.[97] This concluded that the widely used Ayre's spatula is the least effective device for cervical sampling and should be superseded by extended-tip spatulas. Thus, in respect of collecting endocervical cells the odds ratio for the comparison of extended tip versus Ayre's spatula was 2.25 (95% CI 2.06 to 2.44) and for the detection of dyskaryosis the odds ratio was 1.21 (95% CI 1.20 to 1.33). The collection devices that were better at collecting endocervical cells were also more likely to produce adequate smears (no blood or inflammatory cell contamination, and sufficient material collected).

The original report stated "these sort of improvement rates in detection which result from replacing the traditional wooden Ayre's spatula with extended-tip plastic spatulas are of a roughly similar magnitude to the improvements seen with replacing conventional smears with liquid-based methods. This is not to suggest that these two possible changes should be seen as alternatives but it may be important to prioritise their introduction and to ensure that differences in collection device do not confound the comparison of the two cytological techniques."

Use of the Ayre's spatula has now been superseded by that of the extended-tip Aylesby spatula in most parts of the UK. In nine of the 15 most recent studies (published between 1999 and 2002), the most common device in use was a broom-style collection device (Cervex Brush). Only in three studies was the Ayre's spatula used.

Chapter 4

Systematic review of economic evidence for LBC services

Overview of economic assessment

There are very few areas of economic evaluation in which the full range of evidence required to determine cost-effectiveness is forthcoming from a single empirical study. Evaluations of screening programmes, in particular, are unlikely to be informed by such studies owing to the interval between the intervention (the screen) and the range of relevant outcomes [incidence of invasive cancer, mortality avoided, life-years gained (LYG), or quality-adjusted life-years (QALYs) gained].

The use of decision modelling techniques to synthesise data from disparate sources in order to estimate these long-term outcomes, and to attach cost and utility weights to the screen population's health profiles, provides a suitable methodology for the evaluation of screening programmes. Indeed, the vast majority of economic evaluations of cervical screening programmes have been undertaken using modelling methods.

This chapter presents the combined results of the review of the economic and modelling evidence relating to LBC techniques from the original systematic review[1] and an updated review covering literature published since the completion of the earlier report.

Methods

The initial section of the earlier report aimed to review general issues in the health economic modelling of cervical cancer screening, which generated classification criteria (relevant factors and outcomes) for the evaluation of the published evidence on liquid-based services, and provided inputs for the modelling of cervical screening for the UK.

The updated systematic search focused on economic assessments of LBC screening techniques. Details of this systematic search are presented in Chapter 3. A generic proforma for the critical appraisal of modelling studies in health economics, expanded to include the relevant factors specific to cervical cytology screening, was used in systematically reviewing the studies identified. The key outcomes derived were:

- proportion developing invasive cancer
- proportion dying from invasive cancer
- additional days of life/life-years gained
- average lifetime costs
- cost per life-year gained, incremental.

Results

The following sections describe the findings of the review, first with respect to issues relevant to the modelling of cervical screening programmes, and second relating to estimates of the cost-effectiveness of LBC techniques compared with conventional Pap smear testing.

Topic review of issues in health economic modelling of cervical cancer screening

The following factors were identified from the literature on models of cervical cancer as relevant parameters for the development and validation of models to represent the cost-effectiveness of alternative cervical screening programmes. The parameters are categorised as either observable or unobservable clinical input parameters, key clinical events for the validation of cervical screening models or cost parameters.

Observable factors

- Participation rate
- false-positive rate
- preinvasive stages
- invasive cancer
- clinical survival
- death from other causes
- stage at identification
- unnecessary treatments arising from false-positive screen results.

Unobservable factors

- Onset of CIN
- regression of preinvasive stages

- progression of preinvasive stages
- duration of preinvasive and invasive stage
- test sensitivity
- relationship between prognosis and stage at identification.

Observable events for use in calibrating and validating a model

- Clinical incidence
- mortality from cancer
- detection rate preinvasive
- detection rate invasive
- death from other causes.

Costs

- Cost of screen test
- capital purchase costs
- costs of screen-initiated therapies/treatments (e.g. colposcopy).

The key parameter driving the differential long-term effectiveness of alternative screening technologies is the sensitivity of the different technologies (based on the proportion of false-negative results). Test specificity (based on the proportion of false positives), together with the screening test costs, have the largest impact on the costs associated with alternative screening programmes. Specificity may also have a significant impact on programme effectiveness if short-term utility effects are accounted for within an analysis.

Systematic review of economic studies for LBC services

In the original HTA report, the systematic search for health economic studies of LBC services in cervical cancer identified three studies. Two studies were national health technology assessment agency reports, one from the AHCPR of the USA, published in 1999,[26] the other from the Australian Health Technology Advisory Committee, published in 1998.[10] The other study was an article published in a peer-reviewed journal in 1999, which focused on the US healthcare system.[98]

The updated systematic search identified four economic evaluations that have been published since the completion of the original literature search,[95–98] although one of the four identified studies[99] is a journal version of the above AHCPR report. In addition, the draft report of the evaluation of HPV/LBC cervical screening pilot studies in England and Wales includes an assessment of the cost-effectiveness of LBC, which updates the model described in the original HTA report with data obtained from the pilot studies.[1]

The following sections briefly review the comparators included, the methodologies and the results reported by the full set of identified studies. Detailed summary tables of the studies are presented in Appendix 4.

Comparators

The only named LBC technique assessed in any of the evaluations is the ThinPrep (2000?) system. Brown and Garber,[98] and Hutchinson and colleagues[45] compare ThinPrep with 10% random rescreening to conventional Pap smear testing with 10% random rescreening.

The other identified studies do not evaluate named LBC techniques. The AHCPR report and Myers and co-workers[99] evaluate hypothetical new screening techniques (based on LBC and assisted rescreening) with varying levels of sensitivity, specificity and additional cost, with the aim of establishing values for these parameters at which a new technique would be considered cost-effective.

Montz and colleagues[100] and Moss and colleagues[2] estimate the cost-effectiveness of a generic LBC technique compared with conventional Pap smear testing (Montz and colleagues include 10% random rescreening for both interventions[100]) as part of their baseline analysis, whereas Raab and colleagues[101] assess the necessary increase in the number of HSIL test results by an LBC technique, compared with observed detection rates, for it to be cost-effective.

The review by the Australian Health Technology Advisory Committee estimates the potential for health gain from a generic technology aimed at improving the test characteristics.

The studies assess the stated comparators over a series of screening intervals, ranging from 1 to 10 years, other than the Australian report (2-year interval), Raab and colleagues[101] (1-year interval), Montz and colleagues[100] (based on self-reported compliance rates) and Moss and colleagues[2] (5-year interval).

Methodologies

The majority of the identified economic evaluations use a state transition methodology to model the natural history of the disease together with a model of the screening intervention and subsequent diagnosis and treatment.[2,98–100,102,103] Of these five studies, only Moss and co-workers[2] present their analysis from a UK perspective; the remaining studies cover the US perspective.

All of the modelling studies simulate the life experience of a cohort of women, although they apply screening over varying age ranges and assess the cost-effectiveness of alternative screening intervals. The basic structure of the models is similar, with the natural history of cervical cancer being modelled as a progression through a series of precancerous states [defined as either squamous intraepithelial lesions (SILs) or CINs; the AHCPR also include an initial HPV state on the assumption that all cervical cancer arises from HPV infection], from which women progress to cancer (defined as single state or a series of states, e.g. local, regional and distant). The natural history sections of all models, except for Moss and colleagues[2] are populated with age-specific disease incidence, progression and regression rates.

Raab and colleagues[101] state that a decision analytic model is used, but it is unclear what type of model is used. It could be a decision tree that represents one round of screening with life expectancy and treatment cost estimates attached to the different terminal nodes of the tree. The model describes progression rates from HSIL to different stages of cancer; LSIL screen results are ignored on the basis that they will be picked up at the next screen (a single screen interval of 1 year is tested).

The review by the Australian Health Technology Advisory Committee does not estimate the lifetime impact of the technologies; rather, it describes the number of cancer cases detected through the estimation of the number of LSILs and HSILs that progress to cancer. The approach is similar to that adopted by Raab and colleagues, in that the effectiveness of new technologies is described in terms of an increase in the number of positive screen tests. This study also only considers the cost-effectiveness of a single round of screening, and thus does not account for the cumulative effect of screening over specified intervals (i.e. missed abnormalities in one round may be picked up in later rounds).

Assumptions regarding test characteristics vary between the studies; most notably, Brown and Garber[98] assume a sensitivity rate of 80% for conventional Pap smears, whereas the other studies use more conservative estimates (Raab and co-workers[101] do not apply a sensitivity rate as cancer incidence is based on observed test results). Most studies assume a constant sensitivity rate across the different precancer states, but Hutchinson and colleagues[37] present differential sensitivity rates for LSIL and HSIL results, whereas Moss and colleagues[2] present differential sensitivity rates for CIN 1, 2, and 3. Specificity is either not mentioned or assumed to be equal across screening techniques in all baseline analyses.

Moss and colleagues[2] use the same model as used in the original LBC HTA report,[1] and use identical data to populate the model other than for parameters describing the costs and inadequacy rates of conventional Pap smear screening and LBC screening.

Other than Raab and colleagues,[101] who only consider HSIL test results, all of the studies assume that LSIL or worse test results are investigated with colposcopy, and all but one study assume that ASCUS results are rescreened and investigated with colposcopy if the rescreen is abnormal. Brown and Garber[98] treat ASCUS results as normal.

None of the US-based evaluations accommodate the impact of alternative rates of inadequate screens on the costs associated with LBC, while Moss and colleagues[2] assume that inadequate smears are replaced with adequate tests. In the Australian report it is unclear whether savings from reduced inadequate smears are included.

All studies adopt a health service perspective, although Brown and Garber[99] claim a societal perspective in the methodological description. The US studies discount costs and health benefits at 3% (0–5%), whereas Moss and co-workers[2] follow Treasury guidelines and discount costs and health benefits at 6% and 1.5%, respectively.

Results

The main results from the economic studies that presented incremental cost-effectiveness data are presented in *Table 11*.[2,98,100,102,103] The cost data are converted to pounds sterling in the year of the original analysis and then uprated to 2002 costs using the NHS Pay and Prices Index[104] (note that this is not intended to estimate cost-effectiveness in the UK setting, but rather to aid comparison between the results). Only the data relating to conventional Pap smear testing and LBC techniques have been extracted, and cost-effectiveness ratios have been recalculated to account for new rank ordering and the exclusion of dominated and extendedly dominated screening options.[105]

The assorted US-based studies present quite different levels of absolute costs and effects

TABLE 11 *Results reported in identified economic evaluations of LBC*

	Average cost[a]	Cancer incidence[b]	Life-days saved[c]	Cost per life-year saved
AHCPR report, 1999[102d]				
No Pap	£893	3014.6	–	
Pap 3-yearly	£1,108	506	19.2	£2,840
Improved Pap 3-yearly	£1,240	246	21.4	£15,215
Improved Pap 2-yearly	£1,433	132	22.84	£33,988
Improved Pap every year	£2,000	33	23.64	£179,730
Brown and Garber, 1999[98e]				
Pap 4-yearly	£446	330	23.91	
ThinPrep 4-yearly	£505	280	25.07	£14,138
ThinPrep 3-yearly	£695	250	25.73	£80,023
ThinPrep 2-yearly	£1,059	220	26.19	£219,962
ThinPrep every year	£2,194	190	26.8	£517,214
Hutchinson *et al.*, 2000[103f]				
Pap 10-yearly	£556	–	3.5	
ThinPrep 10-yearly	£569	–	5.1	£2,060
ThinPrep 5-yearly	£647	–	6.9	£10,989
ThinPrep 3-yearly	£729	200	7.7	£25,993
ThinPrep 2-yearly	£836	123	8.2	£54,268
ThinPrep every year	£1,191	38	8.8	£150,039
Montz *et al.*, 2001[100g]				
Pap, self-reported compliance	–	11.8 per year	–	
LBC, same compliance	–	8 per year	–	£10,627
Moss *et al.*, 2002[2h]				
Pap 5-yearly	£58.28	–	48.91	
LBC 5-yearly	£57.07	–	49.64	Dominant

[a] Lifetime costs converted to UK pounds at exchange rate in the year of analysis, then uprated to 2002 costs using NHS Pay and Prices Index (other than Moss and colleagues, 2002[2]).
[b] Lifetime cases of cervical cancer cases per 100,000 unless otherwise stated.
[c] Compared with no screening (dominated and extendedly dominated strategies are excluded, other than Moss and colleagues, 2002[2]).
[d] Includes 10% random rescreening; base case assumes 60% reduction in false-negative rate for improved screening (Pap sensitivity 0.51, improved sensitivity 0.804); costs and life-years discounted at 3%, originally presented as 1997 US dollars.
[e] Includes 10% random rescreening, base case assumes Pap sensitivity 0.8, ThinPrep 0.919; costs and life years discounted at 3%, originally presented as 1996 US dollars. Cancer incidence data only available to nearest 10.
[f] Includes 10% random rescreening; base case assumes Pap sensitivity 0.504–0.552 (LSIL–HSIL), ThinPrep 0.75–0.822; costs discounted at 3%, discounting of life-years not mentioned, originally presented as 1997 US dollars.
[g] Includes 10% random rescreening; base case assumes Pap sensitivity 0.51, LBC 0.73; costs and life-years discounted at 3%, originally presented as 1997 US dollars.
[h] LBC data averaged over three sites; base case assumes CIN stage-specific sensitivity rates 0.37–0.5, LBC improves sensitivity by 2–15%. Costs and life-years discounted at 6% and 1.5%, respectively, UK costs originally, year not specified.

(life-days saved), although the relative values of the life-days saved between the screening options are similar between the different studies. Thus, differences in the ICERs are mainly due to differences in the costs associated with each screening strategy.

However, it is noted that the exclusion of dominated strategies leads to the exclusion of conventional Pap smear testing as a screening option other than as the baseline screening option (i.e. the cheapest screening option) in all studies.

Based on a threshold cost-effectiveness ratio of US$50,000, the rearrangement of the US-based cost-effectiveness data shows that LBC is the most cost-effective strategy at either a 2-year or 3-year screening interval (the self-reported compliance rates used by Montz and colleagues[101] equate to a screening interval of between 2 and 3 years).

The Australian report[25] presents a range of estimated costs per additional potential cancer case (avoided), where cancer cases are determined by assuming that 1% and 12% of LSIL and HSIL

screen tests progress to cancer, respectively. A 15% increase in positive screens, of which 90% are LSILs, and an additional cost of Aus$20 per screen, leads to an ICER of Aus$138,000 (£72,108, 2002 costs).

Raab and colleagues[101] present only a figure describing the number of additional HSILs that would need to be detected at a range of additional costs for a new technology to fall within different thresholds for the cost of gaining an additional life-year. This figure shows, for example, that for a cut-off of $50,000 per LYG, and an incremental cost of $10 per test, an additional 236 HSILs would need to be detected per 10,000 women screened.

The UK-based study updates the results of the economic model presented in the earlier HTA report with new data describing screening costs and inadequacy rates, although only results for a 5-year interval are presented. Ordering the results in an incremental manner, using the average values from the three pilot sites for the costs and effects of LBC, this study estimates very little difference in both costs and life-days saved between cervical screening based on conventional Pap smear testing and LBC techniques, although the incremental analysis shows that the LBC techniques gain an extra 0.73 life-days and save £1.21 per woman screened, that is, LBC dominates conventional Pap smear testing.

Conclusions

The identified economic evaluations comparing LBC techniques with conventional Pap smear testing reviewed in this chapter can be placed in three categories. The first category describes those studies that felt that the uncertainty surrounding the relative values of the test characteristics (sensitivity and specificity) of LBC in particular, was too great usefully to inform the results of an economic analysis.[101] These analyses are of limited value to policy makers, other than to emphasise the need for further research (although no potential value for the research is described).

The second category of cost-effectiveness analyses includes the remaining set of US-based analyses.[98,100,102,103] These analyses all estimated a most likely value for the test characteristics of the alternative screening techniques, enabling the calculation of mean cost-effectiveness ratios. In addition to being US based, other key common features of these analyses include the assumption of a generic sensitivity rate (i.e. sensitivity is the same for low- and high-grade lesions) and no consideration of the impact of LBC techniques on the rate of inadequate smears. The relevance of these studies to the UK is limited owing to the use of US-based incidence rates and costs, as well as the general application of the Bethesda classification index to describe precancerous lesions. Furthermore, the assumed improvement in the sensitivity rate of LBC techniques compared with conventional Pap smear testing is significantly higher than that assumed in the earlier UK HTA report,[1] and the subsequent pilot sites evaluation.[2] If the stated sensitivity rates are accepted, the inclusion of differential inadequacy rates further improves the cost-effectiveness of LBC, which could reduce the recommended screening intervals.

However, the apparent cost-effectiveness of LBC derived from the baseline results in this category of analyses is not as clear-cut as it appears. The AHCPR report[102] described substantial uncertainty around the baseline estimates of sensitivity and specificity, and found that both sensitivity and specificity are important in determining cost-effectiveness.

Brown and Garber[98] find that LBC primary screening is dominated, that is costs more and saves fewer life-years, by automated rescreening techniques. Conversely, Hutchinson and colleagues[103] assumed that ThinPrep has a higher sensitivity rate than the automated rescreening techniques and found that the LBC technique is cost-effective.

The third category consists of the only identified UK-based study,[2] which updated the economic analysis reported in the original HTA report.[1] Using data derived from three pilot study sites assessing the using of LBC in UK settings, Moss and colleagues[2] found no evidence to alter any of the parameters specified in the earlier report, other than the costs of the respective screening tests and the assumed inadequacy rates. The assumption of similar rates of sensitivity and specificity in this latter report should not be interpreted as a confirmation of the initially assumed rates, rather that the pilot studies were not designed to estimate sensitivity and specificity. Although there remains significant uncertainty regarding the relative sensitivity of the alternative screening techniques, there appears to be a consensus that the sensitivity of LBC techniques is unlikely to be worse than that of conventional Pap smear testing. If the assumption of equal specificity between the alternative techniques is also strong, then the results of the pilot studies indicate that,

at worst, LBC techniques have very similar aggregate costs and save very similar numbers of life-years. If quality of life effects are incorporated it may be that the reduction in the number of inadequate smears would improve the aggregate utility of women screened. Best case scenarios, in which sensitivity rates are improved with LBC techniques, may increase aggregate costs (owing to additional treatments for women with true-positive smears who would not progress to cancer), although it is likely that the accompanying increase in cancers prevented (and hence life-years saved) would be achieved at a cost-effectiveness ratio well below the commonly quoted £30,000 acceptable threshold. The analysis reported in Chapter 5, which further updates the analysis undertaken by Moss and colleagues[2] confirms this prediction.

However, as alluded to above, a range of economic evaluations was identified in the updated systematic literature search (1999–2002) that assessed the economic impact of cervical screening approaches other than conventional Pap smear testing and LBC techniques. Smith and colleagues[106] analysed the cost-effectiveness of AutoPap, the semi-automated slide analysis device (as included in the analyses reported by Brown and Garber,[98] and Hutchinson and co-workers[103]), and a range of authors reported economic analyses of HPV testing as an adjunct or alternative to Pap smear testing. Another study was identified that evaluated the economic impact of alternative protocols for the management of atypical (ASCUS) screen results.[107]

The aggregate analysis of the cost-effectiveness of potential combinations of these approaches to screening for cervical cancer is outside the scope of the current review, although it is noted that the relative cost-effectiveness of all relevant screening programme configurations should be analysed simultaneously.

Chapter 5

Modelling the health economic impact of LBC within the UK

Model overview

The question to be addressed by the model is: 'What would be the likely impact of the new liquid-based cytology screening techniques, in terms of incidence of cervical cancer, associated mortality, and in terms of the costs and cost-effectiveness, when compared with conventional smear testing for a typical UK population?'

The model developed here provides a macrosimulation of the life experience of a cohort of women followed from the age of 15 to 95 years. The model has three elements: a state transition methodology is used to simulate the natural history of the disease; a model of the screening intervention interacts with this to assess the impact of the screening programme; and a life table is used to reflect age-specific all-cause mortality. Health outcomes, resource utilisation and costs are estimated for the cohort. A health service perspective of costs is taken in the analysis and only direct costs are considered. The baseline analysis discounts costs at 6% and life-years at 1.5%.

The same model as reported in the earlier HTA report is used, which is based closely on the work reported by Sherlaw-Johnson and colleagues.[108] The structure of the model remains the same as that described in the earlier HTA report, though Sherlaw-Johnson and colleagues have updated the parameterisation of their model to incorporate age-specific incidence rates for CIN1 (previously a constant rate had been assumed) and updated estimates of the effectiveness of conventional Pap smear testing,[109] which are included in the current analysis. The updated systematic review has concentrated on updating the test characteristics parameters (sensitivity and specificity) for LBC and conventional Pap smear testing. More reliable estimates of the rate of inadequate smears, and the screening costs, associated with both approaches are also incorporated from the recent evaluation of the HPV/LBC cervical screening pilot studies.[2]

The following sections describe the assumptions around the input parameters for the model, covering the natural history of cervical cancer, the screening interventions, screening and treatment costs and the outcomes collected from the model. The main assumptions are then summarised and a table describing the full set of input parameter values is presented.

Modelling assumptions

Natural history of cervical cancer

Preinvasive cancer is classified histologically into three categories of cervical intraepithelial neoplasia: CIN1, CIN2 and CIN3. For the purposes of this model, incidence of disease is defined as the onset of CIN1. In the absence of any intervention, the disease is assumed to progress through each preinvasive stage and from CIN3 to invasive cancer, with the proviso that regression to a disease-free state may occur from CIN1 only. It is recognised that there is some evidence that the higher grades of CIN may also regress,[110] and this possibility is explored in sensitivity analyses.

The model calculates state transitions at intervals of 6 months. Within any 6-month interval progression can only occur to the next immediate state, with the exception of CIN1 lesions where a proportion of fast growing lesions may progress to CIN3. The baseline disease progression state transition matrix is presented in *Table 12*. Disease progression and the proportion of fast growing cancers are assumed not to be age specific. No further incident cases of CIN1 are assumed to arise after the age of 68 years; preinvasive lesions present at the age of 68 years are assumed to progress at the rates previously identified.

Age-specific all-cause mortality is estimated from interim life tables produced by the Government Actuary's Department based on data for the years 1992–1994 for females in England and Wales.[111] A constant risk is assumed for mortality from invasive cancer. This mortality is based on an average life expectancy with invasive cancer present in an unscreened population of approximately 10 years, corresponding to

approximately 55% overall survival at 5 years postdiagnosis and treatment,[112] and a mean duration prediagnosis of approximately 5 years. This is based crudely on previous modelling work undertaken by Eddy.[113]

Screening interventions

For the purposes of this model, a cohort of 100,000 women aged 15 years is defined. Screening is assumed to be taken up by a certain percentage of women in this cohort, this is defined as the coverage of screening. Baseline coverage is estimated at 85%, ranging from 80 to 90% based on the range of regional coverage rates reported.[6] Women are assumed to attend screening either at the regular intervals or not at all. Screening is undertaken between the ages of 21 and 64 years at regular intervals. The model can be used to evaluate any given screening interval; however, intervals from 2 to 5 years are analysed.

The conventional smear screening test results are classified into five states: negative, borderline, mild, moderate and severe. In addition, screening slides may be classed as inadequate. For the purposes of this model, inadequate slides are simply assumed to require an immediate rescreen; these slides are then assumed to be adequate. The impact of inadequate slides is therefore merely to increase the total number of slides processed by the inadequate percentage. In addition, for the purposes of the model, the states borderline and mild are grouped together, as are the moderate and severe results.

The screen test characteristics are defined in terms of the probability of achieving the different test results given the underlying histological state: the true test specificity and sensitivity. The baseline test characteristics for the conventional smear screen test are given in *Table 12*, which are based on the latest estimate presented by Jenkins and colleagues.[109] This characterisation of test results allows the modelling of differential sensitivity by lesion grade (CIN1, CIN2, CIN3 and invasive cancer).

The England and Wales, and Scottish, pilot studies were not set up to investigate rates of sensitivity. Moss and colleagues[2] did not find any clear evidence of differences between the prepilot (conventional Pap smear) and pilot period in terms of rates of borderline to severe dyskaryosis test results, although the analyses of data describing outcome of referral to colposcopy estimate that the sensitivity rate for CIN3 could have improved from 50% for conventional Pap smear testing to 54% for LBC.

The Scottish report[3] presented data describing the percentage of tests that were unsatisfactory or displayed abnormal results for both conventional Pap smear and LBC (50% of the smears tested during the pilot study at each of the sites continued to use conventional Pap smear testing), although it is unclear how many tests were undertaken for each technique (either 15,000 or 30,000). These data show that LBC testing identified around twice the number of mild, moderate and severe test results compared with conventional Pap smear, and the increase is consistent across the three results. However, no analysis of the outcome of these tests after colposcopy is presented and so it is difficult to assess the impact of these data.

Of the other studies identified in the literature review, only three presented data that could be used to compare LBC and conventional Pap smear testing with respect to separate sensitivity rates for different lesion grades. A meta-analysis of these studies for the three specified histological findings (CIN1, CIN2/3 and invasive cancer) shows that there is no significant difference between the techniques in any of the three categories, although the number of cases included is small.

The small numbers informing differential sensitivity rates precluded their use, so an aggregate estimate of an improvement in sensitivity based on the meta-analysis of false-negative rates for conventional Pap smear testing and LBC screening, as presented in *Figure 2* (Chapter 3), is taken as the best source for the estimation of the relative difference in sensitivity rates between the two screening approaches, even though positive screen results are defined as LSIL+ and so are not strictly comparable to the UK classification system. The relative improvements in sensitivity of LBC compared with conventional Pap smear testing for ordinary and high-risk populations, and the combined estimate, are presented in *Table 12*.

The estimate of improved sensitivity for CIN3 lesions of 4%, presented by Moss and colleagues,[2] is used as the best estimate for such lesions. On the basis of a 7.8% aggregate improvement and a 4% improvement in CIN3 sensitivity, an improvement of 8.42% was imputed for CIN1/2 sensitivity (as shown in *Table 13*).

The majority of the identified studies examined ThinPrep, with a few looking at SurePath. Indirect comparisons of the alternative LBC techniques found no differences between the results, so the modelling analysis does not differentiate between alternative techniques.

TABLE 12 *Estimated improvement in aggregate sensitivity by risk group*

Population	LBC				Conventional				LBC Improvement in sensitivity
	False negatives	Total cases	False-negative rate	Sensitivity	False negatives	Total cases	False-negative rate	Sensitivity	
Ordinary populations	190	870	0.218	0.782	302	895	0.337	0.663	0.179
High-risk populations	587	3010	0.195	0.805	524	2302	0.228	0.772	0.042
Combined	777	3880	0.200	0.800	826	3197	0.258	0.742	0.078

TABLE 13 *Estimation of differential sensitivity rates*

	CIN3	CIN1/2	Aggregate
Proportion of identified cases[a]	0.141	0.859	
Sensitivity[b]			
Conventional Pap smear	0.6400	0.5888	0.5960
LBC	0.6656	0.6384	0.6425
Improvement	4.0%	8.42%	7.80%

[a] Cervical screening programme, England, 2001/02.
[b] Conventional rates from Jenkins and colleagues (1996),[109] CIN3 improvement,[2] aggregate improvement (meta-analysis), CIN1/2 improvement (imputed).

Meta-analysis of the six studies[23,28,30,34,39,41] that compared specificity of conventional Pap smear testing and LBC showed no difference, and the specificity of the LBC techniques is assumed equal to the specificity for conventional Pap smear testing.

Two intervention policies based on screening test results are modelled:

- **policy A**: Immediate colposcopy for all women with an abnormal smear test from borderline/mild or worse.
- **policy B**: Immediate colposcopy for all women with a smear test result of moderate or severe, rescreen at 6 months for all women with a borderline or mild screen test result, and colposcopy for all women who have a second borderline or worse smear test result.

The baseline health and health economic outcomes are presented for policy B.

Colposcopies are assumed to be 100% sensitive and specific. It is assumed that all abnormalities found at colposcopy are treated. An overall effectiveness of treatment is used within the model and those patients successfully treated are assumed to return to the clear state. The baseline effectiveness is taken from the NHS Cervical Screening Programme (NHSCSP) guidelines on quality standards expected from colposcopy.[114]

Costs

Total direct costs of screening, diagnosis and treatment are included within the model and estimated from the following unit costs:

- conventional smear test
- LBC techniques
- colposcopies
- treatment of preinvasive lesions
- treatment of invasive cancer.

The evaluation of the HPV/LBC pilot sites included a detailed costing exercise for both conventional Pap smear testing and LBC testing, which covered primary care costs (e.g. taking smears, administrative letters), as well as the respective costs associated with slide preparation and smear reading.[2] These costs are transferred directly into the current evaluation.

Primary care screening costs were based on questionnaires sent to samples of general practices across the three pilot sites to estimate consultation

costs for LBC, and to a sample of practices in Oxfordshire to obtain equivalent data for conventional Pap smear sample taking. The collected data show a significant difference between the two techniques in total consultation time, with a mean time of 13 minutes and 20 seconds for conventional Pap smear testing and 8 minutes and 35 seconds for LBC. However, additional qualitative responses from smear takers and other practitioners cast doubt on the magnitude of the time saving, such that the base-case time saving is assumed to be 1 minute (the impact of a 5-minute time saving is assessed in the sensitivity analysis). Staff unit costs are applied assuming that practice nurses undertake 80% of samples and GPs take 20%. Administration costs are assumed to be similar between the techniques.

Slide preparation costs include capital and labour costs, which were estimated for three alternative pieces of LBC equipment (ThinPrep T3000 and T2000, and the PrepStain package), as well as for the slide staining equipment required for conventional Pap smear testing. The baseline estimates assume a laboratory processing 60,000 smears per annum. The three LBC approaches involve more preparation costs than conventional Pap smear testing, and the ThinPrep systems require more inputs than the PrepStain system. Similar results are also found for the relative costs of the consumables required for the alternative techniques.

To assess costs associated with screening the smears, screening staff completed record sheets over 3 weeks. The costs attached to these data accounted for different staff mixes used to undertake the different phases of screening (primary screening, checking and rapid review). No significant differences between LBC and conventional Pap smear testing were found, although the conventional approach was slightly more expensive.

The cost analysis also includes various other laboratory costs, such as overheads, non-screening staff time and the cost of non-screening staff (secretaries, etc). These costs were assumed to be equal across the techniques.

Moss and colleagues[2] also estimated the one-off transition cost of converting laboratories to LBC (subsequent training costs are assumed to be similar between the alternative techniques). The transition costs included the time required to provide initial training for smear takers and readers, which includes staff time, travel costs, training coordinator and materials costs. Other costs include handling the backlog of tests during the transition phase, structural changes to laboratories and changes to the barcoding system.

The total national cost was estimated to be £10.1 million. Apportioning these costs as a cost per smear, assuming an average of 3.9 million smears per year over a useful lifetime for LBC of 10 years, leads to an additional cost per LBC smear of £0.26. The transition cost would not vary significantly if alternative assumptions regarding the annual number of smears or the lifetime of the technology varied, e.g. assuming 3 million tests per year and a 5-year lifetime gives a cost per screen of £0.67. Note that the cost of purchasing the slide preparation equipment is not included in the implementation cost of £10.1 million; rather, this cost is included in a separate category (preparation equipment cost) to inform a comparison with conventional preparation equipment costs.

Colposcopy is routinely undertaken in a gynaecology outpatient setting. Practice may vary between individual hospitals, although increasingly colposcopy and treatment by cervical 'conisation' of any abnormalities is undertaken in a single outpatient appointment. In situations where colposcopy and treatment are undertaken at different visits, these would still constitute a single outpatient consultation in terms of charging. Thus, a typical charge for gynaecology outpatient appointments is used as a proxy for the cost of colposcopy and subsequent treatment where necessary, with the recognised proviso that these charges may not represent the true costs of colposcopy and treatment.

Treatment of invasive cancer is dependent on the stage of cancer at diagnosis. Recommended procedures in detection, diagnosis and evaluation of cervical carcinoma are detailed by Obralic and colleagues[112] under the International Federation of Obstetrics and Gynaecology (FIGO) staging system. These provide recommendations for the use of surgery, radiation therapy and chemotherapy, and identify the stages at which these are appropriate. Surgical interventions include cervical conisation, extrafascial hysterectomy and radical hysterectomy with bilateral pelvic lymphadenectomy. Radiation therapy may be appropriate as an adjunct to surgical intervention or may be used with patients who have more advanced disease who are not candidates for radical surgery. Cervical conisation is increasingly being adopted for stage Ia1

carcinomas. Thirty per cent of screen-detected cancers are assumed to be treatable by conisation in the model.

In terms of resource utilisation, hysterectomies are classified as HRG (Health Resource Group) M07, 'Upper genital tract major procedures'. For the purposes of this economic model, the cost associated with HRG M07 has been used as a proxy for the cost of treating the remaining patients diagnosed with invasive cancer. This HRG cost, however, does not take into account the costs of subsequent radiation therapy, palliative care and long-term support. This cost is also assumed to apply to those patients who die from cervical cancer. Thus, this cost is almost certainly an underestimate of the costs associated with treating invasive cancer, which will introduce a bias against screening policies and specifically screening developments that improve screen test characteristics.

Rates of inadequate smears

The evaluation of the England and Wales pilot studies is used to inform inadequacy rates for LBC, as well as for conventional Pap smear testing.[2] Moss and colleagues analysed data describing rates of inadequacy from the three pilot sites over a 5-year period before the introduction of LBC to estimate rates for conventional Pap smear testing, as well as over the 12-month pilot period to obtain rates for LBC.

Lower rates of inadequacy were observed in the LBC techniques than previously assumed,[1] especially at the site using the SurePath system (9.7% conventional, 2% ThinPrep and 0.9% PrepStain). However, the lower inadequacy rates reported at the PrepStain site are tempered by the introduction of new reporting guidelines at this site, which may have increased the number of negative results that would previously have been categorised as inadequate.

Model assumptions and input parameter values

The following points describe the main assumptions in the model used to compare the alternative cervical screening approaches.

- In the absence of any intervention, disease progresses through each preinvasive stage and from CIN3 to invasive cancer, although a proportion of patients may move directly from CIN1 to CIN3.
- Disease can regress to a disease-free state from CIN1 only.
- The model incorporates the age-specific incidence of CIN1 between the ages of 15 and 68 years. No further incident cases of CIN1 are assumed to arise after the age of 68 years.
- Disease progression and the proportion of fast growing cancers are assumed not to be age specific.
- Preinvasive lesions present at the age of 64 years are assumed to progress at the rates previously identified.
- A constant risk is assumed for mortality from invasive cancer.
- Screening is taken up by a certain percentage of women in this cohort.
- Women are assumed to attend screening either at regular intervals or not at all.
- Inadequate slides are assumed to require an immediate rescreen; these subsequent slides are assumed to be adequate.
- Colposcopies are assumed to be 100% sensitive and specific. It is assumed that all abnormalities found at colposcopy are treated.
- HRG M07 is used as a proxy for the cost of treating the remaining patients diagnosed with invasive cancer more advanced than stage Ia1. This HRG cost, however, does not take into account the costs of subsequent radiation therapy, palliative care and long-term support. This cost is also applied to patients who die from cervical cancer.

Table 14 presents all the parameter values used in the model, together with ranges and sources, except for the age-specific incidence rates of CIN1 (Sherlaw-Johnson C: personal communication, as used in reference[109]), which are presented in *Table 15*.

Table 16 presents details of the costings for the alternative screening techniques as adopted from the England and Wales pilot sites evaluation.[2] Three baseline costs for LBC screening are presented, representing the estimated costs for three alternative technologies (ThinPrep3000, ThinPrep2000 and PrepStain), including estimated costs of conversion (spread over the anticipated lifetime of LBC screening: 10 years in the base case). The estimated costs for the PrepStain system are less than conventional Pap smear testing. As there are no grounds to differentiate between the effectiveness of PrepStain and ThinPrep systems the baseline cost-effectiveness analysis uses the estimated costs for the newest ThinPrep system (ThinPrep3000, £25.40 per screen), on the basis that the PrepStain system may be assumed to be at least as cost-effective.

TABLE 14 *Description of parameters used in the model*

Description	Baseline	Minimum	Maximum	Reference
Management variables				
Female population	100,000			–
Start age (years)	18			–
First screen age	21			–
Last screen age	64			–
Policy[a]	B	A		–
Screening interval	3	2	5	–
Discount rate: costs	6%	0%	10%	–
Discount rate: health benefits	1.5%	0%	10%	–
6-month progression rates				
Progression rates from clear to CIN1	See *Table 15*			
Regression rates from CIN1 to clear	2.0%			108
Regression rates from CIN2 to clear	0%		1.5%	110
Regression rates from CIN3 to clear	0%		1.1%	110
Progression rates from CIN1 to CIN2	6.0%			108
Progression rates from CIN1 to CIN3	2.5%			108
Progression rates from CIN2 to CIN3	15%			108
Progression rates from CIN3 to IC	1.0%			108
Progression factor (for sensitivity analysis)[b]	100%	50%	150%	–
Incidence factor (for sensitivity analysis)[c]	100%	75%	125%	–
Effectiveness and mortality				
Effectiveness of cervical conisation	90%	80%	100%	111,112
Effectiveness of hysterectomy	85%	75%	95%	112
Screen-detected cancers suitable for cervical conisation (stage Ia1 carcinomas)	30%	10%	50%	[d]
6-month mortality rates associated with IC	2%	0%	4%	111,115
Test characteristics				
Specificity of test	96.6%	95%	98.2%	109
False borderline/mild test result	2.9%	1.8%	4%	109
False moderate/severe test result	0.5%	0%	1%	109
Proportion of CIN1 lesions that give:				
negative test result	34%	20%	48%	109
borderline/mild test result	52%	41%	63%	109
moderate/severe test result	14%	11%	17%	109
Proportion of CIN2 lesions that give:				
negative test result	59%	40%	78%	109
borderline/mild test result	23%	12%	34%	109
moderate/severe test result	18%	10%	26%	109
Proportion of CIN3 lesions that give:				
negative test result	36%	20%	52%	109
borderline/mild test result	23%	17%	29%	109
moderate/severe test result	41%	31%	51%	109
Proportion of IC that give:				
borderline/mild test result	40%	20%	60%	109
moderate/severe test result	60%	40%	80%	109
Other test characteristics				
Inadequate conventional smear slides	9%	7.8%	11.3%	2
Inadequate LBC samples	1.4%	1.0%	2.4%	2

continued

TABLE 14 *Description of parameters used in the model (cont'd)*

Description	Baseline	Minimum	Maximum	Reference
CIN1/CIN2: sensitivity improvement with LBC	13.4%	6.7%	20.1%	[e]
CIN3/IC: sensitivity improvement with LBC	4%	2%	6%	[e]
Percentage of women who take up screening	85%	80%	90%	2
Treatment costs				
Cost of colposcopy and conisation	£185	£135	£235	[f]
Cost of surgical treatment of invasive cancer	£1,700	£1,000	£2,400	116

[a] Policy B: borderline/mild smears retested at 6 months, followed by colposcopy if retest is not normal; policy A: immediate colposcopy for borderline/mild test results.
[b] This factor is applied to all progression rates simultaneously.
[c] This factor is applied to incidence of CIN1.
[d] McGoogan E: personal communication.
[e] See text.
[f] Typical NHS Trust: personal communication.
IC, invasive cancer.

TABLE 15 *Age-specific progression rates from clear to CIN1*

Age (years)	Probability of contracting CIN (%)	Age (years)	Probability of contracting CIN (%)
15	0.02	31	0.10
16	0.05	32	0.10
17	0.09	33	0.09
18	0.14	34	0.09
19	0.17	35	0.08
20	0.19	36	0.08
21	0.22	37	0.07
22	0.22	38	0.07
23	0.22	39	0.07
24	0.20	40–46	0.06
25	0.19	47–50	0.05
26	0.16	51–52	0.04
27	0.15	53–57	0.03
28	0.13	58–64	0.02
29	0.11	65–67	0.01
30	0.10	68 +	0.00

As used in reference 117.

TABLE 16 *Details of cost estimates for alternative screening techniques*

		Liquid-based cytology		
Cost item	Conventional	ThinPrep3000	ThinPrep2000	PrepStain
Smear taker staff cost	£7.66	£7.08	£7.08	£7.08
Administration cost	£3.00	£3.00	£3.00	£3.00
Preparation equipment cost	£0.04	£0.52	£0.36	£0.22
Preparation staff cost	£0.02	£0.06	£0.41	£0.20
Consumable cost	£0.27	£4.07	£4.07	£2.00
Smear reading cost	£2.26	£1.99	£1.99	£1.99
Other laboratory cost	£8.42	£8.42	£8.42	£8.42
Conversion costs[a]	–	£0.26	£0.26	£0.26
Total (baseline)	£21.67	£25.40	£25.59	£23.17
LBC worst case	£21.67	£28.17	£27.74	£24.50
LBC best case	£21.67	£20.52	£20.71	£19.38

[a] Cost per smear based on 3.9 million smears per year over 10-year useful lifetime for LBC.

Outcomes generated by the model

The model generates a range of health and economic outcomes under a set of screening policy comparisons.

The key health outcomes generated are:

- annual incidence of invasive cancer
- percentage of women having invasive cancer at some point in their life
- life-years (days/hours) gained.

The key resource outcomes generated are:

- number of smear tests undertaken
- number of colposcopies undertaken.

The key health economic outcomes generated are:

- cost per invasive cancer avoided
- cost per life year gained.

Note that insufficient quality of life information is currently available to estimate a cost per QALY, although some assumptions regarding utility values are used as part of the sensitivity analysis.

Model validation

Overall incidence of invasive cancers

Reported incidence of invasive cervical cancers across all ages is 12 per 100,000 per annum,[118] which is comparable with the predicted incidence by the current model of 11.64 for policy B (rescreen at 6 months for all women with a borderline or mild screen test result), 85% coverage and screening at 3-yearly intervals. Implementing policy A under similar assumptions predicts an incidence rate of just over 10.

Age-specific incidence with a policy of no screening

The age-specific incidence figures predicted by the model described here for cervical cancer under a no-screening policy are compared with the equivalent figures predicted by the model described in the AHCPR report. The incidences predicted by the two models are shown in *Figure 3*, which shows that the two models predict virtually the same pattern of incidence over a lifetime.

Age-specific incidence with a policy of screening every 5 years

The age-specific incidence figures for cervical cancer under a policy of screening every 5 years predicted by the model are compared with the equivalent figures from the Trent Cancer Registry for 1993.[118] These incidence figures are shown in *Figure 4*. Rather than settling to a constant level, the age-specific incidence rises gradually over time. There is a similar rise and subsequent decline in incidence in the older age groups. In the model this arises from the discontinuation of regular screening at 64 years of age; this may also be true in practice.

Test programme characteristics

The distribution of test results as a proportion of all tests predicted by the model is compared with the distribution as reported by the NHSCSP[6] and the results are shown in *Table 16*. As can be seen, despite the good overall prediction of invasive cancer incidence under screening, the predicted distribution of test results underestimates the number of borderline/mild and moderate/severe

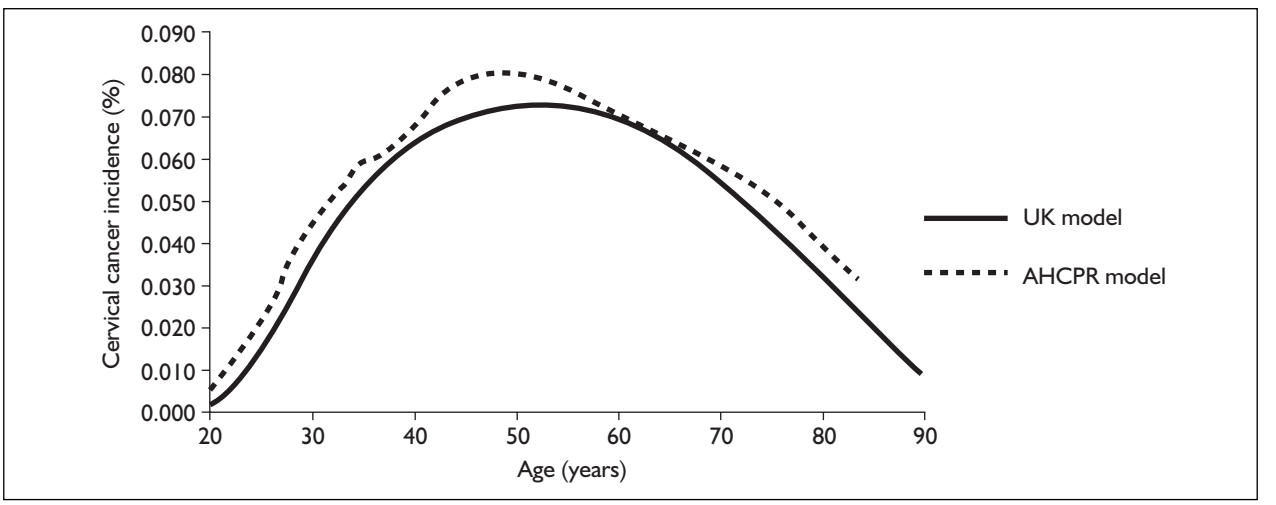

FIGURE 3 *Age-specific incidence of invasive cancer predicted by the UK model and the AHCPR model in the absence of screening*

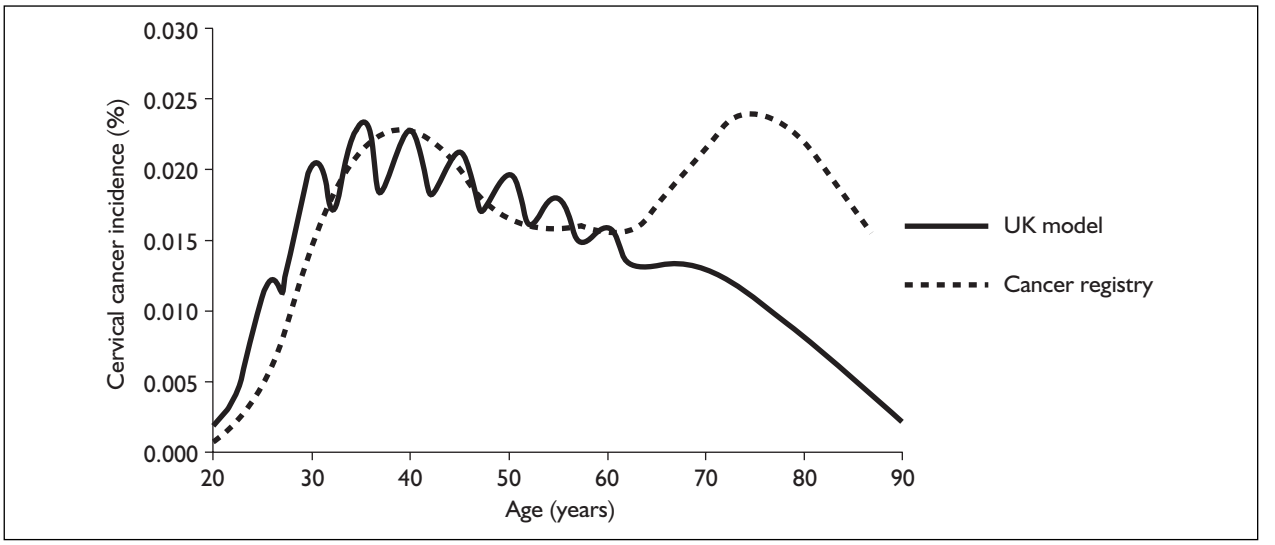

FIGURE 4 *Age-specific incidence of invasive cancer predicted by the UK model under a 3-year screening policy and current reported incidence*

TABLE 17 *Predicted versus actual distribution of test results*

	Specificity	Negative	Borderline/mild	Severe
NHSCSP Statistics	?	93.0%	5.5%	1.5%
UK model	Baseline 96.6%	95.3%	3.6%	1.0%
Revised UK model	94%	92.8%	5.2%	2.0%

test results. The most likely implication of this underestimation, together with the good prediction of overall incidence, is that the baseline test specificity used within the model is too high. Indeed, if the specificity is revised as shown in *Table 17*, the predicted number of tests matches almost exactly the actual recorded distribution. If this is the source of the discrepancy, then the benefits from screening will remain unchanged (morbidity from unnecessary testing excluded), although the costs associated with smear tests and colposcopies will rise. However, since there is little strong evidence to suggest that the specificity of LBC is improved compared with conventional screening (whatever level is set), the impact on the relative costs and cost-effectiveness of LBC versus conventional screening is small.

Modelling results

The results are presented in three sections. The first section describes the baseline results obtained by analysing the model using the most likely values for each input parameter. The second section presents the results of the deterministic sensitivity analyses, which involve the analysis of the model with only a single parameter or limited combinations of parameters being changed to assess the impact on the baseline results. Finally, the results of a fully stochastic analysis of the model is presented in which a distribution of the model's outputs is obtained by analysing the model allowing all parameters to vary between the ranges specified in *Tables 14* and *16*.

Baseline results

Health Outcomes

The key cervical cancer screening programme health outcomes are summarised in *Table 18*. The interventions are set out in increasing order of effectiveness and where incremental outcomes are given these are incremental over the immediately preceding intervention.

Conventional screening at 3–5 years is predicted to reduce the annual incidence of cervical cancer from approximately 54 per 100,000 women per annum to between 12 and 15 per 100,000 per annum. This prediction compares well with the actual incidence currently recorded. The introduction of LBC techniques has the potential to reduce this incidence to between 10 and 13 per 100,000 women per annum.

Conventional screening at a 5-year interval is estimated to increase the life expectancy of the average 18-year-old woman by around 126 days

TABLE 18 *Key health outcomes arising from the introduction of LBC*

		Annual incidence of invasive cancer (%)	Percentage of women who have invasive cancer	Percentage of all deaths from cancer	Incremental life-days gained	Incremental life-days gained (discounted)
No screening		0.0536	3.4213	1.73		
Screening at 5 years	Conventional	0.0152	0.9765	0.08	126.45	56.77
	LBC	0.0127	0.8141	0.05	2.39	1.14
Screening at 3 years	Conventional	0.0117	0.7491	0.03	1.95	0.97
	LBC	0.0103	0.6579	0.02	0.93	0.46
Screening at 2 years	Conventional	0.0101	0.6508	0.02	0.38	0.20
	LBC	0.0093	0.5978	0.01	0.41	0.20

TABLE 19 *Average lifetime resource usage per woman*

		No. of smear tests	No. of colposcopies
No screening	–	–	
Screening at 5 years	Conventional	8.42	0.10
	LBC	7.84	0.11
Screening at 3 years	Conventional	13.99	0.14
	LBC	13.01	0.14
Screening at 2 years	Conventional	20.51	0.18
	LBC	19.08	0.18

(undiscounted). Compared with conventional Pap smear testing, LBC screening at 5-year intervals is estimated to reduce the incidence of cervical cancer and increase life expectancy; however, this improvement does not match the improvement expected from moving from a 5-year to a 3-year screening interval with conventional screening.

LBC screening over a 2-year interval would save the greatest number of life-days (over 132 undiscounted, 60 discounted).

Resource usage

LBC techniques reduce the average lifetime number of smear tests for a woman primarily through the reduction in inadequate slide production and consequential reduction in rescreening. The average number of colposcopies is expected to increase as the number of borderline+ screening test results increases. *Table 19* presents the expected lifetime number of screens and colposcopies for an 18-year-old woman. Note that this presents a health commissioning perspective and therefore includes the whole population, not just individuals who attend screening.

Health economic outcomes

The incremental costs per invasive cancer avoided for the primary screening options under consideration are presented in *Table 20*. These results show that, for screening intervals of both 3 and 2 years, conventional Pap smear testing is extendedly dominated by LBC, e.g. 5-yearly LBC screening has a lower ICER compared with 5-yearly conventional Pap smear screening, than the latter option has compared with no screening.

The presentation of both average and incremental cost-effectiveness ratios illustrates that, compared with conventional screening at 5 years, all of the other screening options appear cost-effective. However, when the appropriate incremental approach to defining cost-effectiveness is estimated, it is apparent that LBC screening at 3-year intervals is potentially the most cost-effective option.

Table 21 presents the cost per life-year gained for the screening options being analysed. The options are arranged in order of increasing effectiveness, and incremental cost-effectiveness is shown. The

TABLE 20 *Incremental cost per invasive cancer avoided*

		Invasive cancers (per 100,000 population)	Total cost	Average cost per cancer avoided[a]	Incremental cost per cancer avoided[b]	Extendedly dominated options excluded[c]
No screening		3421	£315,139			
Screening at 5 years	Conventional	977	£6,097,143		£2,365	
	LBC	814	£6,590,348	£3,037	£3,037	–
Screening at 3 years	Conventional	749	£9,288,541	£14,034	£41,497	
	LBC	658	£10,061,544	£12,442	£8,473	£22,216
Screening at 2 years	Conventional	651	£13,228,210	£21,896	£449,311	
	LBC	598	£14,342,908	£21,775	£21,032	£71,298

Costs discounted at 6%, invasive cancer not discounted.
[a] Compared with conventional screening at 5 years.
[b] Each screening option is compared with the next less costly option, e.g. LBC screening every 5 years is compared with conventional Pap smear testing every 5 years, conventional Pap smear testing every 5 years is compared with no screening.
[c] Options are extendedly dominated if the following option has a lower ICER (i.e. the next option would always be chosen if the dominated option were chosen).

TABLE 21 *Cost per life-year gained of cervical cancer screening interventions*

		Lifetime cost[a]	Incremental LYG[a]	Average cost per LYG[b]	Incremental cost per LYG[c]	Extendedly dominated options excluded[d]
No screening		£315,139				
Screening at 5 years	Conventional	£6,097,143	15,553		£372	
	LBC	£6,590,348	313	£1,577	£1,577	–
Screening at 3 years	Conventional	£9,288,541	265	£10,207	£10,198	
	LBC	£10,061,544	125	£12,679	£6,189	£8,912
Screening at 2 years	Conventional	£13,228,210	56	£22,807	£56,717	
	LBC	£14,342,908	55	£26,372	£20,222	£38,586

Costs discounted at 6%, life-years discounted at 1.5%
[a] Per 100,000 women (uptake rate 85%).
[b] Compared with conventional Pap smear testing at 5-yearly intervals.
[c] Each screening option is compared with next less costly option, e.g. LBC screening every 5 years is compared with conventional Pap smear testing every 5 years, conventional Pap smear testing every 5 years is compared with no screening.
[d] Options are extendedly dominated if the following option has a lower ICER (i.e. the next option would always be chosen if the dominated option were chosen).

results show that the 2- and 3-year conventional Pap smear screening options are extendedly dominated, and when the cost-effectiveness ratios are re-estimated to exclude dominated options, screening at a regular interval of 3 years using LBC is cost-effective, while screening at 2-year intervals approaches a reasonable level of cost-effectiveness.

Deterministic sensitivity analysis

Disease natural history

Table 22 describes the impact on the cost per life-year saved of decreasing and increasing the incidence rates for CIN1. The main result of this sensitivity analysis is that if the incidence of CIN is 25% higher then 2-yearly screens, using LBC would be cost-effective assuming a £30,000 threshold for the acceptable cost of gaining an additional life-year.

As noted above, there is some evidence that CIN2 and CIN3 lesions can regress.[110] *Table 23* presents the results of analyses incorporating the possibility of such regressions to a clear state. Such data assumptions reduce the cost-effectiveness of screening, although the impact is not large.

TABLE 22 *Sensitivity analysis for CIN1 incidence rates*

Disease progression		Incremental cost per LYG[a] 75%	Baseline	125%
No screening		–	–	–
Screening at 5 years	Conventional	£641	£372	£247
	LBC	£2,743	£1,577	£1,039
Screening at 3 years	Conventional	£18,028	£10,198	£6,575
	LBC	Ext. dom. (£15,711)	Ext. dom. (£8,912)	Ext. dom. (£5,767)
Screening at 2 years	Conventional	£100,491	£56,717	£36,455
	LBC	Ext. dom. (£68,177)	Ext. dom. (£38,586)	Ext. dom. (£24,893)

[a] Cost-effectiveness ratios comparing screening options with the next less costly option are presented; in cases of dominance the revised ratio excluding the dominated option is presented in parentheses.
Ext. dom., extendedly dominant.

TABLE 23 *Sensitivity analysis for disease regression rates (from CIN2 and CIN3)*

Disease progression		Incremental cost per LYG[a] Regression from CIN2 (1.5%) and CIN3 (1.1%)	Baseline
No screening		–	–
Screening at 5 years	Conventional	£499	£372
	LBC	£2,004	£1,577
Screening at 3 years	Conventional	£11,897	£10,198
	LBC	Ext. dom. (£10,454)	Ext. dom. (£8,912)
Screening at 2 years	Conventional	£62,734	£56,717
	LBC	Ext. dom. (£43,453)	Ext. dom. (£38,586)

[a] Cost-effectiveness ratios comparing screening options with the next less costly option are presented; in cases of dominance the revised ratio excluding the dominated option is presented in parentheses.

There is no direct, and little indirect evidence regarding the natural history of cervical cancer in terms of the progression rates between preinvasive states. What evidence does exist has been generated from the fitting of mathematical models, such as the one described here, where the structure is based on a hypothesised course for the disease. The impact of doubling and halving the disease progression rates is examined in *Table 24*. Reducing the progression rates increases the revised cost-effectiveness ratio for 3-yearly LBC screening quite substantially, such that 5-yearly screening could be the most cost-effective option.

Sensitivity analysis for test characteristics

The impact of uncertainty concerning the improvements in test sensitivity obtained from LBC-based screening is presented in *Table 25*. These results show that LBC is a more cost-effective option at 3- and 2-yearly screening intervals when sensitivity is lower than when the higher estimates of sensitivity are used. This is because, at the higher sensitivity rates, there are fewer missed cases when screening at 5-yearly intervals. Indeed, a 2-yearly screening programme may be cost-effective if the lower rates of LBC sensitivity are proven.

There remains some uncertainty around the sensitivity rates associated with conventional Pap smear testing, such that the impact of alternative assumptions regarding these rates is tested in *Table 26*. These results show that if sensitivity is better than assumed in the baseline (lower false-negative rate), LBC becomes relatively less cost-effective, although similar conclusions may be reached about 3-yearly LBC screening being the most cost-effective option. However, if Pap smear testing is less sensitive than assumed in the baseline, then 2-yearly LBC screening may be cost-effective.

TABLE 24 *Sensitivity analysis for disease progression rates*

Disease progression		Incremental cost per LYG[a]		
		50%	**Baseline**	**150%**
No screening		–	–	–
Screening at 5 years	Conventional	£904	£372	£249
	LBC	£4,227	£1,577	£969
Screening at 3 years	Conventional	£32,451	£10,198	£5,715
	LBC	Ext. dom. (£27,605)	Ext. dom. (£8,912)	Ext. dom. (£5,074)
Screening at 2 years	Conventional	£214,244	£56,717	£28,534
	LBC	Ext. dom. (£132,914)	Ext. dom. (£38,586)	Ext. dom. (£20,527)

[a] Cost-effectiveness ratios comparing screening options with the next less costly option are presented; in cases of dominance the revised ratio excluding the dominated option is presented in parentheses.

TABLE 25 *Sensitivity analysis for improvement in test sensitivity of LBC*

		Incremental cost per LYG[a]		
Sensitivity improvement			**Baseline**	
CIN1/CIN2		**4.2%**	**8.4%**	**12.6%**
CIN3		**2%**	**4%**	**6%**
No screening		–	–	–
Screening at 5 years	Conventional	£372	£372	£372
	LBC	£2,907	£1,577	£1,145
Screening at 3 years	Conventional	£6,599	£10,198	£19,181
	LBC	Ext. dom. (£7,247)	Ext. dom. (£8,912)	Ext. dom. (£11,193)
Screening at 2 years	Conventional	£28,385	£56,717	£293,248
	LBC	Ext. dom. (£29,961)	Ext. dom. (£38,586)	Ext. dom. (£50,654)

[a] Cost-effectiveness ratios comparing screening options with the next less costly option are presented; in cases of dominance the revised ratio excluding the dominated option is presented in parentheses.

The impact of uncertainty concerning improvements in the rate of inadequate cervical smears, as well as the combination of test inadequacy and low and high sensitivity rates for LBC, is presented in *Table 27*. These results show that assuming an equal inadequacy rate does not change the magnitude of the relevant incremental ratios by a large amount.

Sensitivity analysis for costs

The impact of uncertainty concerning the increase in marginal costs arising from the introduction of LBC is presented in *Table 28*. Using the upper bound of the estimated costs for LBC does not greatly affect relative cost-effectiveness.

Sensitivity analysis for discounting of costs and life-years gained

The impact of different assumptions concerning the discounting of costs and life-years gained is presented in *Table 29*. It can be seen that discounting assumptions, especially regarding the discounting of life-years gained, has a marked impact on the potential cost-effectiveness of both conventional and LBC techniques. Nevertheless, liquid-based cytology at a screening interval of 5 years remains a cost-effective option under all discounting options. The importance of the discounting assumptions arises from the fact that most benefits are distant in the future relative to screening costs. This is especially true when estimating the expected life costs at the age of 18 years. The impact of discounting would be expected to lessen as the remaining life benefits at increasing ages are estimated. This would tend to increase the relative benefits to be obtained from screening at reduced intervals at ages where the incidence of preinvasive disease is highest. A

TABLE 26 *Sensitivity analysis for improvement in test sensitivity of conventional Pap smear testing*

		Incremental cost per LYG[a]		
Sensitivity[b]			**Baseline**	
CIN1		**20%**	**34%**	**48%**
CIN2		**40%**	**59%**	**78%**
CIN3		**20%**	**36%**	**52%**
No screening		–	–	–
Screening at 5 years	Conventional	£367	£372	£379
	LBC	£2,005	£1,577	£1,257
Screening at 3 years	Conventional	£14,884	£10,198	£7,341
	LBC	Ext. dom. (£12,914)	Ext. dom. (£8,912)	Ext. dom. (£6,374)
Screening at 2 years	Conventional	£90,848	£56,717	£37,894
	LBC	Ext. dom. (£60,911)	Ext. dom. (£38,586)	Ext. dom. (£25,139)

[a] Cost-effectiveness ratios comparing screening options with the next less costly option are presented; in cases of dominance the revised ratio excluding the dominated option is presented in parentheses.
[b] FNR, false-negative rate.

TABLE 27 *Sensitivity analysis for improvement in test adequacy*

		Incremental cost per LYGa		
% improvement in inadequacy rate		**0%**	**0%**	**Baseline 9–1.4%**
Sensitivity improvement		**Baseline**		**Baseline**
CIN1/CIN2		**13.4%**	**4.2%**	**13.4%**
CIN3/cancer		**4%**	**2%**	**4%**
No screening				–
Screening at 5 years	Conventional	£372	£372	£372
	LBC	£2,968	£5,504	£1,577
Screening at 3 years	Conventional	£8,555	£5,539	£10,198
	LBC	£11,661	£21,023	Ext. dom. (£8,912)
Screening at 2 years	Conventional	£44,475	£22,276	£56,717
	LBC	Ext. dom. (£41,354)	£67,585	Ext. dom. (£38,586)

[a] Cost-effectiveness ratios comparing screening options with the next less costly option are presented; in cases of dominance the revised ratio excluding the dominated option is presented in parentheses.

two-way sensitivity analysis for the marginal costs arising from the introduction of LBC and discounting assumptions is also presented in *Table 29*.

Sensitivity analysis for quality of life

The final deterministic sensitivity analysis tested the impact of the effects of the screening programme on women's quality of life. These analyses assumed that quality of life could be affected in three ways. First, women with invasive cancer are assumed to experience reduced quality of life for the remainder of their life. Second, women who undergo a colposcopy following an abnormal screening result (regardless of the outcome of the colposcopy) are assumed to experience a temporary decrease in their quality of life. Third, women who receive a borderline result following screening for cervical cancer (which is subsequently followed by a clear result) are also assumed to experience a temporary decrease in their quality of life.

Table 30 presents the results of analyses of a range of assumptions regarding the possible utility decrement associated with abnormal screen results

TABLE 28 *Sensitivity analysis for marginal sample cost for LBC*

Marginal cost of LBC		Incremental cost per LYG[a]		
		–£1.15	**Baseline £3.73**	**£6.50**
No screening		–	–	–
Screening at 5 years	Conventional	£372	£372	£372
	LBC	Dominant (£325)	£1,577	£3,601
Screening at 3 years	Conventional	£14,411	£10,198	£7,807
	LBC	Dominant (£7,276)	Ext. dom. (£8,912)	£14,151
Screening at 2 years	Conventional	£88,096	£56,717	£38,905
	LBC	Dominant (£31,492)	Ext. dom. (£38,586)	£46,368

[a] Cost-effectiveness ratios comparing screening options with the next less costly option are presented; in cases of dominance the revised ratio excluding the dominated option is presented in parentheses.

TABLE 29 *Sensitivity analysis for discount rates*

Discount factors	Cost	Incremental cost per LYG[a]			
	Cost	**0%**	**6%**	**6%**	**6%**
	Life-years	**0%**	**1.5%**	**6%**	**6%**
Additional cost of LBC		**Baseline (£3.73)**	**Baseline (£3.73)**	**Baseline (£3.73)**	**£6.50**
No screening		–	–	–	–
Screening at 5 years	Conventional	£515	£372	£3,040	£3,040
	LBC	£2,310	£1,577	£9,995	£22,817
Screening at 3 years	Conventional	£20,326	£10,198	£58,548	£44,819
	LBC	Ext. dom. (£17,148)	Ext. dom. (£8,912)	Ext. dom. (£51,143)	£81,125
Screening at 2 years	Conventional	£115,346	£56,717	£267,543	£183,523
	LBC	Ext. dom. (£73,798)	Ext. dom. (£38,586)	Ext. dom. (£196,382)	£256,488

[a] Cost-effectiveness ratios comparing screening options with the next less costly option are presented; in cases of dominance the revised ratio excluding the dominated option is presented in parentheses.

TABLE 30 *Sensitivity analysis for quality of life impact of screening*

Utility values[a]		Incremental cost per QALY gained			
		IC: 0.6 Borderline: 0.95 Colposcopy: 0.9	**IC: 0.6 Borderline: 0.975 Colposcopy: 0.95**	**IC: 0.6 Borderline: 0.98 Colposcopy: 0.97**	**Baseline: no utility adjustments**
No screening		–	–	–	–
Screening at 5 years	Conventional	£266	£253	£250	£372
	LBC	£1,096	£1,066	£1,050	£1,577
Screening at 3 years	Conventional	Dominated	Dominated	Dominated	£10,198
	LBC	Dominated	Dominant (£69,299)	Dominant (£18,368)	Ext. dom. (£8,912)
Screening at 2 years	Conventional	Dominated	Dominated	Dominated	£56,717
	LBC	Dominated	Dominated	Dominated	Ext. dom. (£38,586)

[a] The utility value for IC is applied over the remainder of a woman's life, whereas the utility values for receiving a borderline or colposcopy are only applied to the year in which the event occurs.

and subsequent treatment. These results show that if abnormal screening results have a disutility effect on women, then the likelihood of a 5-yearly screening interval being the optimal screening option is substantially increased. Assuming a single annual utility decrement of 2% for women experiencing a borderline result followed by a clear result, and a 3% decrement for women undergoing a colposcopy, the incremental cost per QALY of moving from a 5-yearly screening programme (with LBC) to a 3-yearly LBC screening programme is over £18,000. If the respective utility decrements are 2.5% and 5%, then the cost per QALY for 3-year LBC rises to almost £70,000.

Stochastic sensitivity analysis

To analyse the combined effect of uncertainty in all the input parameters on the baseline results, a stochastic analysis of the model was undertaken in which the input parameters were allowed to vary between the ranges specified in *Tables 14* and *16*. The uncertainty around each parameter was described in the form of a triangular distribution, whereby the range for each parameter informed the minimum and maximum values for each distribution. The advantage of using the triangular distribution to represent uncertainty around parameters within the model is that a definitive range for the parameter of interest is specified and the sampled values will not fall outside that range. Limitations of the triangular distribution include the fact that the shape of the distribution is rigid and may not represent the true form of the distribution accurately. The triangular distribution is also not part of a conjugate family of distributions, which makes it more difficult to update triangular distributions when more data to inform a particular distribution become available.

Model outputs were obtained for 5000 separate iterations, each informed by a random sample of input parameters from the specified distributions.

The results of the stochastic analysis are also presented in the form of a cost-effectiveness acceptability curve, which describes the probability that each of the available screening options will be the optimal screening programme at different levels of willingness to pay to gain an additional life-year. This curve is estimated by defining the optimal programme within each of the 5000 iterations undertaken to inform the stochastic analysis, on the basis of the programme with the highest incremental net benefits at each willingness to pay level. The estimated acceptability curve is presented in *Figure 5*.

The acceptability curve shows that at all levels of willingness to pay to gain life-years the model predicts that LBC screening every 5 years is most

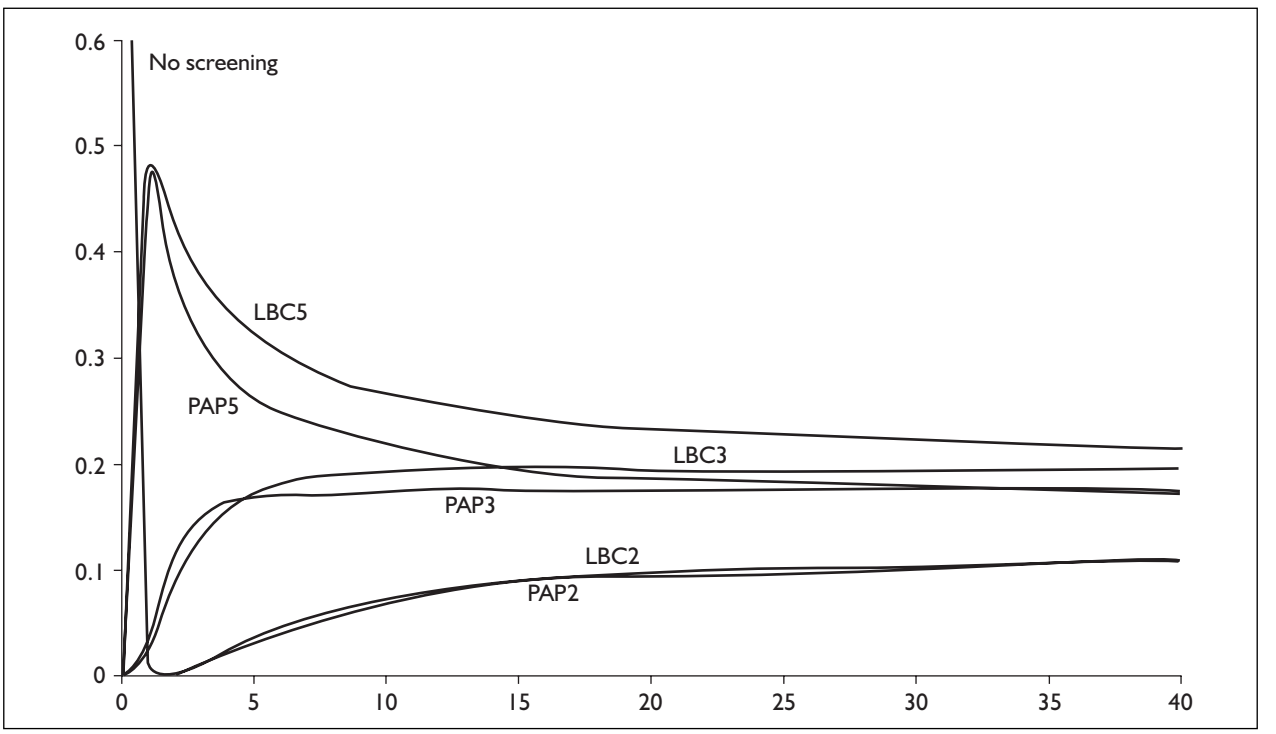

FIGURE 5 *Cost-effectiveness acceptability curve for seven screening options for cervical cancer*

likely to produce the highest net benefits, although the probability decreases as the threshold increases towards £40,000 per life-year gained, reaching a stable level at around 22%, while the probability of 3-yearly screening with LBC increases to around 20%. The probability of conventional Pap smear screening being cost-effective at 5- and 3-yearly intervals follows a similar pattern to that for 3- and 5-yearly LBC screening, but at slightly lower levels. The probability of 2-yearly screening using either LBC or conventional Pap smear is almost identical over the whole range of values.

Conclusions of economic modelling analysis

Simplifying assumptions have been incorporated into the modelling analysis of the cost-effectiveness of alternative cervical screening options, such as the use of constant rates of progression between alternative CIN stages and invasive cancer, and the assumption of 100% sensitivity and specificity of colposcopy. In addition, morbidity and mortality associated with invasive cancer have been modelled crudely; specifically, the costs are underestimated and survival is overestimated for the highest grade cancers; again, this would introduce a small bias against improved screening techniques.

However, since the original modelling analysis reported in the earlier HTA report, more certain estimates of the cost per slide associated with both conventional Pap smear testing and the new LBC screening techniques, as well as more concrete estimates of the relative inadequacy rates associated with the two techniques, have become available.[102] The baseline results with these new data indicate that LBC is a cost-effective alternative to conventional Pap smear screening at all three screening intervals, and comparing LBC across the screening intervals indicates that a 3-year interval is almost certainly cost-effective compared with a 5-year interval. Several of the analyses indicate that, using LBC, a 2-year interval may well be cost-effective.

The stochastic sensitivity analysis describes the impact of the total uncertainty in the model by varying all parameters simultaneously to define a distribution of the model's outputs that can be analysed statistically. The results of the stochastic analysis show that LBC screening at 3-yearly intervals is the most likely cost-effective option if society is willing to spend between £10,000 and £50,000 to gain additional life-years.

The main economic analysis uses the number of life-years saved by alternative screening options as the main measure of health benefits, rather than the preferred measure of QALYs, because of the uncertainties surrounding utility values associated with the various health states associated with cervical cancer and screening, for example, no reliable work has been undertaken to estimate the utility effects of alternative screening test results or the impact of being in a presymptomatic cancer state. However, a range of utility decrements is associated with the screening outcome's borderline result followed by a clear result, and the experience of a colposcopy, as well as estimating a utility value for women diagnosed with cervical cancer. The results of these analyses show that the utility decrements had a significant impact on the choice of screening interval, whereby seemingly small utility decrements resulted in LBC screening at 3-year intervals producing fewer QALYs at greater cost than LBC screening at 5-year intervals.

Chapter 6
Conclusions

Implications of screening tests

Financial impact for patients and others

The potential benefits to women screened, in addition to the potential reductions in invasive cancer and mortality, include reduced anxiety associated with a reduced need for repeat screening due to inadequate specimens, and associated reductions in travelling and related expenses. No attempt has been made to quantify these benefits in the reported economic analyses.

Society and legal implications

Problems in relation to cervical screening have resulted in litigation. Although there is a potential to reduce payments for damages and associated litigation costs if false-negative results are reduced, LBC will have a sensitivity that is not perfect, so false-negative results will still occur. There has been no attempt to quantify benefits with respect to reduced litigation costs in the reported economic analyses.

Health targets

Reduction in cancer mortality is a key target in the NHS plan for investment and reform.[119]

Fair access and equity issues

The uptake of cervical screening is not uniform across the country and some disadvantaged groups of the population are said to have lower utilisation rates. Improvements in cervical cytology methods should be considered alongside ways to improve uptake and to make provision of this service more equitable.

Dissemination and implementation

It is not within the scope of this report to produce a detailed dissemination and implementation plan for the NHS for LBC. If a decision is made to adopt LBC then such a plan would be needed, which would need to consider aspects such as training, workforce planning, quality management and the relevant logistics (e.g. storage space).

Recommendations for research

This updated analysis provides more certainty with regard to the potential cost-effectiveness of LBC compared with conventional Pap smear testing. A full cost-effectiveness study of LBC based on a trial of its introduction in a low-prevalence population would provide more definitive information than is possible by modelling studies, although the results of the modelling analysis provide a robust argument that LBC is a cost-effective alternative to conventional cervical cancer screening, such that the large expenditure required to fund a trial is probably not justified.

The sensitivity analyses undertaken around hypothesised utility values generated preliminary estimates of cost-effectiveness with respect to QALYs gained, which showed that such factors could influence the choice of screening programme. Therefore, further research may be worthwhile in the area of utility assessment, particularly with respect to the short-term impact of false-positive screen results.

However, as described in Chapter 4, a range of economic evaluations was identified in the updated systematic search (1999–2002) that assessed the economic impact of cervical screening approaches other than conventional Pap smear testing and LBC techniques, including semi-automated slide analysis, HPV testing as an adjunct or alternative to Pap smear testing, and protocols for the management of atypical screen results.

The aggregate analysis of the cost-effectiveness of potential combinations of these approaches to screening for cervical cancer is outside the scope of the current review, although it is noted that the relative cost-effectiveness of all relevant screening programme configurations should be analysed simultaneously.

Acknowledgements

The original HTA report provided the backbone for this report, so the main author of the original report (Nick Payne) provided much input. Indeed, the following paragraph describes the acknowledgements from the original report.

The assistance and advice from Julietta Patnick and Richard Winder from the NHS Cervical Screening Programme and from Chris Sherlaw-Johnson and Steven Gallivan from the Clinical Operational Research Unit at University College London is gratefully acknowledged. Suzy Paisley from ScHARR undertook the literature searches and gave advice and support. Gill Rooney, Andrea Shippam and Liz Clayton provided support in the production of the document. For the updated report, Naomi Brewer from ScHARR undertook the literature searches and gave advice.

Contributions of authors

Jon Karnon (Senior Operational Research Analyst) carried out the review of the economic literature, and undertook the statistical analyses and the economic modelling analysis. Jean Peters (Senior Lecturer) carried out the review of the effectiveness of the technology and edited the background information. John Platt (Senior Nursing Lecturer) was involved with the review of the effectiveness of the technology. Jim Chilcott (Senior Operational Research Analyst) built the economic model and advised on the reanalysis. Euphemia McGoogan (Associated Medical Director) provided clinical advice throughout the project. Naomi Brewer (Information Officer) conducted the literature searches and gave advice.

Funding

The production of this report was supported by NHS Research and Development funding.

References

1. Payne N, Chilcott J, McGoogan E. Liquid-based cytology in cervical screening: a rapid and systematic review. *Health Technol Assess* 2000; **4**(18):1–73.
2. Moss SM, Gray A, Legood R, Henstock E. Evaluation of HPV/LBC cervical screening pilot studies (First report on evaluation of LBC). London: Department of Health. 2002.
3. Liquid Based Cytology Steering Group. Scottish Cervical Screening Programme. Feasibility study of the Steering Group about the introduction of thin layer cytology. Edinburgh: Scottish Executive. 2002.
4. Sasieni P, Adams J. Changing rates of adenocarcinoma and adenosquamous carcinoma of the cervix in England. *Lancet* 2001;**357**:1490–3.
5. NHS Cervical Screening Programme. *Cervical Screening Programme Review: A National Priority*. London: Department of Health. 1999.
6. Department of Health. Statistical Bulletin. Cervical Screening Programme, England: 1997–98. *Government Statistical Services Bulletin*. London: Department of Health. 1999.
7. Duncan D. Guidelines for clinical practice and programme management. NHS Cervical Screening Programme, No. 8. London: Department of Health. 1997.
8. NHS Cervical Screening Programmes. *NHS Cervical Screening 2002 Review*. London: Department of Health. 2002.
9. Last JM. *A dictionary of epidemiology*. 2nd ed. Oxford: Oxford University Press. 1988.
10. Australian Health Technology Advisory Committee. *Review of Automated and Semi-automated Cervical Screening Devices*. Canberra: Australian Department of Health and Aging. 1998. pp. 1–86.
11. Fahey MT, Irwig L, Macaskill P. Meta-analysis of Pap test accuracy. *Am J Epidemiol* 1995;**141**:680–9.
12. Boyko EJ. Re: 'Meta-analysis of Pap test accuracy'. *Am J Epidemiol* 1996;**143**:406–7.
13. NHS Executive. *The Performance of the NHS Cervical Screening Programme in England*. HC 678, Session 199. London: Department of Health. 1998.
14. NHS Cervical Screening Programme. *Cervical Screening: A Pocket Guide*. London: Department of Health. 1999.
15. Steven FS, Palcic B, Sin J, Desai M. A simple clinical method for the preparation of improved cervical smears – approximating to monolayers. *Anticancer Res* 1997;**17**:629–32.
16. Neugebauer D, Otto K, Soost HJ. Numerical analysis of cell populations in smear and monolayer preparations from the uterine cervix. I. The proportions of isolated, abnormal epithelial cells in slides from one applicator. *Anal Quant Cytol* 1981;**3**:91–5.
17. Näslund I, Auer G, Pettersson F, Sjovall K. The pulse wash instrument. A new sampling method for uterine cervical cancer detection. *Am J Clin Oncol* 1986;**9**:327–33.
18. Näslund I, Auer G, Pettersson F, Sjovall K. Evaluation of the pulse wash sampling technique for screening of uterine cervical carcinoma. *Acta Radiol Oncol* 1986;**25**:131–6.
19. Zahniser DJ, Sullivan PJ. CYTYC Corporation [review]. *Acta Cytol* 1996;**40**:37–44.
20. Manos MM, Kinney WK, Hurley LB, Sherman ME, Shieh-Ngai J, Kurman RJ, *et al*. Identifying women with cervical neoplasia: using human papillomavirus DNA testing for equivocal Papanicolaou results. *JAMA* 1999;**281**:1605–10.
21. Linder J. Recent advances in thin-layer cytology. *Diagn Cytopathol* 1998;**18**:24–32.
22. Sherman ME, Schiffman MH, Lorincz AT, Herrero R, Hutchinson ML, Bratti C, *et al*. Cervical specimens collected in liquid buffer are suitable for both cytologic screening and ancillary human papillomavirus testing. *Cancer* 1997;**81**: 89–97.
23. Ferenczy A, Franco E, Arseneau J, Wright TC, Richart RM. Diagnostic performance of Hybrid Capture human papillomavirus deoxyribonucleic acid assay combined with liquid-based cytologic study. *Am J Obstet Gynecol* 1996;**175**:651–6.
24. Broadstock M. Effectiveness and cost effectiveness of automated and semi-automated cervical screening devices: a systematic review of the literature. *New Zealand Health Technology Assessment Report* 2000;**3**(1).
25. Vassilakos P, Schwartz D, de Marval F, Yousfi L, Broquet G, Mathez-Loic F *et al*. Biopsy-based comparison of liquid-based, thin-layer preparations to conventional Pap smears. *Journal of Reproductive Medicine* 2000;**45**:11–16.

26. Bastian L, Datta S, Hasselblad V, Hickey J, Myers E, Nanda K. Evidence Report No. 5, Summary. *Evaluation of Cervical Cytology*. Rockville, MD: Agency for Health Care Policy and Research. Publication No. 99-E010. 1999.

27. Obwegeser JH, Brack S. 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 Cytol* 2001;**45**:709–14.

28. Bergeron C, Bishop J, Lemarie A, Cas F, Ayivi J, Huynh B, Barrasso R. Accuracy of thin-layer cytology in patients undergoing cervical cone biopsy. *Acta Cytol* 2001;**45**:519–24.

29. Yeoh GPS, Chan KW. Cell block preparation on residual ThinPrep® sample. *Diagn Cytopathol* 1999;**21**:427–31.

30. Sheets EE, Constantine NM, Dinisco S, Dean B, Cibas ES. Colposcopically directed biopsies provide a basis for comparing the accuracy of ThinPrep and Papanicolaou smears. *Journal of Gynecologic Techniques* 1995;**1**:27–33.

31. Corkill M, Knapp D, Hutchinson ML. Improved accuracy for cervical cytology with the ThinPrep method and the endocervical brush-spatula collection procedure. *Journal of Lower Genital Tract Disease* 1998;**2**:12–16.

32. Sherman ME, Mendoza M, Lee KR, Ashfaq R, Birdsong GG, Corkill ME, *et al*. Performance of liquid-based, thin-layer cervical cytology: correlation with reference diagnoses and human papillomavirus testing. *Mod Pathol* 1998;**11**:837–43.

33. Bishop JW, Bigner SH, Colgan TJ, Husain M, Howell LP, McIntosh KM, *et al*. Multicenter masked evaluation of AutoCyte PREP thin layers with matched conventional smears. Including initial biopsy results. *Acta Cytol* 1998;**42**:189–97.

34. Bolick DR, Hellman DJ. Laboratory implementation and efficacy assessment of the ThinPrep cervical cancer screening system. *Acta Cytol* 1998;**42**: 209–13.

35. Inhorn SL, Wilbur D, Zahniser D, Linder J. Validation of the ThinPrep Papanicolaou test for cervical cancer diagnosis. *Journal of Lower Genital Tract Disease* 1998;**2**:208–12.

36. Ashfaq R, Gibbons D, Vela C, Saboorian MH, Iliya F. ThinPrep Pap test. Accuracy for glandular disease. *Acta Cytol* 1999;**43**:81–5.

37. Hutchinson ML, Zahniser DJ, Sherman ME, Herrero R, Alfaro M, Bratti MC, *et al*. 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* 1999; **87**:48–55.

38. Vassilakos P, Saurel J, Rondez R. Direct-to-vial use of the AutoCyte PREP liquid-based preparation for cervical-vaginal specimens in three European laboratories. *Acta Cytol* 1999;**43**:65–8.

39. Ferris DG, Heidemann NL, Litaker MS, Crosby JH, Macfee MS. The efficacy of liquid-based cervical cytology using direct-to-vial sample collection. *J Fam Pract* 2000;**49**:1005–11.

40. Minge L, Fleming M, VanGeem T, Bishop JW. AutoCyte Prep system vs. conventional cervical cytology. Comparison based on 2,156 cases. *J Reprod Med* 2000;**45**:179–84.

41. Park IA, Lee SN, Chae SW, Park KH, Kim JW, Lee HP. 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 Cytol* 2001;**45**:525–31.

42. Corkill M, Knapp D, Martin J, Hutchinson ML. Specimen adequacy of ThinPrep sample preparations in a direct-to-vial study. *Acta Cytol* 1997;**41**:39–44.

43. Bishop JW. Comparison of the CytoRich system with conventional cervical cytology. Preliminary data on 2,032 cases from a clinical trial site. *Acta Cytol* 1997;**41**:15–23.

44. Ferenczy A, Robitaille J, Franco E, Arseneau J, Richart RM, Wright TC. Conventional cervical cytologic smears vs. ThinPrep smears. A paired comparison study on cervical cytology. *Acta Cytol* 1996;**40**:1136–42.

45. Hutchinson ML, Agarwal P, Denault T, Berger BM, Cibas ES. A new look at cervical cytology. ThinPrep multicenter trial results. *Acta Cytol* 1992;**36**:499–504.

46. Ferris DG, Wright TC, Jr. Litaker MS., Richart RM, Lorincz AT, Sun XW, Woodward L. Comparison of two tests for detecting carcinogenic HPV in women with Papanicolaou smear reports of ASCUS and LSIL. *J Fam Pract* 1998;**46**:136–41.

47. Kobelin MH, Kobelin CG, Burke L, Lavin P, Niloff JM, Kim YB. Incidence and predictors of cervical dysplasia in patients with minimally abnormal Papanicolaou smears. *Obstet Gynecol* 1998;**92**:356–9.

48. Anon. Achievable standards, benchmarks for reporting, criteria for evaluating cervical cytopathology. Workshop report. *Cytopathology* 1995;**6**(Suppl 2):1–32.

49. Hutchinson ML, Cassin CM, Ball HG. The efficacy of an automated preparation device for cervical cytology. *Am J Clin Pathol* 1991;**96**:300–5.

50. Awen C, Hathway S, Eddy W, Voskuil R, Janes C. Efficacy of ThinPrep preparation of cervical smears: a 1,000-case, investigator-sponsored study. *Diagn Cytopathol* 1994;**11**:33–6; Discussion 36–7.

51. Laverty CR, Thurloe JK, Redman NL, Farnsworth A. An Australian trial of ThinPrep: a new cytopreparatory technique. *Cytopathology* 1995;**6**:140–8.

52. Wilbur DC, Cibas ES, Merritt S, James LP, Berger BM, Bonfiglio TA. ThinPrep Processor. Clinical trials demonstrate an increased detection rate of abnormal cervical cytologic specimens. *Am J Clin Pathol* 1994;**101**:209–14.

53. Aponte-Cipriani SL, Teplitz C, Rorat E, Savino A, Jacobs AJ. Cervical smears prepared by an automated device versus the conventional method. A comparative analysis. *Acta Cytol* 1995;**39**:623–30.

54. Tezuka F, Oikawa H, Shuki H, Higashiiwai H. Diagnostic efficacy and validity of the ThinPrep method in cervical cytology. *Acta Cytol* 1996; **40**:513–18.

55. Bur M, Knowles K, Pekow P, Corral O, Donovan J. Comparison of ThinPrep preparations with conventional cervicovaginal smears. Practical considerations. *Acta Cytol* 1995;**39**:631–42.

56. Wilbur DC, Dubeshter B, Angel C, Atkison KM. Use of thin-layer preparations for gynecologic smears with emphasis on the cytomorphology of high-grade intraepithelial lesions and carcinomas. *Diagn Cytopathol* 1996;**14**:201–11.

57. Lee KR, Ashfaq R, Birdsong GG, Corkill ME, McIntosh KM, Inhorn SL. Comparison of conventional Papanicolaou smears and a fluid-based, thin-layer system for cervical cancer screening. *Obstet Gynecol* 1997;**90**:278–84.

58. Roberts JM, Gurley AM, Thurloe JK, Bowditch RC, Laverty CR. Evaluation of the ThinPrep Pap test as an adjunct to the conventional Pap smear. *Med J Aust* 1997;**167**:466–9.

59. Wang TY, Chen HS, Yang YC, Tsou MC. Comparison of fluid-based, thin-layer processing and conventional Papanicolaou methods for uterine cervical cytology. *J Formos Med Assoc* 1999;**98**:500–5.

60. Monsonego J, Autillo-Touati A, Bergeron C, Dachez R, Liaras J, Saurel J, *et al*. Liquid-based cytology for primary cervical cancer screening: a multi-centre study. *Br J Cancer* 2001;**84**:360–6.

61. Biscotti CV, O'Brien DL, Gero MA, Gramlich TL, Kennedy AW, Easley KA. Thin-layer Pap test vs. conventional Pap smear. Analysis of 400 split samples. *J Reprod Med* 2002;**47**:9–13.

62. Luthra UK, Chishti M, Dey P, Jolly SV, Abdulla M, Das DK, *et al*. Performance of monolayered cervical smears in a gynecology outpatient setting in Kuwait. *Acta Cytol* 2002;**46**:303–10.

63. Ring M, Bolger N, O'Donnell M, Malkin A, Bermingham N, Akpan E, *et al*. Evaluation of liquid-based cytology in cervical screening of high-risk populations: a split study of colposcopy and genito-urinary medicine populations. *Cytopathology* 2002;**13**:152–9.

64. Vassilakos P, Cossali D, Albe X, Alonso L, Hohener R, Puget E. Efficacy of monolayer preparations for cervical cytology: emphasis on suboptimal specimens. *Acta Cytol* 1996; **40**:496–500.

65. Takahashi M, Naito M. Application of the CytoRich monolayer preparation system for cervical cytology. A prelude to automated primary screening. *Acta Cytol* 1997;**41**:1785–9.

66. Howell LP, Davis RL, Belk TI, Agdigos R, Lowe J. The AutoCyte preparation system for gynecologic cytology. *Acta Cytol* 1998;**42**:171–7.

67. Geyer JW, Hancock F, Carrico C, Kirkpatrick M. Preliminary evaluation of Cyto-Rich: an improved automated cytology preparation. *Diagn Cytopathol* 1993;**9**:417–22.

68. Sprenger E, Schwarzmann P, Kirkpatrick M, Fox W, Heinzerling RH, Geyer JW, Knesel EA. The false negative rate in cervical cytology. Comparison of monolayers to conventional smears. *Acta Cytol* 1996;**40**:81–9.

69. Laverty CR, Farnsworth A, Thurloe JK, Grieves A, Bowditch RC. Evaluation of the CytoRich slide preparation process. *Anal Quant Cytol Histol* 1997;**19**:239–45.

70. Wilbur DC, Facik MS, Rutkowski MA, Mulford DK, Atkison KM. Clinical trials of the CytoRich specimen-preparation device for cervical cytology. Preliminary results. *Acta Cytol* 1997;**41**:24–9.

71. Stevens MW, Nespolon WW, Milne AJ, Rowland R. Evaluation of the CytoRich technique for cervical smears. *Diagn Cytopathol* 1998;**18**:236–42.

72. McGoogan E, Reith A. Would monolayers provide more representative samples and improved preparations for cervical screening? Overview and evaluation of systems available. *Acta Cytol* 1996; **40**:107–19.

73. Austin RM, Ramzy I. Increased detection of epithelial cell abnormalities by liquid-based gynecologic cytology preparations. A review of accumulated data. *Acta Cytol* 1998;**42**:178–84.

74. Weintraub J. The coming revolution in cervical cytology: a pathologist's guide for the clinician. *References en Gynecologie Obstetrique* 1997;**5**:1–6.

75. Dupree WB, Suprun HZ, Beckwith DG, Shane JJ, Lucente V. The promise of a new technology. The Leigh Valley Hospital's experience with liquid-based cytology. *Cancer* 1998;**84**:202–7.

76. Papillo JL, Zarka MA, St John TL. Evaluation of the ThinPrep Pap test in clinical practice. A seven-month, 16,314-case experience in northern Vermont. *Acta Cytol* 1998;**42**:203–8.

77. Vassilakos P, Griffin S, Megevand E, Campana A. CytoRich liquid-based cervical cytologic test. Screening results in a routine cytopathology service. *Acta Cytol* 1998;**42**:198–202.

78. Carpenter AB, Davey DD. ThinPrep Pap Test: performance and biopsy follow-up in a university hospital. *Cancer* 1999;**87**:105–12.

79. Diaz-Rosario LA, Kabawat SE. Performance of a fluid-based, thin-layer Papanicolaou smear method in the clinical setting of an independent laboratory and an outpatient screening population in New England. *Arch Pathol Lab Med* 1999;**123**: 817–21.

80. Guidos BJ, Selvaggi SM. Use of the ThinPrep Pap test in clinical practice. *Diagn Cytopathol* 1999; **20**:70–3.

81. Tench W. Preliminary assessment of the AutoCyte PREP. Direct-to-vial performance. *J Reprod Med* 2000;**45**:912–16.

82. Weintraub J, Morabia A. Efficacy of a liquid-based thin layer method for cervical cancer screening in a population with a low incidence of cervical cancer. *Diagn Cytopathol* 2000;**22**:52–9.

83. Marino JF, Fremont-Smith M. Direct-to-vial experience with AutoCyte PREP in a small New England regional cytology practice. *J Reprod Med* 2001;**46**:353–8.

84. Day SJ, Deszo EL, Freund GG. Dual sampling of the endocervix and its impact on AutoCyte Prep endocervical adequacy. *Am J Clin Pathol* 2002; **118**:41–6.

85. Baker JJ. Conventional and liquid-based cervicovaginal cytology: a comparison study with clinical and histologic follow-up. *Diagn Cytopathol* 2002;**27**:185–8.

86. Shield PW, Nolan GR, Phillips GE, Cummings MC. Improving cervical cytology screening in a remote, high risk population. *Med J Aust* 1999;**170**:255–8.

87. Cheuvront DA, Elston RJ, Bishop JW. Effect of a thin-layer preparation system on workload in a cytology laboratory. *Lab Med* 1998;**29**:174–9.

88. McGoogan E. Improved adequacy rates using ThinPrep Pap test for routine cytopathology. *Cytopathology* 1999;**10** (Suppl 1):2–2.

89. Papillo JL, Lee KR, Manna EA. Clinical evaluation of the ThinPrep method for the preparation of nongynecologic material [letter]. *Acta Cytol* 1992; **36**:651–2.

90. Papillo JL. Current status of cytotechnology manpower: will thin layer preparations play an important role? *Diagn Cytopathol* 1994;**10**:385–7.

91. Iverson DK. Impact of training on cytotechnologists' interpretation of gynecologic thin-layer preparations. *Diagn Cytopathol* 1998;**18**:230–5.

92. Spitzer M. Cervical screening adjuncts: recent advances [review]. *Am J Obstet Gynecol* 1998; **179**:544–56.

93. Hutchinson ML, Isenstein LM, Goodman A, Hurley AA, Douglass KL, Mui KK, *et al*. Homogeneous sampling accounts for the increased diagnostic accuracy using the ThinPrep processor. *Am J Clin Pathol* 1994;**101**:215–19.

94. ACOG committee opinion. New Pap test screening techniques. *Int J Gynecol Obstet* 1998;**63**:312–14.

95. Wain GV. Automation in cervical cytology: whose cost and whose benefit? *Med J Aust* 1997; **167**:460–1.

96. Sawaya GF, Grimes DA. New technologies in cervical cytology screening: a word of caution. *Obstet Gynecol* 1999;**94**:307–10.

97. Martin-Hirsch P, Lilford R, Jarvis G, Kitchener HC. Efficacy of cervical-smear collection devices: a systematic review and meta-analysis. *Lancet* 1999;**354**:1763–70.

98. Brown AD, Garber AM. Cost-effectiveness of three methods to enhance the sensitivity of Papanicolaou testing. *JAMA* 1999;**281**:347–53.

99. Myers ER, McCrory DC, Nanda K, Bastian L, Matchar DB. Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. *Am J Epidemiol* 2000; **151**:1158–71.

100. Montz FJ, Farber FL, Bristow RE, Cornelison T. Impact of increasing Papanicolaou test sensitivity and compliance: a modeled cost and outcomes analysis. *Obstet Gynecol* 2001;**97**:781–8.

101. Raab SS, Zaleski S, Silverman J. The cost-effectiveness of cytology laboratory and new cytology technologies in cervical cancer prevention. *Anat Pathol* 1999;**111**:259–66.

102. Braly P, Kinney W. *A review of AHCPR Evidence Report/Technology Assessment: Evaluation of Cervical Cytology Impact of the ThinPrep Pap Test on Cervical Cancer Screening*. Boxborough, MA: Cytyc Corporation. 1999. pp. 3–8.

103. Hutchinson ML, Berger BM, Farber FL. Clinical and cost implications of new technologies for cervical cancer screening: the impact of test sensitivity. *American Journal of Managed Care* 2000;**6**:766–80.

104. Department of Health. *NHS Pays and Prices Index: Health Services Cost Index*. London: Department of Health. 2003.

105. Karlsson G, Johannesson M. The decision rules of cost-effectiveness analysis. *Pharmacoeconomics* 1996;**9**:113–20.

106. Smith BL, Lee M, Leader S, Wertlake P. Economic impact of automated primary screening for cervical cancer. *J Reprod Med* 1999;**44**:518–28.

107. Kim JJ, Wright TC, Goldie SJ. Cost-effectiveness of alternative triage strategies for atypical squamous cells of undetermined significance. *JAMA* 2002;**287**:2382–90.

108. Sherlaw-Johnson C, Gallivan S, Jenkins D, Jones MH. Cytological screening and management of abnormalities in prevention of cervical cancer: an overview with stochastic modelling. *J Clin Pathol* 1994;**47**:430–5.

109. Jenkins D, Sherlaw-Johnson C, Gallivan S. Can papilloma virus testing be used to improve cervical cancer screening? *Int J Cancer* 1996;**65**: 768–73.

110. Oster AG. Natural history of cervical intraepithelial neoplasia: a critical review. *Int J Gynaecol Pathol* 1993;**12**:186–92.

111. Government Statistical Service. *Review of the Registrar General on Deaths in England and Wales 1993–95: Mortality Statistics – General*. Series DH1. 1993. London: HMSO. p. 221.

112. Obralic N, Katsanis WA, Gibb RK, Doering DL. Cervical cancer. In Djulbegovic B, Sullivan D, editors. *Decision Making in Oncology: Evidence Based Management*. New York, NY: Churchill Livingstone. 1997. pp. 283–7.

113. Eddy DM. Screening for cervical cancer. *Ann Intern Med* 1990;**113**:214–26.

114. NHS Cervical Screening Programme. *Standards for the Colposcopy Service*. 1996. pp. 5–9. London: Department of Health.

115. Zelen M. Optimal scheduling of examinations for the early detection of disease. *Biometrika* 1993; **80**:279–93.

116. NHS. NHS Reference costs 2002. http://www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4069646&chk=vzKK5z

117. Tucker JH, Stark MH, Eason P, Duvall E. Analysis of rare high-DNA cell populations in serous effusions using continuous-motion imaging. *Analyt Cell Pathol* 1991;**3**:233–42.

118. Office for National Statistics. Cancer statistics, registrations. Series MBI, number 26. London: HMSO. 1993. pp. 26–7.

119. *The NHS Plan: A Plan for Investment. A Plan for Reform*. Presented to parliament by the Secretary of State for Health By Command of Her Majesty. Cm 4818-I. London: HMSO. 2000.

Appendix 1

Electronic bibliographic databases searched

1. CCTR (Cochrane Controlled Trials Register)
2. CDSR (Cochrane Database of Systematic Reviews)
3. EMBASE
4. MEDLINE
5. NRR (National Research Register)
6. NHS DARE (Database of Assessments of Reviews of Effectiveness)
7. NHS EED (Economic Evaluations Database)
8. NHS HTA (Health Technology Assessment)
9. PreMEDLINE
10. Science Citation Index
11. Social Sciences Citation Index

Appendix 2

Other sources searched

1. AHRQ (Agency for Healthcare Research and Quality), USA
2. Australian Department of Health and Ageing
3. MSAC (Australian Medical Services Advisory Committee)
4. ASERNIP-S (Australian Safety and Efficacy Register of New Interventional Procedures – Surgical)
5. Bandolier
6. CCOHTA (Canadian Coordinating Office for Health Technology Assessment)
7. CellPath plc
8. INAHTA (International Network of Agencies for Health Technology Assessment) Clearinghouse
9. NGC (National Guidelines Clearinghouse)
10. NCCHTA (National Coordinating Centre for Health Technology Assessment)

Appendix 3

Search strategies used

CDSR, CCTR, DARE, NHS EED and NHS HTA

2002, Issue 3
1999–2002
The Cochrane Library, Update Software (CD ROM version)
Search undertaken October 2002

#1 CERVIX-NEOPLASMS:ME
#2 CERVICAL-INTRAEPITHELIAL-NEOPLASIA:ME
#3 CERVIX-DYSPLASIA:ME
#4 VAGINAL-SMEARS:ME
#5 CYTOLOGICAL-TECHNIQUES:ME
#6 HISTOCYTOLOGICAL-PREPARATION-TECHNIQUES:ME
#7 CYTODIAGNOSIS:ME
#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9 FLUID AND BASED
#10 THINLAYER
#11 THINPREP
#12 THIN NEAR PREP*
#13 THIN NEAR LAYER*
#14 MONOLAYER
#15 MONO NEAR LAYER
#16 LIQUID*
#17 CYTYC
#18 CYTORICH
#19 CYTO AND RICH
#20 AUTOCYTE AND PREP
#21 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
#22 #8 AND #21

CDSR, DARE and NHS HTA: for systematic reviews of Pap smears only

2002, Issue 3
1999–2002
The Cochrane Library, Update Software (CD ROM version)
Search undertaken October 2002

#1 PAPILLOMAVIRUS-HUMAN*:ME
#2 HPV
#3 HUMAN AND PAPILLOMAVIRUS
#4 PAP* NEAR SMEAR*
#5 SMEAR* NEAR TEST*
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 VAGINAL-SMEARS:ME
#8 CERVIX-NEOPLASMS:ME
#9 CERVIX-DYSPLASIA:ME
#10 CERVICAL-INTRAEPITHELIAL-NEOPLASIA:ME
#11 CYTOLOGICAL-TECHNIQUES:ME
#12 HISTOCYTOLOGICAL-PREPARATION-TECHNIQUES:ME
#13 CYTODIAGNOSIS:ME
#14 #8 OR #9 OR #10 OR #11 OR #12 OR #13
#15 #6 AND #14

Citation Indexes (Science and Social Sciences)

1999–2002
Web of Science
Search undertaken October 2002

Database limits:
DocType=All document types; All languages;
Databases=SCI-EXPANDED, SSCI;
Timespan=1999-2002.

((cervix or cervical or vagina* or cervicovagina*) and (fluid based or thinlayer* or thinprep or thin layer* or thin prep* or monolayer* or mono layer* or cytyc or cytorich or cyto rich or autocyte prep or liquid*))

Citation Indexes (Science and Social Sciences): modelling search

1999–2002
Web of Science
Search undertaken October 2002

Database limits:
DocType=All document types; All languages;
Databases=SCI-EXPANDED, SSCI;
Timespan=1999-2002.

((cervi* screen* or cervi* smear*) and (model*))

EMBASE

1999–2002
SilverPlatter WebSPIRS
Search undertaken October 2002

#1 'Vagina-smear' / all subheadings
#2 Uterine cervix cytology
#3 'Uterine cervix cytology' / all subheadings
#4 Explode 'uterine-cervix-cancer' / all subheadings
#5 Explode 'diagnosis-' / all subheadings
#6 'Prevention-' / all subheadings
#7 'Diagnosis -' / all subheadings
#8 'Screening-' / all subheadings
#9 #5 or #6 or #7 or #8
#10 #4 and #9
#11 #1 or #2 or #3 or #10
#12 Fluid based
#13 Thinlayer
#14 Thin prep
#15 Thin near prep*
#16 Thin near layer*
#17 Monolayer*
#18 Mono near layer*
#19 Liquid*
#20 Cytyc
#21 Cytorich
#22 Cyto rich
#23 Autocyte prep
#24 #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23
#25 #11 and #24
#26 #25 and (PY=1999-2002)

EMBASE: Modelling search

1999–2002
SilverPlatter WebSPIRS
Search undertaken October 2002

#1 'Vagina-smear' / all subheadings
#2 'Uterine cervix cytology' / all subheadings
#3 'Uterine cervix cancer' / all subheadings
#4 'Cytodiagnosis' / all subheadings
#5 'Cancer cytodiagnosis' / all subheadings
#6 'Mass screening' / all subheadings
#7 'Cancer screening' / all subheadings
#8 #4 or #5 or #6 or #7
#9 #3 and #8
#10 #1 or #2 or #9
#11 'Model' / all subheadings
#12 'Nonbiological model' / all subheadings
#13 'Population model' / all subheadings
#14 'Mathematical model' / all subheadings
#15 'Statistical model' / all subheadings
#16 'Stochastic model' / all subheadings
#17 markov
#18 #11 or #12 or #13 or #14 or #15 or #16 or #17
#19 #10 and #18
#20 (model*) in TI
#21 #10 and #20
#22 #19 or #21
#23 #22 and (PY=1999-2002)

MEDLINE: sensitivity/specificity search

1999–2002
Ovid Biomed
Search undertaken October 2002

#1 Cervix neoplasms/
#2 Cervical intraepithelial neoplasia/
#3 Cervix dysplasia/
#4 Vaginal smears/
#5 Cytological techniques/
#6 Histocytological preparation techniques/
#7 Cytodiagnosis/
#8 Or/1-7
#9 Fluid based.tw
#10 Thinlayer.tw
#11 Thinprep.tw
#12 (Thin adj3 prep$).tw
#13 (Thin adj3 layer$).tw
#14 Monolayer$.tw
#15 (Mono adj3 layer$).tw
#16 Liquid$.tw
#17 Cytyc.tw
#18 Cytorich.tw
#19 Cyto rich.tw
#20 Autocyte prep.tw
#21 Or/9-20
#22 Exp "Sensitivity and specificity"/
#23 Sensitivity.tw
#24 Exp Diagnosis/
#25 Exp Pathology/
#26 Specificity.tw
#27 Or/22-26
#28 8 and 21 and 27

MEDLINE: economics search

1999–2002
Ovid Biomed
Search undertaken October 2002

#1 Cervix neoplasms/
#2 Cervical intraepithelial neoplasia/
#3 Cervix dysplasia/

#4 Vaginal smears/
#5 Di.fs
#6 Exp diagnosis/
#7 or/1-3
#8 5 or 6
#9 7 and 8
#10 4 or 9
#11 Fluid based.tw
#12 Thinlayer.tw
#13 Thinprep.tw
#14 (Thin adj3 prep$).tw
#15 (Thin) adj3 (layer$).tw
#16 Monolayer$.tw
#17 (Mono adj3 layer$).tw
#18 Liquid$.tw
#19 Cytyc.tw
#20 Cytorich.tw
#21 Cyto rich.tw
#22 Autocyte prep.tw
#23 Or/11-22
#24 10 and 23
#25 Economics/
#26 Exp "Costs and cost analysis"/
#27 Economic value of life/
#28 Exp Economics, hospital/
#29 Exp Economics, medical/
#30 Economics, nursing/
#31 Exp models, economic/
#32 Economics, pharmaceutical/
#33 Exp "Fees and charges"/
#34 Exp Budgets/
#35 Ec.fs
#36 (Cost or costs or costed or costly or costing$).tw
#37 (Economic$ or pharmacoeconomic$ or price$ or pricing).tw
#38 Or/25-37
#39 24 and 38

MEDLINE: Modelling search

1999–2002
Ovid Biomed
Search undertaken October 2002

#1 Vaginal smears/
#2 Cervix neoplasms/
#3 Cytodiagnosis/
#4 Mass screening/
#5 3 or 4
#6 2 and 5
#7 1 or 6
#8 Models, theoretical/
#9 Models, organizational/
#10 Exp models, statistical/
#11 Markov Chains/
#12 Or/8-11
#13 7 and 12

NRR

2002, Issue 3
Department of Health, Update Software (CD ROM version)
Search undertaken October 2002

#1 CYTOL
#2 FLUID NEXT BASED
#3 THINLAYER
#4 THINPREP
#5 THIN NEAR LAYER*
#6 THIN NEAR PREP*
#7 MONOLAYER*
#8 MONO NEAR LAYER*
#9 CYTYC
#10 CYTORICH
#11 CYTO NEXT RICH
#12 AUTOCYTE NEXT PREP
#13 LIQUID
#14 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
#15 CERVIX OR CERVICAL OR VAGINA*
#16 #14 AND #15
#17 PAP NEAR SMEAR*
#18 HPV
#19 HUMAN PAPILLOMA VIRUS
#20 SMEAR*
#21 #17 OR #18 OR #19 OR #20
#22 #15 AND #21
#23 SENSITIVITY
#24 SPECIFICITY
#25 SENSITIVITY-AND-SPECIFICITY*:ME
#26 DIAGNOSIS*:ME
#27 PATHOLOGY*:ME
#28 #23 OR #24 OR #25 OR #26 OR #27
#29 #22 AND #28
#30 #16 OR #29

PreMEDLINE: sensitivity/ specificity search

14 October 2002
Ovid Biomed
Search undertaken October 2002

#1 (Cervix$ adj3 neoplasm$).tw
#2 (Cervi$ adj3 intraepithelial$ adj3 neoplas$).tw
#3 (Cervi$ adj3 dysplasia$).tw
#4 (Vaginal$ adj3 smear$).tw

#5 (Cytologi$ adj3 technique$).tw
#6 (Histocytologi$ adj3 prep$ adj3 technique$).tw
#7 Cytodiagno$.tw
#8 Or/1-7
#9 Fluid based.tw
#10 Thinlayer.tw
#11 Thinprep.tw
#12 (Thin adj3 prep$).tw
#13 (Thin adj3 layer$).tw
#14 Monolayer$.tw
#15 (Mono adj3 layer$).tw
#16 Liquid$.tw
#17 Cytyc.tw
#18 Cytorich.tw
#19 Cyto rich.tw
#20 Autocyte prep.tw
#21 Or/9-20
#22 Sensitivity.tw
#23 Diagnosis.tw
#24 Pathology.tw
#25 Specificity.tw
#26 Or/22-25
#27 8 and 21 and 26

Appendix 4

Systematic review of economic evaluations of LBC techniques

TABLE 31 *Review of economic evaluations included in the original LBC review*

Study	Brown and Garber, 1999[98]	AHCPR, 1999;[102] Myers et *al.*, 2000[99] [a]	Australian Health Technology Advisory Committee, 1998[25]
Title	Cost-effectiveness of three methods to enhance the sensitivity of Papanicolaou testing	Evaluation of cervical cytology; Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis	Review of automated and semi-automated cervical screening devices
Statement of the problem	Evaluation of cost-effectiveness of ThinPrep as a primary screen with 10% random rescreening, and AutoPap and Papnet as rescreening selection devices, compared with conventional Pap smear testing with 10% random rescreening and no screening	What are the ranges of incremental cost, sensitivity and screening frequency that meet conventional levels of cost per life-year saved (defined as US$50,000) for technologies that improve conventional test performance by (1) improving the sensitivity of the initial screening step or (2) allowing 100% rescreening at improved sensitivity	To provide an estimate of the potential additional costs and benefits of the use of automated and semi-automated technologies in a 2-year screening cycle. Slide preparation and automated rescreening devices are not considered separately. The analysis aims to investigate the likely performance of a generic technology for improving test characteristics compared with a baseline conventional test screening
Discussion of the need for modelling	Implied by the lack of empirical economic evidence, but not stated directly	Systematic search undertaken for economic evidence	A dearth of health economic evidence for the monolayer technologies identified through a systematic search
Description of the relevant factors and outcomes	Factors include disease incidence and progression, age dependent; regression of preinvasive lesions; test characteristics; success of treatment for diagnosed abnormalities, stage dependent; all-cause mortality; costs of screening and treatment Health benefits are years of life saved	Factors include age-specific prevalence of HPV infection, LSIL and HSIL; progression and regression rates associated with HPV infection, LSIL and HSIL; test characteristics; unrelated mortality and hysterectomy rates; diagnosis and treatment management strategies; stage-specific treatment success rates; stage-specific cancer survival; screening and treatment costs Health benefits are life-years saved.	Factors include increase in low and high-grade abnormalities detected; progression of low- and high-grade lesions to invasive cancer Health benefits are measured in terms of "additional cancer cases detected"
Description of model, including type of model, time frame, perspective and setting	A nine-state, time-varying state transition model is used to model the life experience of cohort of women aged 20–65 years. The model used is not fully described but is attributed to Eddy A societal perspective is used to analyse costs. A rate of 3% (0–5%) is used to discount both health benefits and costs	A 20-state Markov model of the natural history of cervical cancer with an intervention model of possible screening strategies is used to model the life experience of cohort of women aged 15–85 years. A direct healthcare perspective is used to analyse costs. A rate of 3% (0–5%) is used to discount both health benefits and costs	A simple model for estimating the number of cancer cases potentially avoided is described.

continued

TABLE 31 *Review of economic evaluations included in the original LBC review (cont'd)*

Study	Brown and Garber, 1999[98]	AHCPR, 1999;[102] Myers *et al.*, 2000[99] a, b[a]	Australian Health Technology Advisory Committee, 1998[25]
Description of data sources, with description of respective strengths and weaknesses	Test characteristics obtained from a systematic search and review (MEDLINE; key journals were handsearched and the equipment suppliers were contacted for unpublished evidence). Disease progression rates are not given but again referenced to Eddy. All direct costs of screening are included (training costs not included). Data from peer-reviewed published articles, manufacturers' publicly available documentation and survey of pathology laboratories in Northern California. Capital and training costs not included but estimated at under US$0.25 per slide and equal for all technologies. References included Costs of care figures from Eddy updated to 1996 US dollars. Marginal consumable cost of ThinPrep $9.75	Test characteristics obtained from a systematic search and review (MEDLINE, CancerLit, HealthSTAR, CINAHL, EMBASE and EconLit databases. Recently published journals were handsearched and web resources were consulted). Full inclusion/exclusion criteria and results are reported and estimates of test characteristics are made. Precancerous lesions are classified according to the Bethesda system; invasive cancer is staged according to the FIGO classification system Costs of screening, diagnosing and treating cervical cancer were estimated using private insurance claims, Medicare fee schedules and secondary data sources Costs were adjusted to 1997 US dollars	The model assumes that the new techniques increase the total proportion of abnormal readings while the distribution of these readings between grades is unchanged. A wide range of values for the relative increase in abnormalities is used Average unit costs for treatment and diagnosis are estimated from routinely available Australian statistics A range of generic marginal test costs is evaluated
Key stated assumptions relating to model structure and data	All cancers develop from preinvasive lesions, which may spontaneously regress. The majority of cancers (85–90%) develop from a long preinvasive phase	All cervical cancer arises from HPV infection. HPV can progress directly to LSIL or HSIL HPV infection can regress to a well state, LSIL can regress to a latent HPV state or well, and HSIL can regress to LSIL, HPV or well Women treated for SIL have a reduced progression rate. Parameter estimates were chosen to bias results in favour of improving test sensitivity A hysterectomy state is included, although the natural history model was not corrected for hysterectomy rates.	

continued

TABLE 31 *Review of economic evaluations included in the original LBC review (cont'd)*

Study	Brown and Garber, 1999[98]	AHCPR, 1999;[102] Myers *et al.*, 2000[99] a, b[a]	Australian Health Technology Advisory Committee, 1998[25]
Definition of test results and abnormal test result threshold	Abnormal test results are categorised as LSIL, HSIL or cancer	Abnormal test results are categorised as atypical (ASCUS or AGUS), LSIL, HSIL or cancer, although true positives are based on histological diagnosis of LSIL or worse Invasive cancer is staged according to the FIGO classification system (stages I–IV, plus terminal care)	
Representation of inadequacy rates	No mention of differential inadequacy rates	No mention of differential inadequacy rates	
Management strategy for atypical screening results	ASCUS results are treated as normal screens and not investigated further	ASCUS results are rescreened within 6 months and receive colposcopy if results are abnormal	
Test characteristics parameters	Conventional Pap smear testing, 80% sensitivity Primary ThinPrep screen, 91.9% sensitivity, with 10% random rescreening, 92.6% sensitivity AutoPap and Papnet-assisted rescreening, 95.4% and > 97% (97% was assumed to be the maximum) sensitivity, respectively Sensitivity and specificity do not differentiate between the higher disease states	Conventional Pap smear testing, 51% sensitivity, 97% specificity New technologies, 51–99% sensitivity, 97–72.75% specificity Sensitivity and specificity do not differentiate between the higher disease states	
Disease progression rates	Disease progression rates are not given, but referenced to Eddy	Age-specific regression rates: HPV: 70% regress over 18 months, age 15–24 years, 50% age 25–29, 15% age 30+. LSIL: 90% of regressions go directly to well, 65% regress over 72 months, age 15–34 years, 40% age 35+. HSIL: 50% each regress to LSIL and well, 35% regress over 72 months Progression rates: HPV to LSIL: 20% over 36 months, 10% progress directly to HSIL; LSIL to HSIL: 10% over 72 months age 15–34 years, 35% age 35+; HSIL to cancer: 40% over 120 months	

continued

TABLE 31 *Review of economic evaluations included in the original LBC review (cont'd)*

Study	Brown and Garber, 1999[98]	AHCPR, 1999;[102] Myers *et al.*, 2000[99] a, b[a]	Australian Health Technology Advisory Committee, 1998[25]
Screening intervals tested	1, 2, 3 and 4 years	1, 2, 3 and 5 years	
Marginal cost of new technology	ThinPrep US$9.75, AutoPap $5.00, Papnet $10.00	Baseline US$10, range $0–15	
Validation	Not mentioned	Model predicted peak cancer incidence and age-specific incidence curves similar to referenced unscreened populations. Age-specific prevalences of HPV, LSIL and HSIL are consistent with cross-sectional data	
Results	Pap smear with AutoPap-assisted rescreen is the most cost-effective option for all intervals above 1 year (conventional Pap smears are cost-effective for a 1-year interval). Comparison between screening intervals presented diagrammatically, assuming a $50,000 threshold, AutoPap-assisted rescreen testing every 4 years is most cost-effective option	Comparing different sensitivity rates separately across increasing screening intervals (with threshold of $50,000) for a test with baseline sensitivity (51%) the optimal interval is 2 years; if sensitivity is increased to 75% the optimal interval is 3 years	
Sensitivity analysis results	Parameters: range of population (e.g. risk of cancer, ages screened) and test characteristics, and treatment costs and discount rate Cancer incidence has the largest effect of the population parameters. If sensitivity of conventional screening were 50% (commonly assumed by other studies) AutoPap rescreening would dominate conventional screening. ThinPrep is cost-effective if additional sensitivity is 50% higher than baseline assumption	Parameters: sensitivity, specificity and screening cost Threshold analyses for combinations of sensitivity and specificity are presented for separate screening intervals, e.g. for a 3-year interval. To get under the $50,000 threshold a new technology would need to increase sensitivity by 45% and not lose more than around 10% specificity	

continued

TABLE 31 *Review of economic evaluations included in the original LBC review (cont'd)*

Study	Brown and Garber, 1999[98]	AHCPR, 1999;[102] Myers *et al.*, 2000[99] a, b[a]	Australian Health Technology Advisory Committee, 1998[25]
Discussion	Results are not sensitive to all but the largest changes in test characteristics, although such changes are within the reported ranges The discussion centres on rescreening strategies (as ThinPrep primary screening is shown to be non-cost-effective). Previous work is cited that implies that manual rescreening of 100% tests is more cost-effective than Papnet or AutoPap. Findings may change as new evidence on sensitivity becomes available, especially if tests differ in classification of alternative stages of abnormality ThinPrep may be used to detect HPV as part of a triage system (large clinical trial mentioned: ascus/lsil triage study for cervical cancer (ATLS)).	New tests with increased sensitivity, even with low marginal test costs, will disproportionately increase total costs relative to health benefits (life-years saved), i.e. the cost-effectiveness ratio will increase relative to Pap smears compared with no screening Small changes in test specificity can have a great impact on cost-effectiveness. Documentation of specificity is essential The impact of morbidity on quality of life may be incorporated by linking treatment data to different stages of cervical cancer. It is also necessary to account for false positives on quality of life Main message: improved sensitivity is not enough for a new test to be cost-effective. New tests based on specific HPV types or that use biomarkers may improve specificity and reduce screening frequency, and can be used in conjunction with less expensive treatments of low-grade abnormalities	

[a] Myers *et al.* present the results of the AHCPR analysis in a peer-reviewed journal.

TABLE 32 *Review of economic evaluations identified in addition to those included in the original LBC review*

Study	Hutchinson *et al.*, 2000[103]	Montz *et al.*, 2001[100]	Raab *et al.*, 1999[101]
Title	Clinical and cost implications of new technologies for cervical cancer screening: the impact of test sensitivity	Impact of increasing Papanicolaou sensitivity and compliance: a modelled cost and outcomes analysis	The cost-effectiveness of the cytology laboratory and new cytology technologies in cervical cancer prevention
Statement of the problem	To compare available technologies for cervical screening using actual programme utilisation patterns (for validation). New technologies are conventional screening with Autopap selected rescreening, conventional screening with AutoPap prescreening, ThinPrep primary testing with 10% rescreening	To model the impact of increasing screening compliance or implementing LBC in populations with known compliance patterns and risk profiles on rates of detection of cervical precancers, compared with conventional Pap smear testing with 10% random rescreening	To study the cost-effectiveness component of the laboratory in cervicovaginal screening, and to assess how cost-effectiveness changed with the introduction of new technologies. Cost-effectiveness is assessed using laboratory-based costs alone, and overall costs
Discussion of the need for modelling	Implied by the lack of empirical economic evidence, although not stated directly	Implied by the lack of empirical economic evidence, although not stated directly	Due to the need to incorporate treatment and follow-up costs and probabilities in the determination of the overall cost-effectiveness of screening
Description of the relevant factors and outcomes	Factors include age-specific hysterectomy rates; test characteristics; age-specific incidence of CIN lesions; progression and regression of CIN lesions; compliance rates; incidence rates by stage; age-specific deaths in screened and unscreened cohorts; screening and treatment costs Health benefits are the average incidence of cervical cancer over the course of screening and life-years saved	As for Hutchinson *et al.*, 2000	Factors include distribution of screening results; progression of HSIL to cancer (total and within 1 year); stage of cancer at diagnosis; probability of HSIL given alternative atypical screening results, stage-specific life expectancies; screening and treatment costs; increase in HSIL diagnoses required for new technologies to be cost-effective Health effects are cancers developing, false-positive results and life expectancy

continued

TABLE 32 *Review of economic evaluations identified in addition to those included in the original LBC review (cont'd)*

Study	Hutchinson *et al.*, 2000[103]	Montz *et al.*, 2001[100]	Raab *et al.*, 1999[101]
Description of model, including type of model, time frame, perspective and setting	A Markov model describes progression from a screening pool to four test result states (true and false positive and negative), as well as to cancer diagnosis, hysterectomy and non-cancer death. Other states describe progression from cancer treatment (one-cycle tunnel state) and cancer survival to further survival or death. Women aged 20–65 are included. Natural history of cervical cancer includes only two precancer stages: CIN and CIS A payer perspective included only medical costs and health benefits. Costs and outcomes are both discounted at 3%	As for Hutchinson *et al.*, 2000	Unclear what type of model is used, but could be decision tree to represent one round of screening with life expectancy estimates added to end-points A healthcare perspective is implied, life expectancies discounted at 5%, but no other details of discounting are presented
Description of data sources, with description of respective strengths and weaknesses	"Widely accepted reference values are used in determining the effect [an] event or intervention may have." No details of literature review given. Sensitivity same as baseline figures from AHCPR, age-specific CIN incidence from literature. Cancer incidence and mortality rates from US National Cancer institute, hysterectomy rates from the Centers for Disease Control. Screening compliance rates from referenced survey. Effectiveness rates for new technologies taken from manufacturers' submissions for FDA approval	As for Hutchinson *et al.*, 2000	Baseline test result distribution and laboratory costs direct from hospital records. Life expectancies from Surveillance, Epidemiology and End Results (SEER) and National Center for Statistics. Probability and other cost data from literature (no details of search given)
Key stated assumptions relating to model structure and data	Women treated for CIN or CIS are returned to the screening pool. CIN and CIS lesions can both regress. Differentiates between preparation error (abnormal cells not represented) and screening error (abnormal cells present but missed) (which occur in a ratio of 3:1)	As for Hutchinson *et al.*, 2000	Sampling or screening errors do not occur (sensitivity = 100%, although alternative techniques pick up different numbers of cases, i.e. analysis disregards missed cases)

continued

TABLE 32 *Review of economic evaluations identified in addition to those included in the original LBC review (cont'd)*

Study	Hutchinson *et al.*, 2000[103]	Montz *et al.*, 2001[100]	Raab *et al.*, 1999[101]
Definition of test results and abnormal test result threshold	Positive screening results are categorised as LSIL, HSIL, AGUS, squamous cell carcinoma or adenocarcinoma. Women with ASCUS results were referred for a second screen within a year True-positive test results are categorised as all grades of CIN, CIS or cancer	As for Hutchinson *et al.*, 2000	Abnormal test results are categorised as atypical (ASCUS or AGUS), LSIL, HSIL or cancer. False positives based on those not having evidence of disease on follow-up LSILs were assumed not to progress to cancer as women assumed to have yearly smears
Representation of inadequacy rates	Differential inadequacy rates mentioned in discussion: up to 50% reduction in inadequate screens, which if included would reduce cost-effectiveness ratio	As for Hutchinson *et al.*, 2000	The micro-costing of the screen costs accounted for a rescreen rate, although no differential rate is included.
Management strategy for atypical screening results	All women with a positive screening result are forwarded to colposcopy and treated appropriately. Women with ASCUS results are referred for a second screen within a year and referred for colposcopy if ASCUS or worse	As for Hutchinson *et al.*, 2000	LSILs and atypical screen results are not studied because it is assumed that, if they progress to HSIL, they will be picked up at the next annual screen
Test characteristics parameters	Conventional Pap smear testing, 50.4% (LSIL) and 55.2% (HSIL) sensitivity AutoPap rescreening, 55.3% (LSIL) and 52.3% (HSIL) sensitivity AutoPap prescreening, 55.2% (LSIL) and 59.2% (HSIL) sensitivity ThinPrep primary screening 75% (LSIL) and 82.2% (HSIL) sensitivity	Conventional Pap smear, 51% sensitivity LBC, 73% sensitivity	False negatives are not recorded, only the difference in abnormal screens where the same proportion of abnormal screen results is assumed to represent HSIL, of which a constant proportion will progress to cancer
Disease progression rates	Age-specific regression rates: CIN 65% regress over 6 years, age 20–34; 40% regress over 6 years, age 35+. CIS: 35% regress over 6 years Progression rates: CIN to IS: 6 years, CIS to cancer 10 years. 10% of CIN cases that progress to cancer progress within 1 year	As for Hutchinson *et al.*, 2000	10% HSILs progress to cancer, 25% of the 10% progress within 1 year
Screening intervals tested	1, 2, 3, 5 and 10 years	Baseline compliance based on self-reported survey, increased compliance rates based on government targets for 2000 and 2010	1 year

continued

TABLE 32 *Review of economic evaluations identified in addition to those included in the original LBC review (cont'd)*

Study	Hutchinson *et al.*, 2000[103]	Montz *et al.*, 2001[100]	Raab *et al.*, 1999[101]
Marginal cost of new technology	US$9.75	As for Hutchinson *et al.*, 2000	US$0–50
Validation	Compared with cancer incidence rates based on self-reported compliance rates, e.g. 85% every 2 years, 5% every 5 years, 5% every 10 years and 5% never	As for Hutchinson *et al.*, 2000	Not mentioned
Results	ThinPrep is the most cost-effective option for all intervals above 1 year (conventional Pap smears are cost-effective for a 1-year interval). Comparison between screening intervals presented diagrammatically: assuming a $50,000 threshold, ThinPrep testing every 2 years is most cost-effective option	LBC gains additional life-years at a cost of US$15,296 given self-reported compliance rates	New technologies included as part of sensitivity analysis. Only presented is the cost per additional HSIL detected, for a range of potential additional costs of new technology. If a new technology costs an additional US$10, then 236 additional HSILs would need to be detected to get under the $50,000 threshold (1-year screening interval)
Sensitivity analysis results	Parameters: test sensitivity and intervention costs Using lower sensitivity rates and treatment costs reduced the cost-effectiveness of new technologies, but the rank order remained the same Also tests cost-effectiveness using data describing actual compliance rates (as used for validation), which shows that ThinPrep is cost-effective in the full population, but not in a population comprising women who are screened at least every 3 years	Parameters: test sensitivity and compliance rates Incidence rates, not cost-effectiveness ratios are presented for alternative sensitivity rate assumptions. LBC is shown to be cost-effective over all compliance assumptions	As above
Discussion	Regarding the effectiveness of rescreening devices, states that studies are underway that will provide better estimates (manufacturer's data are used in current study) Lack of hard data on management of ASCUS screens, analysis of follow-up protocols require. If test sensitivity is increased by 50% with a new test, the new test will be cost-effective despite increased per-test cost	The use of LBC in conjunction with efforts to increase compliance is recommended	Cervicovaginal screening of low-risk groups may not be cost-effective, although other patient outcomes (patient satisfaction or freedom of choice) may justify screening such groups If women receive yearly smears, the added cost of a new technology to detect LSILs is not justified. The cost of a new technology would have to be low to justify a modest gain in HSIL detection

CIS, carcinoma *in situ*.

Health Technology Assessment Programme

Prioritisation Strategy Group

Members

Chair,
Professor Tom Walley,
Director, NHS HTA Programme, Department of Pharmacology & Therapeutics, University of Liverpool

Professor Bruce Campbell, Consultant Vascular & General Surgeon, Royal Devon & Exeter Hospital

Professor Shah Ebrahim, Professor in Epidemiology of Ageing, University of Bristol

Dr John Reynolds, Clinical Director, Acute General Medicine SDU, Radcliffe Hospital, Oxford

Dr Ron Zimmern, Director, Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

HTA Commissioning Board

Members

Programme Director,
Professor Tom Walley,
Director, NHS HTA Programme, Department of Pharmacology & Therapeutics, University of Liverpool

Chair,
Professor Shah Ebrahim,
Professor in Epidemiology of Ageing, Department of Social Medicine, University of Bristol

Deputy Chair,
Professor Jenny Hewison,
Professor of Health Care Psychology, Academic Unit of Psychiatry and Behavioural Sciences, University of Leeds School of Medicine

Dr Jeffrey Aronson
Reader in Clinical Pharmacology, Department of Clinical Pharmacology, Radcliffe Infirmary, Oxford

Professor Ann Bowling, Professor of Health Services Research, Primary Care and Population Studies, University College London

Professor Andrew Bradbury, Professor of Vascular Surgery, Department of Vascular Surgery, Birmingham Heartlands Hospital

Professor John Brazier, Director of Health Economics, Sheffield Health Economics Group, School of Health & Related Research, University of Sheffield

Dr Andrew Briggs, Public Health Career Scientist, Health Economics Research Centre, University of Oxford

Professor Nicky Cullum, Director of Centre for Evidence Based Nursing, Department of Health Sciences, University of York

Dr Andrew Farmer, Senior Lecturer in General Practice, Department of Primary Health Care, University of Oxford

Professor Fiona J Gilbert, Professor of Radiology, Department of Radiology, University of Aberdeen

Professor Adrian Grant, Director, Health Services Research Unit, University of Aberdeen

Professor F D Richard Hobbs, Professor of Primary Care & General Practice, Department of Primary Care & General Practice, University of Birmingham

Professor Peter Jones, Head of Department, University Department of Psychiatry, University of Cambridge

Professor Sallie Lamb, Research Professor in Physiotherapy/Co-Director, Interdisciplinary Research Centre in Health, Coventry University

Professor Julian Little, Professor of Epidemiology, Department of Medicine and Therapeutics, University of Aberdeen

Professor Stuart Logan, Director of Health & Social Care Research, The Peninsula Medical School, Universities of Exeter & Plymouth

Professor Tim Peters, Professor of Primary Care Health Services Research, Division of Primary Health Care, University of Bristol

Professor Ian Roberts, Professor of Epidemiology & Public Health, Intervention Research Unit, London School of Hygiene and Tropical Medicine

Professor Peter Sandercock, Professor of Medical Neurology, Department of Clinical Neurosciences, University of Edinburgh

Professor Mark Sculpher, Professor of Health Economics, Centre for Health Economics, Institute for Research in the Social Services, University of York

Professor Martin Severs, Professor in Elderly Health Care, Portsmouth Institute of Medicine

Dr Jonathan Shapiro, Senior Fellow, Health Services Management Centre, Birmingham

Ms Kate Thomas, Deputy Director, Medical Care Research Unit, University of Sheffield

Professor Simon G Thompson, Director, MRC Biostatistics Unit, Institute of Public Health, Cambridge

Ms Sue Ziebland, Senior Research Fellow, Cancer Research UK, University of Oxford

Current and past membership details of all HTA 'committees' are available from the HTA website (www.ncchta.org)

Diagnostic Technologies & Screening Panel

Members

Chair,
Dr Ron Zimmern, Director of the Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

Ms Norma Armston, Freelance Consumer Advocate, Bolton

Professor Max Bachmann Professor Health Care Interfaces, Department of Health Policy and Practice, University of East Anglia

Professor Rudy Bilous Professor of Clinical Medicine & Consultant Physician, The Academic Centre, South Tees Hospitals NHS Trust

Dr Paul Cockcroft, Consultant Medical Microbiologist/Laboratory Director, Public Health Laboratory, St Mary's Hospital, Portsmouth

Professor Adrian K Dixon, Professor of Radiology, Addenbrooke's Hospital, Cambridge

Dr David Elliman, Consultant in Community Child Health, London

Professor Glyn Elwyn, Primary Medical Care Research Group, Swansea Clinical School, University of Wales Swansea

Dr John Fielding, Consultant Radiologist, Radiology Department, Royal Shrewsbury Hospital

Dr Karen N Foster, Clinical Lecturer, Dept of General Practice & Primary Care, University of Aberdeen

Professor Antony J Franks, Deputy Medical Director, The Leeds Teaching Hospitals NHS Trust

Mr Tam Fry, Honorary Chairman, Child Growth Foundation, London

Dr Edmund Jessop, Medical Adviser, National Specialist Commissioning Advisory Group (NSCAG), Department of Health, London

Dr Jennifer J Kurinczuk, Consultant Clinical Epidemiologist, National Perinatal Epidemiology Unit, Oxford

Dr Susanne M Ludgate, Medical Director, Medical Devices Agency, London

Dr William Rosenberg, Senior Lecturer and Consultant in Medicine, University of Southampton

Dr Susan Schonfield, CPHM Specialised Services Commissioning, Croydon Primary Care Trust

Dr Margaret Somerville, Director of Public Health, Teignbridge Primary Care Trust

Professor Lindsay Wilson Turnbull, Scientific Director, Centre for MR Investigations & YCR Professor of Radiology, University of Hull

Professor Martin J Whittle, Head of Division of Reproductive & Child Health, University of Birmingham

Dr Dennis Wright, Consultant Biochemist & Clinical Director, Pathology & The Kennedy Galton Centre, Northwick Park & St Mark's Hospitals, Harrow

Pharmaceuticals Panel

Members

Chair,
Dr John Reynolds, Clinical Director, Acute General Medicine SDU, Oxford Radcliffe Hospital

Professor Tony Avery, Professor of Primary Health Care, University of Nottingham

Professor Stirling Bryan, Professor of Health Economics, Health Services Management Centre, University of Birmingham

Mr Peter Cardy, Chief Executive, Macmillan Cancer Relief, London

Dr Christopher Cates, GP and Cochrane Editor, Bushey Health Centre

Professor Imti Choonara, Professor in Child Health, University of Nottingham, Derbyshire Children's Hospital

Mr Charles Dobson, Special Projects Adviser, Department of Health

Dr Robin Ferner, Consultant Physician and Director, West Midlands Centre for Adverse Drug Reactions, City Hospital NHS Trust, Birmingham

Dr Karen A Fitzgerald, Pharmaceutical Adviser, Bro Taf Health Authority, Cardiff

Mrs Sharon Hart, Managing Editor, *Drug & Therapeutics Bulletin*, London

Dr Christine Hine, Consultant in Public Health Medicine, Bristol South & West Primary Care Trust

Professor Stan Kaye, Professor of Medical Oncology, Consultant in Medical Oncology/Drug Development, The Royal Marsden Hospital

Ms Barbara Meredith, Project Manager Clinical Guidelines, Patient Involvement Unit, NICE

Dr Frances Rotblat, CPMP Delegate, Medicines Control Agency, London

Professor Jan Scott, Professor of Psychological Treatments, Institute of Psychiatry, University of London

Mrs Katrina Simister, New Products Manager, National Prescribing Centre, Liverpool

Dr Richard Tiner, Medical Director, Association of the British Pharmaceutical Industry

Dr Helen Williams, Consultant Microbiologist, Norfolk & Norwich University Hospital NHS Trust

Therapeutic Procedures Panel

Members

Chair,
Professor Bruce Campbell,
Consultant Vascular and General Surgeon, Royal Devon & Exeter Hospital

Dr Mahmood Adil, Head of Clinical Support & Health Protection, Directorate of Health and Social Care (North), Department of Health, Manchester

Dr Aileen Clarke, Reader in Health Services Research, Public Health & Policy Research Unit, Barts & the London School of Medicine & Dentistry, Institute of Community Health Sciences, Queen Mary, University of London

Mr Matthew William Cooke, Senior Clinical Lecturer and Honorary Consultant, Emergency Department, University of Warwick, Coventry & Warwickshire NHS Trust, Division of Health in the Community, Centre for Primary Health Care Studies, Coventry

Dr Carl E Counsell, Senior Lecturer in Neurology, University of Aberdeen

Dr Keith Dodd, Consultant Paediatrician, Derbyshire Children's Hospital

Professor Gene Feder, Professor of Primary Care R&D, Barts & the London, Queen Mary's School of Medicine and Dentistry, University of London

Professor Paul Gregg, Professor of Orthopaedic Surgical Science, Department of Orthopaedic Surgery, South Tees Hospital NHS Trust

Ms Bec Hanley, Freelance Consumer Advocate, Hurstpierpoint

Ms Maryann L. Hardy, Lecturer, Division of Radiography, University of Bradford

Professor Alan Horwich, Director of Clinical R&D, The Institute of Cancer Research, London

Dr Phillip Leech, Principal Medical Officer for Primary Care, Department of Health, London

Dr Simon de Lusignan, Senior Lecturer, Primary Care Informatics, Department of Community Health Sciences, St George's Hospital Medical School, London

Dr Mike McGovern, Senior Medical Officer, Heart Team, Department of Health, London

Professor James Neilson, Professor of Obstetrics and Gynaecology, Dept of Obstetrics and Gynaecology, University of Liverpool, Liverpool Women's Hospital

Dr John C Pounsford, Consultant Physician, North Bristol NHS Trust

Dr Vimal Sharma, Consultant Psychiatrist & Hon Snr Lecturer, Mental Health Resource Centre, Victoria Central Hospital, Wirrall

Dr L David Smith, Consultant Cardiologist, Royal Devon & Exeter Hospital

Professor Norman Waugh, Professor of Public Health, University of Aberdeen

Expert Advisory Network

Members

Professor Douglas Altman,
Director of CSM & Cancer Research UK Med Stat Gp, Centre for Statistics in Medicine, University of Oxford, Institute of Health Sciences, Headington, Oxford

Professor John Bond,
Director, Centre for Health Services Research, University of Newcastle upon Tyne, School of Population & Health Sciences, Newcastle upon Tyne

Mr Shaun Brogan,
Chief Executive, Ridgeway Primary Care Group, Aylesbury

Mrs Stella Burnside OBE,
Chief Executive, Office of the Chief Executive. Trust Headquarters, Altnagelvin Hospitals Health & Social Services Trust, Altnagelvin Area Hospital, Londonderry

Ms Tracy Bury,
Project Manager, World Confederation for Physical Therapy, London

Mr John A Cairns,
Professor of Health Economics, Health Economics Research Unit, University of Aberdeen

Professor Iain T Cameron,
Professor of Obstetrics and Gynaecology and Head of the School of Medicine, University of Southampton

Dr Christine Clark,
Medical Writer & Consultant Pharmacist, Rossendale

Professor Collette Mary Clifford,
Professor of Nursing & Head of Research, School of Health Sciences, University of Birmingham, Edgbaston, Birmingham

Professor Barry Cookson,
Director, Laboratory of Healthcare Associated Infection, Health Protection Agency, London

Professor Howard Stephen Cuckle,
Professor of Reproductive Epidemiology, Department of Paediatrics, Obstetrics & Gynaecology, University of Leeds

Professor Nicky Cullum,
Director of Centre for Evidence Based Nursing, University of York

Dr Katherine Darton,
Information Unit, MIND – The Mental Health Charity, London

Professor Carol Dezateux,
Professor of Paediatric Epidemiology, London

Mr John Dunning,
Consultant Cardiothoracic Surgeon, Cardiothoracic Surgical Unit, Papworth Hospital NHS Trust, Cambridge

Mr Jonothan Earnshaw,
Consultant Vascular Surgeon, Gloucestershire Royal Hospital, Gloucester

Professor Martin Eccles,
Professor of Clinical Effectiveness, Centre for Health Services Research, University of Newcastle upon Tyne

Professor Pam Enderby,
Professor of Community Rehabilitation, Institute of General Practice and Primary Care, University of Sheffield

Mr Leonard R Fenwick,
Chief Executive, Newcastle upon Tyne Hospitals NHS Trust

Professor David Field,
Professor of Neonatal Medicine, Child Health, The Leicester Royal Infirmary NHS Trust

Mrs Gillian Fletcher,
Antenatal Teacher & Tutor and President, National Childbirth Trust, Henfield

Professor Jayne Franklyn,
Professor of Medicine, Department of Medicine, University of Birmingham, Queen Elizabeth Hospital, Edgbaston, Birmingham

Ms Grace Gibbs,
Deputy Chief Executive, Director for Nursing, Midwifery & Clinical Support Servs, West Middlesex University Hospital, Isleworth

Dr Neville Goodman,
Consultant Anaesthetist, Southmead Hospital, Bristol

Professor Alastair Gray,
Professor of Health Economics, Department of Public Health, University of Oxford

Professor Robert E Hawkins,
CRC Professor and Director of Medical Oncology, Christie CRC Research Centre, Christie Hospital NHS Trust, Manchester

Professor F D Richard Hobbs,
Professor of Primary Care & General Practice, Department of Primary Care & General Practice, University of Birmingham

Professor Allen Hutchinson,
Director of Public Health & Deputy Dean of ScHARR, Department of Public Health, University of Sheffield

Dr Duncan Keeley,
General Practitioner (Dr Burch & Ptnrs), The Health Centre, Thame

Dr Donna Lamping,
Research Degrees Programme Director & Reader in Psychology, Health Services Research Unit, London School of Hygiene and Tropical Medicine, London

Mr George Levvy,
Chief Executive, Motor Neurone Disease Association, Northampton

Professor James Lindesay,
Professor of Psychiatry for the Elderly, University of Leicester, Leicester General Hospital

Professor Rajan Madhok,
Medical Director & Director of Public Health, Directorate of Clinical Strategy & Public Health, North & East Yorkshire & Northern Lincolnshire Health Authority, York

Professor David Mant,
Professor of General Practice, Department of Primary Care, University of Oxford

Professor Alexander Markham,
Director, Molecular Medicine Unit, St James's University Hospital, Leeds

Dr Chris McCall,
General Practitioner, The Hadleigh Practice, Castle Mullen

Professor Alistair McGuire,
Professor of Health Economics, London School of Economics

Dr Peter Moore,
Freelance Science Writer, Ashtead

Dr Andrew Mortimore,
Consultant in Public Health Medicine, Southampton City Primary Care Trust

Dr Sue Moss,
Associate Director, Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton

Professor Jon Nicholl,
Director of Medical Care Research Unit, School of Health and Related Research, University of Sheffield

Mrs Julietta Patnick,
National Co-ordinator, NHS Cancer Screening Programmes, Sheffield

Professor Robert Peveler,
Professor of Liaison Psychiatry, University Mental Health Group, Royal South Hants Hospital, Southampton

Professor Chris Price,
Visiting Chair – Oxford, Clinical Research, Bayer Diagnostics Europe, Cirencester

Ms Marianne Rigge,
Director, College of Health, London

Dr Eamonn Sheridan,
Consultant in Clinical Genetics, Genetics Department, St James's University Hospital, Leeds

Dr Ken Stein,
Senior Clinical Lecturer in Public Health, Director, Peninsula Technology Assessment Group, University of Exeter

Professor Sarah Stewart-Brown,
Director HSRU/Honorary Consultant in PH Medicine, Department of Public Health, University of Oxford

Professor Ala Szczepura,
Professor of Health Service Research, Centre for Health Services Studies, University of Warwick

Dr Ross Taylor,
Senior Lecturer, Department of General Practice and Primary Care, University of Aberdeen

Mrs Joan Webster,
Consumer member, HTA – Expert Advisory Network

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.ncchta.org) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@soton.ac.uk
http://www.ncchta.org

ISSN 1366-5278