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Rapid review

Liquid-based cytology in cervical screening: a rapid and systematic review

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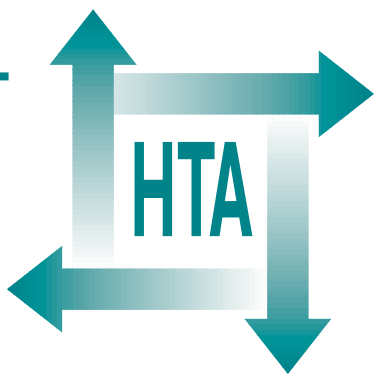
Health Technology Assessment
NHS R&D HTA Programme



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Liquid-based cytology in cervical screening: a rapid and systematic review

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The research reported in this monograph was commissioned by the HTA programme (project number 99/18/01) on behalf of the National Institute for Clinical Excellence (NICE). Rapid reviews are completed in a limited time to inform the appraisal and guideline development processes managed by NICE. The review brings together evidence on key aspects of the use of the technology concerned. However, appraisals and guidelines produced by NICE are informed by a wide range of sources. Any views expressed in this rapid review are therefore those of the authors and not necessarily those of the HTA programme, NICE or the Department of Health.

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Contents

List of abbreviations

AGUS	atypical glandular cells of uncertain significance
AHCPR	Agency for Health Care Policy and Research
ASCUS	atypical squamous cells of uncertain significance
CI	confidence interval
CIN	cervical intraepithelial neoplasia
CSP	Cervical Screening Programme
FDA	Food and Drug Administration
HGIL	high-grade glandular intraepithelial lesion
HPV	human papillomavirus
HRG	health resource group
HSIL	high-grade squamous intraepithelial lesion
LSIL	low-grade squamous intraepithelial lesion
NICE	National Institute for Clinical Excellence
RCT	randomised controlled trial

Executive summary

Background

Around 4 million women per annum in England have a cervical screening test. Currently the age-standardised incidence of cervical cancer is around 9.3 per 100,000 per annum. The mortality rate in 1997 was 3.7 per 100,000 per annum.

Liquid-based cytology 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 cervical cancer.

Methods

Data sources

Three types of literature search were performed:

- clinical effectiveness search
- cost-effectiveness search
- modelling search.

The first two concentrated on liquid-based cytology, while the modelling search addressed the wider topic of modelling studies in respect of cervical screening. The databases searched were:

- MEDLINE
- EMBASE
- Science Citation Index
- Cochrane Library
- NHS CRD: DARE, NEED and HTA
- HealthSTAR
- National Research Register.

Inclusion and exclusion criteria

All health technology assessment and related secondary research studies were included. Primary research studies were included if they attempted to measure an outcome of importance, such as comparison of liquid-based cytology with conventional cervical smears in respect of an assessment of sensitivity and/or specificity, categorisation of specimens, percentage of inadequate or unsatisfactory specimens and specimen interpretation times. All databases were searched up to November 1999. Additional material identified up to February 2000 was also included.

Data extraction

Data were extracted by one of the authors. Key tabulations and calculations for summary tables were checked by entering the published study data (where available) into a spreadsheet and re-calculating the relevant percentages. Only those studies with a clear tabulation of the numerical data were used in the conventional smear versus liquid-cytology assessments.

Results

Number and quality of studies and direction of evidence

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

Effectiveness

There is some evidence that liquid-based cytological methods offer the following advantages over traditional smear techniques:

- a reduction in the proportion of inadequate specimens
- an improvement in sensitivity
- a possible reduction in specimen interpretation times.

Costs

The estimated annual gross cost of consumables and operating equipment associated with the new technique, based on a marginal cost per slide that includes capital equipment costs depreciated over a period of 6 years, is about £16 million in England.

Cost-effectiveness

There are no studies that provide direct evidence regarding the cost-effectiveness of liquid-based cytology screening. Analyses based on models of disease natural history, however, give a cost-effectiveness of under £10,000 per life-year gained, when screening is undertaken every 5 years, and under £20,000 per life-year gained at a 3-year interval, except under certain assumptions in respect of marginal costs and discount rates.

Sensitivity analyses

These results in respect of cost-effectiveness are relatively stable under most conditions. The key uncertainties are the marginal costs associated with liquid-based cytology, assumptions about improvements in sensitivity and specificity, and discounting both in terms of costs, but particularly in terms of benefits.

Limitations of the calculations (assumptions made)

There is inadequate evidence concerning the underlying natural history of the disease. Similarly, the true sensitivity of the screening tests, both conventional smears and liquid-based cytology, is unobservable without subjecting women to otherwise unnecessary and relatively invasive investigations. These characteristics have thus been estimated by fitting mathematical models of the disease and intervention to observable events such as actual incidence.

Conclusions

From the evidence available, it is likely that the liquid-based cytology technique will reduce the number of false-negative test results, reduce the number of unsatisfactory specimens and may decrease the time needed for examination of specimens by cytologists. It is not possible to be certain whether this will reduce the incidence of invasive cancer, but modelling studies have suggested that this would occur.

In this review, it became clear that increasing the coverage of the programme, and the use of more effective cervical specimen collection devices are also important ways of reducing the burden of the invasive cervical cancer. The use of automated image analysis devices, and of other testing of the specimens (such as for human papillomavirus) have not been covered in this review.

Recommendations for research

A full cost-effectiveness study of liquid-based cytology based on a trial of its introduction in low-prevalence populations would provide more definitive information than is possible by modelling studies. However, an assessment of the uncertainties about the values and assumptions used in the economic model indicates that the key areas for further research are:

- the marginal cost per sample of the new technologies compared with conventional screening methods
- the improvement in the rate of inadequate samples and the relative specificity of the liquid-based cytology techniques.

Expiry date

It is recommended that the conclusions from this report are revisited in July 2001 or earlier if new trials and technologies emerge before then.

Chapter 1

Aims and background

Aim of the review

The question to be addressed in this report is: "What is the effectiveness and cost-effectiveness of liquid-based cytology for cervical screening compared with conventional smear testing?"

Liquid-based cytology 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-negative results and inadequate slides. It would, however, involve significant capital investment, reorganisation of the service, and significant running costs.

The underlying health problem

The age-standardised incidence of invasive cervical cancer in England in 1997 was estimated to be 9.3 per 100,000 per annum,[1] and recent trends are shown in *Table 1*. There was a reduction in incidence during the 1990s following the peak incidence of the mid-to-late 1980s.

Mortality from cervical cancer has been falling in England by 1–2% each year (*Table 1*) 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. In 1997, therefore, the age-standardised mortality rate was 3.7 per 100,000 per annum.

Significance in terms of ill-health

For an average health authority of 500,000 population there are around 30 incident cases of invasive cervical cancer each year and about 13 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 pre-malignant 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 are invited to be screened (though coverage figures are usually estimated from the 25–64 year age group),[2] and the national policy is that eligible women should be screened every 3–5 years. In 1997–98 in England, 3.9 million women were screened, the majority after a formal invitation from the screening programme. Coverage was relatively high – just over 85% of women[2] (i.e. the proportion of eligible women who have been screened in less than 5 years since their last test). In that time, laboratories examined an estimated 4.4 million smears.[2] Coverage has increased substantially in the past 10 years from a figure of only 22% in 1987–88.

Screening at present involves taking a sample of cells from the cervix uteri obtained under direct vision using a vaginal speculum. Usually a wooden Aylesbury spatula is used to sweep around the cervix and take a sample of cells. After taking the sample, 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 each smear takes about 4–10 minutes and is often repeated by a second cytologist. Thus, the

TABLE 1 *Age-standardised incidence and mortality from cervical cancer, England (1979–97)*

	'79	'80	'81	'82	'83	'84	'85	'86	'87	'88	'89	'90	'91	'92	'93	'94	'95	'96	'97
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	n/a	9.3

Rates per 100,000 per annum – directly age-standardised using the European standard population. Incidence was not given for 1996 and the 1997 value is an estimate[1]

actual screening rate is slower. It is important to emphasise the need for a high degree of training for all staff involved.[1] A quality assurance programme has been introduced with guidelines for clinical practice and programme management.[3]

Women who have negative smears and no signs of abnormality will be invited for re-screening 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 time period to referral for colposcopy and biopsy. Treatment is then in accordance with the result of this more definitive examination.

Currently (data for England, 1997–98) 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.[2] Women with changes in these latter two categories are referred for immediate colposcopy.[4] 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.[1]

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, blood, incorrectly labelled, or fail to contain sufficient numbers of the right type of cells. In these cases the woman is re-called so that the smear can be repeated. Currently around 9% of smears are reported as inadequate.[4]

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.

Limitations of cervical screening testing methods

Like all screening tests, the cervical smear or any new cytological method 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.[5] In other words, sensitivity assesses the propensity of a test to avoid false-negative results (i.e. giving a negative result when disease is actually present in the woman). These false-negative results 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.[6]

Specificity is the proportion of truly non-diseased persons who are so identified by the screening test.[5] In other words, specificity assesses the propensity of a test to avoid false-positive results (i.e. giving a positive result when the true result is negative). In assessing the performance of a new test compared with the current screening methods

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

	Approximate no. per annum in average health authority (500,000 population)
No. of cervical smears taken	44,000
No. of repeat cervical smears	4000–4400 (i.e. about 9–10% of 44,000)
Total no. of referrals for colposcopy	1200 [a]
No. of referrals for colposcopy for higher-grade lesions	700 (i.e. about 1.6% of smears)

[a] *Based on a census carried out by the National Audit Office*

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 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 for example Fahey *et al.*).[7]

A wide range of performance has been reported by Fahey and co-workers for sensitivity and specificity with current cervical smear tests.[7] 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's 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.[8]

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 and/or ensure women do not miss a screening round than 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 pre-cancerous lesions, has been estimated to cost about £135 million each year in England,[9] though it is unclear whether this includes all the relevant costs.

Variation in services: coverage and screening interval

Currently 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 have coverage below the national target of 80%, while ten health authorities have coverage of over 90%. Three-year testing coverage is more variable, with only three health authorities having a coverage of 80% or more, while 12 have coverage of under 60%.[2] This reflects the fact that about 60% of health authorities invite women every 3 years, and 15% have a mixed policy, inviting women every 3–5 years depending on their age.[10]

The new intervention in cervical screening

Intervention

Liquid-based cytology for cervical screening aims to improve the quality of the conventional cervical smear through an improved slide preparation technique. 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 the cervical specimen cytology have also been made in the past. For example, Steven and co-workers suggested chemical depolymerisation of cervical mucin to help produce monolayers.[11] Neugebauer and co-workers in 1981 described a sedimentation velocity separation method,[12] and a pulse wash method was suggested by Näslund and co-workers.[13,14]

The liquid-based cytology technique that is the subject of the present report involves not making a smear of the material obtained on the spatula/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.[15] Moreover, improved fixation allows more consistent staining.

Thus, these 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 papillomavirus (HPV), chlamydia, and other molecular biological tests.[16–19] Testing for HPV, however, 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 prior to 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 might lead to discrepancies.

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.

AutoCytePrep® – Previously known as CytoRich™ (CellPath plc, Hemel Hempstead, 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 (CytoRich). 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 an AutoCytePrep 'robot', which handles 48 samples at a time. The cell pellet is re-suspended and an aliquot is 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 AutoCytePrep system. (*Note that we have used the newer name AutoCyte except where quoting the results from a paper or report about the product that has described it as CytoRich.)

CYTOSCREEN® (Altrix Healthcare plc, 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 the National Institute for Clinical Exzcellence (NICE), October 1999).

LABONORD Easy Prep® (Surgipath Europe Ltd, 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).

ThinPrep® (Cytyc UK Ltd, Crawley, UK)

This was approved by the FDA in 1996 and is currently available as the ThinPrep®2000 System. A plastic collection device is rinsed thoroughly into a vial containing a proprietary transport fluid (PreservCyt®). In the laboratory, each vial is placed

individually in the ThinPrep2000 Processor. There are three key phases to the process:

- dispersion – to produce a randomised cell suspension breaking up cell clumps and mucus
- 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
- 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. In the USA, FDA approval has been given to the ThinPrep2000 System. The ThinPrep®3000 process system (expected to be released in April 2000) is designed to improve productivity further by providing automated batch-processing of up to 80 specimens per cycle.

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 liquid-based cytology 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 involved

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 general practitioner or practice nurse, at a community clinic such as a family planning or well-woman clinic, or at a colposcopy clinic. Using the liquid-based cytology method would not change these arrangements, though 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, there is the possibility that it will not be possible to use the Royal Mail, (as occurs in some areas) if fluids containing alcohols are used in the transport medium.

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 liquid-based cytology 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 liquid-based cytology. Instead of making smears on glass slides, vials of transport/preservative fluid are required. The collection devices are broadly similar to those in conventional use but must be made of plastic. However, instead of producing and fixing a smear at the time of obtaining the specimen, the material is transferred to the vial of transport fluid and 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 requiring 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 also.

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.

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, liquid-based cervical cytology has not been introduced for cervical screening in the UK. It is, however, being used routinely in at least some laboratories in most developed countries.

Anticipated costs

The marginal gross cost of consumables and relevant equipment associated with introducing the new technique in a typical health authority population of 500,000, and generating around 44,000 smears, is approximately £160,000 per annum. In England (4.4 million smears annually) the cost is estimated at around £16 million per annum. This cost may decrease if liquid-based specimens reduce numbers of inadequate smears and thus reduce the need to recall women for a repeat smear. Moreover, these costs are intended to give a **generic** estimate – individual products may be able to be introduced at lower costs than these.

Chapter 2

Effectiveness of liquid-based cytology in cervical screening

Methods for reviewing effectiveness

Three types of literature search were performed:

- clinical effectiveness search
- cost-effectiveness search
- modelling search.

The first two concentrated on liquid-based cytology, while the modelling search addressed the wider topic of modelling studies in respect of cervical screening.

Industry submissions to NICE were included in the review.

The databases searched were:

- MEDLINE
- EMBASE
- Science Citation Index
- Cochrane Library
- NHS CRD: DARE, NEED and HTA
- HealthSTAR
- National Research Register.

Web pages were contacted for International Network of Agencies for Health Technology Assessment members and other health technology assessment organisations to determine if health technology assessment reports had been produced on this topic.

A citation search was carried out for studies included in the Australian Health Technology Advisory Committee report.[6]

Search strategies for the MEDLINE searches are shown in appendix 1. Search strategies for all the other databases are available from the authors.

Inclusion and exclusion criteria

All health technology assessment and related secondary research studies were included. Primary research studies were included if they attempted to measure an outcome of importance, such as comparison of liquid-based cytology with conventional cervical smears in respect of an assessment of sensitivity and/or specificity, categorisation of specimens, percentage of inadequate or unsatisfactory specimens and specimen interpretation times. All databases were searched from 1966 to November 1999. Additional material identified up to February 2000 was also included.

Data extraction strategy

Data were extracted by one of the authors. Key tabulations and calculations for summary tables were checked by entering the published study data (where available) into a spreadsheet and re-calculating 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 liquid-cytology assessments. Other comments on the quality of studies and study design are made later in the text in relation to specific study types.

Results

Quantity and quality of research available

In considering what literature should be looked for, the following principles were kept in mind in terms both of 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.
- 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 pre-cancerous 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 that the additional detection results in earlier treatment by an interval that reduces incidence, morbidity and/or mortality. It should not be automatically assumed that the detection of additional abnormalities will automatically lead to a reduction in these outcome measures.[6]
- Improvements in specificity may be a proxy for reductions in unnecessary repeat screening examinations and indeed further more invasive investigations and treatment.
- Other outcome measures such as the proportion of inadequate or unsatisfactory smears may be important both in reducing 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

A small number of reviews from other health technology assessment centres were 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).

Australian Health Technology Advisory Committee Report – April 1998[6]

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

- 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 cytologic 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 AutoCytePrep and ThinPrep were as follows.

- There were few peer-reviewed studies of AutoCytePrep found for evaluation. To date, all comparative studies of AutoCytePrep and conventional smears have been prospective and have used the split-sample technique. There is one study comparing ThinPrep and AutoCytePrep.
- AutoCytePrep 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 AutoCytePrep is used.
- A high level of concurrence between AutoCytePrep and conventional smears has been found.
- There is evidence that the AutoCytePrep technique leads to lower rates of missed diagnoses (i.e. greater sensitivity) compared with conventional smears, but there are insufficient data to estimate reliably the magnitude of relative improvement.
- There is evidence that screening time is shorter with AutoCytePrep.
- 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 (extent 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 Au$70 million (~ £29 million) per 2-year screening cycle (in a population just over a quarter the size of England and Wales with a lower coverage rate). If this replaced conventional practice there would be offset savings of Au$25 million (~ £10 million). It was estimated that the costs per additional cancer prevented would be Au$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 88–99%). The newer method gives enhanced preservation and distribution of the cells making slides easier and quicker to view, though fatigue sets in more quickly. The report states that "reduced total number of cells can increase the number of unacceptable slides," though this is not quantified. Many studies were found reporting that monolayer preparation slightly improves detection of low and high-grade disease, perhaps due 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, and training and quality-control for laboratories and programmes. Again the coverage may be lower in Canada than in England and Wales.

AHCPR – January 1999[21]

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 liquid-based cytology 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 re-screening) 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 re-screening 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 that is "within the range of accepted health care practices" (i.e. below $50,000 (~ £30,000) per life-year).

Primary research literature

The primary research literature search identified several types of study, and there was a very substantial overlap between primary sources we identified and those that were use in the secondary research reviews that have been described and discussed in the previous section. There were no trials identified that 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. Any attempt to determine the effect of the liquid-based cervical cytology on these outcome measures can only be arrived at by attempts at modelling with, therefore, all the assumptions and subsequent uncertainties about the conclusions.

Sensitivity and specificity studies

Some studies were identified that attempted to determine the sensitivity and specificity of the new technique (*Table 3*). Sensitivity is the proportion of true positives identified as such, and specificity is the proportion of true negatives correctly identified. In order to determine sensitivity and specificity, a gold standard diagnostic measure is needed. This implies that all those having the screening test should, in addition, have the gold standard test administered too. No studies were identified 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.

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

Study/population	Methodology	Smear sensitivity	Smear specificity	Liquid-based sensitivity	Liquid-based specificity	Definition of positives and of reference standard
Sheets *et al*., 1995[22] 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[19] 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[23] 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[24] 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[25] Mixed hospital and HMO-served populations, USA	AutoCytePrep	78.5% (73/93)		89.2% (83/93)		LSIL+ based on positive biopsy patients (part of a larger study)
Bollick & Hellman, 1998[26] 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[27] 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
Asfaq *et al*., 1999[28] Population with high glandular abnormality rates, USA	ThinPrep	56.4% (22/39)		84.6% (22/26)		Glandular lesions based on biopsy confirmation. Numbers are small
Hutchinson *et al*., 1999[29] Population with high incidence of cervical cancer, Costa Rica	ThinPrep	68.7% (222/323)		87.9% (284/323)		LSIL+ based on a final diagnosis, which was made by a combination of cytology, histology and cervicography
Data on file, CellPath, 1999 Three USA sites	AutoCytePrep	77.2% (363/470)		76.8% (361/470)		LSIL+ graded as such by three reference pathologists
Vassilakos *et al*., 2000[30] Random sample from large Swiss population	AutoCytePrep	88.6% (124/140)		91.0% (690/758)		HSIL+ confirmed by histology after colposcopy, but includes only ASCUS+ smears so may overestimate sensitivity

LSIL+, low-grade squamous intraepithelial lesions or higher; HSIL+, high-grade squamous intraepithelial lesions or higher (as defined in the Bethesda system – see also Table 4*); HMO, Health Maintenance Organisation*

In all the studies in these two categories, the sensitivity was higher (or the same) in the liquid-based cytology group. In several cases the numbers were very small and the differences were often small and/or not statistically significant.

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 liquid-based cytology. Two specimens are produced for each patient screened therefore – a conventional smear and a liquid-based preparation. 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*) there are many different comparisons possible. However, the main outcome comparison in these studies seems to be those with a diagnosis of LSIL+ (as defined in the Bethesda system; also known as mild dyskaryosis in the UK classification system). The use of this outcome threshold for comparing these slide preparation methods is justified firstly 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 get used to and gain experience with the new slide preparation method. Finally, the AHCPR report[21] implies that the LSIL+ threshold is frequently used in the USA as an indication for colposcopy (and indeed sometimes a lower threshold is advocated).[32]

It should be further emphasised that split-sample studies are not the ideal study design. In order to assess the key test characteristics of sensitivity, specificity and positive/negative predictive values, one needs a gold standard comparison and, as has been stated earlier, few of these studies exist. However, the split-sample studies do 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.[31] 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 liquid-based cytology. An example of the sort of tabulation that was used to provide these results is shown in *Table 5*.[29]

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

TABLE 4 *Comparison of UK and Bethesda classification systems*[30]

UK	Result code	Bethesda
Inadequate	1	Unsatisfactory
Negative	2	Negative
Borderline changes (HPV is borderline in UK but LSIL in Bethesda system)	8	Atypical squamous cells of uncertain significance (ASCUS); atypical glandular cells of uncertain significance (AGUS)
Mild dyskaryosis	3	LSIL
Moderate dyskaryosis	7	HSIL
Severe dyskaryosis	4	HSIL
Severe dyskaryosis ?invasive	5	Carcinoma
Glandular neoplasia	6	?High-grade glandular intraepithelial lesion (HGIL)

TABLE 5 – See printed report.

reasons for choosing to report the LSIL+ cut-off in summarising the results from other studies has been 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, 7 and *8* summarise these results from the studies examined. Overall, the liquid-based method seems 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 liquid-based cytology being considered LSIL+ by conventional smear). Studies are of variable size and of 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 is also variably reported. Some, albeit a minority, of these split-specimen studies find that liquid-based cytology classifies 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 is shown by 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 (if indeed they exist!).

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, 7* and *8* gives an indication of this – the proportion of LSIL+ (by both methods) varied from only just over 1% to over 50%. In the UK-screened population one would only expect about 4% to be in this LSIL+ category (i.e. mild dyskaryosis or more).[2]

A review of split-sample studies was carried out by Austin and Ramzy in 1998.[33] 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 indicate that the liquid-based method has a greater sensitivity.

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

Further discussion of the interpretation of split-sample studies is provided in *Assessment of effectiveness* below.

TABLE 6 *ThinPrep split-sample studies*

Study/country	No. of samples/women	Conv > liq LSIL+	Liq > conv LSIL+	Both LSIL+
Hutchinson *et al.*, 1991[34] USA	443	0.45%	1.13%	18.7%
Hutchinson *et al.*, 1992[35] USA	2655	0.68%	2.64%	12.3%
Awen *et al.*, 1995[36] USA	1000	0.0%	0.5%	1.3%
Laverty *et al.*, 1995[37] Australia	1872	2.4%	3.3%	7.5%
Wilbur *et al.*, 1994[38] USA	3218	0.8%	3.1%	17.0%
Aponte-Cipriani *et al.*, 1995[39] USA	665	0.5%	0.8%	3.0%
Sheets, 1995[22] USA	782	1.5%	3.3%	29.4%
Tezuka *et al.*, 1996[40] Japan	215	2.3%	0.0%	54.4%
Ferenczy *et al.*, 1996[41] Canada/USA	364	7.7%	8.8%	33.5%
Wilbur *et al.*, 1996[42] USA	259	3.1%	1.9%	13.5%
Lee *et al.*, 1997[44] USA	6747	1.9%	3.3%	6.1%
Roberts *et al.*, 1997[43] Australia	35,560	0.3%	0.5%	1.7%
Corkill *et al.*, 1998[23] USA	1583	0.8%	3.7%	1.9%
Hutchinson *et al.*, 1999[29] Costa Rica	8636	2.5%	2.8%	2.4%
Bur *et al.*, 1995[45] USA	128	1.6%	1.6%	19.5%

Conv > liq LSIL+, this signifies the proportion where the conventional smear result was LSIL+ but the liquid-based method result was negative or ASCUS

Liq > conv LSIL+, this signifies the 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*

Two-cohort studies

The next type of study identified is what we have called here a two-cohort analysis. This examines two groups of women, usually from two different time 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 from the same underlying population, with similar levels of cervical cancer and pre-cancerous 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, an increase in the

TABLE 7 *AutoCytePrep split-sample studies*

Study/country	No. of samples/women	Conv > liq LSIL+	Liq > conv LSIL+	Both LSIL+
Vassilakos *et al.*, 1996[46] Switzerland	560	0.5%	1.3%	3.2%
Takahashi & Naito, 1997[47] Japan	2000	0.4%	0.3%	3.2%
Howell *et al.*, 1998[48] USA	852	0.8%	1.1%	2.5%
Geyer *et al.*, 1993[49] USA	551	0.0%	0.7%	12.5%
Sprenger *et al.*, 1996[50] Germany	2863	2.0%	5.1%	36.2%
Bishop, 1997[51] USA	2032	1.1%	3.1%	3.1%
Laverty *et al.*, 1997[52] Australia	2064	3.9%	1.6%	5.0%
Wilbur *et al.*, 1997[53] USA	277	1.1%	6.1%	2.9%
Data on file, CellPath, 1997	8983	1.6%	2.15	5.7%
Stevens *et al.,* 1998[54] Australia	1325	1.3%	0.2%	3.9%

TABLE 8 *ThinPrep and AutoCytePrep combined – split-sample study*

Study/country	No. of samples/women	Conv > liq LSIL+	Liq > conv LSIL+	Both LSIL+
McGoogan & Reith, 1996[55] Scotland	3091	1.0%	0.3%	3.6%

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 do. Vassilakos and co-workers[56] found that this increased from 0.38% to 0.68% with the use of the AutoCyte liquid-based cytology method, and Diaz-Rosario and Kabawat[62] found a similar increase of 0.27% to 0.53% using ThinPrep. Both these two large studies also found a decrease in specimens graded as ASCUS.

However, as has been discussed earlier in respect of the 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 a considerable variation between studies in both the definition of an inadequate (sometimes referred to as an unsatisfactory) specimen and the proportion of slides classified as such. However, 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. These results are summarised in *Table 10*. More studies show a higher inadequate

TABLE 9 *Two-cohort studies*

Study/country	Method	No. conventional smear	No. liquid-based	Conventional smears LSIL+	Liquid-based LSIL+
Vassilakos *et al.*, 1999[56] Switzerland and France	AutoCyte	88,569	111,358	1.58%	2.52%
Vassilakos *et al.*, 1998[57] Switzerland	CytoRich	15,402	32,655	1.1%	3.6%
Weintraub, 1997[58] Switzerland	ThinPrep	35,000	18,000	0.70%	2.27%
Bolick & Hellman, 1998[26] USA	ThinPrep	39,408	10,694	1.12%	2.92%
Dupree *et al.*, 1998[59] USA	ThinPrep	22,323	19,351	1.19%	1.67%
Papillo *et al.*, 1998[60] USA	ThinPrep	18,569	8541	1.63%	2.48%
Carpenter & Davey, 1999[61] USA	ThinPrep	5000	2727	7.7%	10.5%
Diaz-Rosario & Kabawat, 1999[62] USA	ThinPrep	74,573	56,095	1.85%	3.24%
Guidos & Selvaggi, 1999[63] USA	ThinPrep	5423	9583	1.11%	3.70%

specimen rate with conventional smears than with the liquid-based method. 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 we have more to gain in this respect from the introduction of liquid-based cytology. (There are, however, differences between 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. However, if this is done (simple pooled analysis), the liquid-based methods seem to have an unsatisfactory specimen rate of half that for conventional smears (relative risk, 0.54; 95% CI, 0.51 to 0.56).

Finally, with respect to specimen adequacy, the introduction of liquid-based cytology 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 few studies.[19,55] 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.[55] Papillo and co-workers found that there are potential savings of 60% in slide evaluation time for liquid-based methods over conventional preparations, though as slide preparation time is longer, the actual savings are reduced slightly.[67] 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".[68]

The need for continuous major adjustments in focus is eliminated as the cells are

TABLE 10 *Specimens classed as inadequate or unsatisfactory (the higher figure is shown in* ***bold****)*

	Inadequate or unsatisfactory specimens		
Study	**Conventional smear**	**Liquid-based**	**System**
Bolick & Hellman, 1998[26]	**1.1% (427/39,408)**	0.29% (31/10,694)	ThinPrep
Carpenter & Davey, 1999[61]	**0.6% (of 5000)**	0.3% (of 2727)	ThinPrep
Diaz-Rosario & Kabawat, 1999[62]	0.22% (163/74,573)	**0.67% (374/56,095)**	ThinPrep
Dupree *et al.,* 1998[59]	2.0% (447/22,323)	**3.8% (731/19,351)**	ThinPrep
Guidos & Selvaggi, 1999[63]	**1.2% (65/5423)**	0.45% (43/9583)	ThinPrep
Lee *et al*., 1997[43]	1.6% (114/7223)	**1.9% (136/7223)**	ThinPrep
Roberts *et al*., 1997[44]	**3.5% (1258/35,560)**	0.66% (235/35,560)	ThinPrep
Shield *et al*., 1999[64]	**17.3% (of 300)**	6.3% (of 300)	ThinPrep
Weintraub, 1999[58]	**0.70% (of 13,163)**	0.26% (of 18,294)	ThinPrep
Hutchinson *et al*., 1991[34]	0.67% (3/446)	0.67% (3/446)	ThinPrep
Laverty *et al*., 1995[37]	1.5% (of 2026)	**5.2% (of 2026)**	ThinPrep
Aponte-Cipriani *et al*., 1995[39]	2.7% (of 854)	**8.5% (of 854)**	ThinPrep
Bishop *et al*., 1998[25]	**1.0% (89/9212)**	0.6% (54/9212)	AutoCyte
Cheuvront *et al*., 1998[65]	0.67% (141/21,000)	**0.73% (15/2047)**	AutoCyte
Vassilakos *et al*., 1996[46]	**5.2% (29/560)**	3.8% (21/560)	CytoRich
Laverty *et al*., 1997[52]	**2.6% (56/2125)**	0.28% (6/2125)	CytoRich
Howell *et al*., 1998[48]	**0.35% (3/853)**	0.0% (0/853)	AutoCyte
Wilbur *et al.,* 1997[53]	**3.6% (10/280)**	1.1% (3/280)	CytoRich
McGoogan, 1999[66]	**8.0% (40/500)**	2.4% (12/500)	ThinPrep
Vassilikos *et al*., 1999[56] (Swiss results)	**13.4% (2070/15,402)**	2.7% (891/32,655)	AutoCyte
Vassilikos *et al*., 1999[56] (French results)	**2.5% (1615/63,853)**	0.54% (383/71,017)	AutoCyte
Data on file, CellPath, 1997	**1.0% (89/9212)**	0.6% (54/9212)	CytoRich
Data on file, CellPath, 1999	0.33% (8/2438)	**0.78% (19/2438)**	CytoRich

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 over-interpreted enhanced cytological features observed in thin-layer preparations.[34] Iverson reported that a short educational intervention (over 4 $^{1}/_{2}$ hours) did not improve the test scores between a control and experimental group of cytotechnologists.[69] 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 assure accurate interpretation. Spitzer, reviewing recent advances in cervical screening, also draws attention to the training required, particularly in relation to differences in cellular appearance in these preparations.[70] A laboratory guidance document and training log are being agreed for use in Scotland for the demonstration projects set up there.

Homogeneity of specimens Hutchinson and co-workers[71] 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 liquid-based cytological 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 – though this is hard to quantify with the data available in the published literature; this has the potential to help avoid missing a diagnosis of a lesion requiring further treatment
- a probable decrease in specimen interpretation times – though this is reported in relatively few studies; if confirmed, this may imply that a reduction of primary screener hours is possible
- the potential to employ more easily other tests such as HPV on the liquid-based specimen collected; in this context the National Screening Committee is considering 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.

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

- There are no RCTs 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 re-training 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.[72] This too concluded that there was no large, population-based prospective study to determine whether any of these techniques (including liquid-based cytology) 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 liquid-based cytology techniques compare with other methods of quality improvement, such as random re-screening of a mandated proportion of smears, directed re-screening of high-risk groups and rapid re-screening.[73]

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

Assessing 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, of course, is to reduce the mortality and morbidity from invasive cervical cancer. To this end there is a cervical screening programme and it is arguably the sensitivity of the programme as a whole that needs to be considered. This can be influenced by a number of factors beyond that 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 than 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 pre-malignant 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 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 whom uptake is low, should be considered.

Assessment of liquid-based cytology using split-sample studies

Much of the evidence cited in support of liquid-based cytology is based on results from split-specimen studies. Here the cervical specimen is split between making a conventional smear and use for a liquid-based method. This may be an unfair assessment of both techniques because clearly less of the specimen is available for either. 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.[74] Although the two-cohort study methodology does not have the in-built comparison mechanism, it might 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, which is 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.[75] 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 bi-directional. Compared with conventional smears, they might re-classify some relatively low-grade smears as higher grade or re-classify some relatively high-grade smears as low grade. Although additional higher-grade smears might be uncovered, some might 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.[75]

Specimen collection devices and the effectiveness of specimen collection

In comparing conventional cervical smears with liquid-based cytology and examining the associated literature it became clear that it is important also to consider the specimen collection device. While a full systematic review of this issue was not within the terms of the present report we have considered the recently published systematic review and meta-analysis by Martin-Hirsch and co-workers.[76] 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).

These improvement rates in detection that 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.

Chapter 3

Systematic review of economic evidence for liquid-based cytology services

Overview of economic assessment

Few direct assessments, and fewer RCTs, have been undertaken within the field of cervical cancer screening for either the major clinical or economic outcomes, for example incidence of invasive cancer, mortality avoided, life-years gained, cost per cancer avoided, or cost per life-year gained. The vast majority of assessments in this field have been undertaken using modelling methods.

The cervical cancer screening modelling literature is briefly reviewed and a systematic review of published evidence on the economics of using liquid-based cytology techniques is presented.

Methods

The purpose of this review is to generate classification criteria, (relevant factors and outcomes), for the evaluation of the published evidence on liquid-based services and to provide input for the modelling of implications for the UK.

A systematic search has also been undertaken for economic assessments of new liquid-based cytology-based screening techniques. Details of this systematic search are presented in chapter 2. A generic proforma for the critical appraisal of modelling studies in health eco-nomics, expanded to include the relevant factors specific to cervical cytology screening, is used in systematically reviewing the studies identified.

Key health economic results for liquid-based technologies have been derived and converted to approximate £ sterling. Note that this is not intended to estimate cost-effectiveness in the UK setting but rather to aid comparison between the results. The key outcomes derived are:

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

Results of topic review for issues in health economic modelling

Literature on cervical cancer screening modelling identified through topic review can be found in appendix 2, together with a summary of the objectives and methodologies described in these papers. The following factors have been identified from the literature on models of cervical cancer and characterised into observable and unobservable phenomena, and key clinical events.

Unobservable factors

- Onset of cervical intraepithelial neoplasia (CIN)
- Regression of pre-invasive stages
- Progression of pre-invasive stages
- Duration of pre-invasive and invasive stage
- Test sensitivity
  – pre-invasive stage
  – invasive stage
- Relationship between prognosis and stage at identification.

Observable factors

- Participation rate
- False-positive rate
- Pre-invasive stages
- Invasive cancer
- Clinical survival
- Death from other causes
- Morbidity associated with
  – stage at identification
  – unnecessary treatments arising from false-positive screen results.

Observable events for use in calibrating and validating a model

- Clinical incidence
- Mortality from cancer
- Detection rate pre-invasive
- 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 within the assessment, which differentiates between the screening technologies under review, is the sensitivity and specificity of the different technologies.

Results of systematic review of economic studies

The systematic search for health economic studies of liquid-based cytology services in cervical cancer identified three studies. Two studies were national health technology assessment agency reports, one from the AHCPR of USA, published in 1999,[21] the other from the Australian Health Technology Advisory Committee, published in 1998.[6] The remaining study by Brown and Garber was published in a peer-reviewed journal in 1999 and focused on the US healthcare system.[77] The methodological summary of these studies is presented in appendix 3.

The AHCPR report[21] and the Brown and Garber[77] paper both 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. Both models simulate the life experience of a typical US cohort of women, though over slightly different age ranges; Brown and Garber cover the age range from 20 to 65 years, and the AHCPR report covers the age range 15 to 85 years. Both models use age-specific disease incidence, progression and regression characteristics. The Brown and Garber model uses a nine-state model of disease natural history, while the AHCPR report uses a 20-disease state model. The Brown and Garber model does not include HPV within its scope while the AHCPR model does. The close relationship between the Brown and Garber model and the AHCPR model is mainly because both are based on the model of cervical cancer screening developed and reported by Eddy.[84] The AHCPR study also uses the Eddy study in quantifying the disease progression element. Both models take a direct health service cost perspective, though the Brown and Garber study claims a societal perspective in the methodological description, and both discount costs and health benefits at 3% (0–5%).

The major distinction between the studies is that, while Brown and Garber pursue the individual cost-effectiveness of the three technologies under evaluation, the AHCPR study recognises the limitations of the available evidence and focuses on generic technologies for improving primary screen and re-screen characteristics, such as liquid-based cytology and automated re-screening technologies.

The review by the Australian Health Technology Advisory Committee,[6] in comparison, is a much simpler model than the two US studies. Rather than attempting to estimate the lifetime impact of the technologies, it estimates the potential for health gain from a generic technology aimed at improving the test characteristics obtained over the 2-year screening cycle currently implemented within Australia. In this approach it is more similar to the AHCPR report. The Australian analysis provides very broad estimates of the cost-effectiveness of the new technologies. As both conservative and liberal biases exist within the analysis it is difficult to interpret the marginal cost-effectiveness estimates given. For example, though potential offset savings from replacement of existing procedures are discussed, it is unclear whether savings from reduced inadequate smears are included, and it is unclear whether these are included in the headline results presented.

Conclusions

The headline health economic results from the AHCPR[21] and the Brown and Garber[77] studies are summarised in *Tables 11* and *12*, respectively. For the purposes of this report the results for the liquid-cytology techniques have been extracted and the results for the automated screening techniques have been removed, this has altered the structure and figures of the incremental analysis presented in the AHCPR report.

The baseline estimates of the cost per invasive cancer avoided for improved screening at 3 years compared with conventional screening at the same interval is approximately US$50,000 (~ £30,000) in the AHCPR report, US$270,000 (~ £160,000) for ThinPrep in the Brown and Garber report and AU$240,000 (~ £100,000) in the Australian guidelines.

In the AHCPR analysis, the baseline estimate of cost per life-year gained for the improved primary screening technologies, compared with the

TABLE 11 *Cost-effectiveness results derived from AHCPR*[21]

	Average cost (US$)	Incremental cost (US$)	% developing invasive cancer	% dying from invasive cancer	Incremental life days	Incremental cost per invasive cancer avoided (US$)	Incremental cost per life-year gained (US$)
No screening	893		3.01	1.06			
Triennial conventional smear	1108	215	0.51	0.12	19.2	8571	4087
Triennial improved primary screening	1240	132	0.25	0.05	2.2	50,769	21,900
Biennial conventional smear	1255	15	0.31	0.07	–0.65	Dominated	Dominated
Biennial improved primary screening	1433	178	0.13	0.04	1.44	102,890	45,118
Annual conventional smear	1702	269	0.11	0.02	0.06	1,169,565	4,921,417
Annual improved primary screening	2000	298	0.03	0.01	0.63	392,105	641,357

TABLE 12 *Cost-effectiveness results from Brown and Garber*[76]

	Lifetime costs (US$)	% developing invasive cancer	% dying from invasive cancer	Additional days of life	Cost per life-year gained over no screening (US$)	Incremental cost per invasive cancer avoided (US$)	Incremental cost per life-year gained (US$)
Quadrennial conventional smear	446	0.33	0.10	23.91	6808		
Quadrennial ThinPrep	505	0.28	0.09	25.07	7352	118,000	18,565
Triennial conventional smear	614	0.28	0.09	24.93	8990		
Triennial ThinPrep	695	0.25	0.07	25.73	9859	270,000	36,956
Biennial conventional smear	939	0.24	0.08	25.72	13,326		
Biennial ThinPrep	1059	0.22	0.07	26.19	14,759	600,000	93,191
Annual conventional smear	1955	0.20	0.06	26.56	26,867		
Annual ThinPrep	2194	0.19	0.06	26.80	29,881	2,390,000	363,479

conventional screening at 3 years, is approximately US$22,000 (~ £13,200); this compares with an estimate of $37,000 (~ £22,000) for ThinPrep from the Brown and Garber report.

The AHCPR economic evaluation provides an excellent summary of the potential cost-effectiveness of liquid-based cytology within the US environment. The reporting of the study is complete in all aspects with the frequently missing areas of model validation handled thoroughly. The reporting of the Brown and Garber study suffers from the restrictions of space, imposed by its inclusion in a peer-reviewed journal, and hence

some of the reporting is incomplete. Given the high level of uncertainty in many of the parameters, a major omission in Brown and Garber study is an indication of the likely range of the key outcomes. In particular, the interpretation of the point estimates of the marginal cost-effectiveness may be highly misleading.

Neither the AHCPR, Brown and Garber nor the Australian reports directly compare 3-year screening with screening at longer intervals. The AHCPR report only considers screening intervals shorter than 3 years and the Brown and Garber report does not make a direct comparison between 3- and 4-year screening, though the figures presented imply a marginal cost-effectiveness in the region of US$60,000 (~ £35,000) for conventional screening.

The AHCPR conclude:

> "We found that under favourable assumptions the use of technologies that improve initial screening sensitivity ... can have acceptable cost-effectiveness with conventional screening at a frequency of every three years. However, cost-effectiveness of these new technologies (and conventional smear screening) is directly related to the frequency of screening, with longer intervals resulting in lower cost-effectiveness estimates. Our 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. However, there is substantial uncertainty about the estimates of sensitivity and specificity of the new technologies compared with each other and with conventional smear testing. It is clear from our sensitivity analysis that both sensitivity and specificity are important in determining cost-effectiveness. Although it is clear that both types of technology provide an improvement in effectiveness at higher cost, the imprecision in estimates of their effectiveness makes drawing conclusions about the relative cost-effectiveness of thin-layer cytology and computerised rescreening technologies problematic."

The Brown and Garber report compares automated re-screening techniques with ThinPrep and conventional screening techniques. This report concludes that the liquid-based cytology primary screening technique is dominated, that is costs more and is less clinically effective than the automated re-screening techniques.

> "Technological enhancements to an already highly effective screening test may not be cost-effective compared with other common screening interventions. If added to annual screening, the ... technologies have little effect on life expectancy. The major barrier to prevention of cervical cancer is not the accuracy of the Pap test, but the failure to be screened at all. These technological improvements in the Pap test can be cost-effective when used as part of less-frequent screening. However, if their high cost deters participation in cervical cancer screening programmes they will not reduce the toll of the disease."

Chapter 4

Modelling the health economic impact of liquid-based cytology within the UK

Modelling methods

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 macro-simulation of the life experience of a cohort of women followed from age 18 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. All costs have been discounted at 6%, and life-years at 1.5% (following the agreement by NICE to use these Treasury recommended rates). In addition, a range of discount factors from 0% to 10% has also been investigated.

The model is based closely on the work reported by Sherlaw-Johnson and co-workers.[97] The Sherlaw-Johnson model provides the structure and parameterisation for the disease natural history and is the basis of the conventional smear-test characteristics.

Natural history of cervical cancer

Pre-invasive cancer is classified histologically into three categories of cervical intraepithelial neoplasia; CIN1, CIN2, 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 pre-invasive stage and from CIN3 to invasive cancer, with the proviso that regression to a disease-free state may occur from CIN1 only.

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, or others may regress to clear. The baseline disease progression state transition matrix is presented in *Table 13*. Though there exists evidence to indicate that incidence of pre-invasive lesions is age-specific, the model assumes a constant incidence between the ages of 18 and 64 years. No further incident cases of CIN1 are assumed to arise after the age of 64 years. As the incidence is likely to be higher in the early years this may mean that the peak prevalence of lesions in the early years is underestimated; this would lead to the effects of screening strategies being potentially underestimated. Disease progression and the proportion

TABLE 13 *Percentage of women transferring between states at 6 months (after Sherlaw-Johnson[97])*

	New state				
	Clear	**CIN1**	**CIN2**	**CIN3**	**Invasive cancer**
Original state					
Clear	99.88%	0.12%	0%	0%	0%
CIN1	2%	89.5%	6%	2.5%	0%
CIN2	0%	0%	85%	15%	0%
CIN3	0%	0%	0%	99%	1%
Invasive cancer	0%	0%	0%	0%	100%

of fast-growing cancers are similarly assumed not to be age-specific. Pre-invasive lesions present at the age of 64 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 1992–94 for females within England and Wales.[115] A constant risk is assumed for mortality from invasive cancer. This mortality is based upon 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 post-diagnosis and treatment,[116] and a mean duration pre-diagnosis of approximately 5 years. This is based crudely upon previous modelling work undertaken by Eddy.[84]

The cervical cytology screening interventions

For the purposes of this model, a cohort of 100,000 women aged 18 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.[2] Women are assumed either to attend screening 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 3 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 re-screen; 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. Also, 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 (i.e. the true test specificity and sensitivity). The baseline test characteristics for the conventional smear screen test are given in *Table 14*. This characterisation of test results allows the modelling of differential sensitivity by lesion grade. This is in contrast to the constant sensitivity assumed in the AHCPR model.

Improvements on the conventional screen test are represented by absolute changes in the screen test result proportions for the given disease state, grouped into:

- clear for test specificity
- CIN1 and CIN2 lesion sensitivity, and
- CIN3 and invasive cancer sensitivity.

There is insufficient evidence of differential rates of sensitivity improvement between the identified liquid-based cytology techniques. For the purposes of this analysis a generic baseline improvement in sensitivity has been assumed to arise from all liquid-based cytology techniques. These baseline improvements are:

- an absolute improvement of 15% in sensitivity for CIN1 and CIN2 lesions, for example an increase from 60% to 75% for CIN1 identified as borderline or worse
- an absolute increase of 2% in sensitivity for CIN3 lesions and invasive cancer.

The specificity of the liquid-based cytology techniques is assumed to remain unchanged from the conventional specificity.

Two intervention policies based on screening test results are modelled:

TABLE 14 *Test characteristic for the conventional smear test (after Sherlaw-Johnson[96])*

Disease state	Negative	Borderline/mild	Moderate/severe
Clear	98.0%	1.8%	0.2%
CIN1	57.0%	39.0%	4.0%
CIN2	63.0%	22.0%	15.0%
CIN3	0.0%	50.0%	50.0%
Invasive cancer	0.0%	60.0%	40.0%

- 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. Re-screen 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 key 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 (NHS CSP) screening programme guidelines on quality standards expected from colposcopy.[117]

Costs

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

- conventional smear test
- liquid-based cytology techniques
- colposcopy
- treatment of pre-invasive lesions
- treatment of invasive cancer.

The costs of a conventional smear have been taken from the NHS CSP analysis of costs undertaken in 1994, uplifted to 1999 values.[118] This analysis was based on a bottom-up, activity-based costing with allocation of department and general overhead costs. The costs per smear included primary care costs, health authority costs and cytology laboratory costs. The baseline estimate of the cost per smear is approximately £55. No consistent range of costs is presented in the report, therefore a range of ± 20% is investigated. Note that the figure of £135 million for the programme given in chapter 1 (*Current service provision*) tends to imply a lower cost. However, as was pointed out, and as discussed with the NHS CSP staff, the £135 million estimate may not include all the relevant cost elements, and the bottom-up costing used here[118] is more likely to be reliable.

The marginal costs of the liquid-based cytology techniques have been estimated from the associated increases in the cost of consumables and the capital cost of the equipment. Overall human resource costs for sample preparation and analysis (taken together) are assumed to remain constant. The marginal costs are therefore likely to be underestimated with the likely increases in costs arising from a number of sources, including:

- training both within sample collection and cytological preparation and analysis
- transportation of screening samples from primary care to the cytology laboratories
- storage of samples.

Table 15 presents the marginal cost per sample of the two major liquid-based cytology techniques identified in this report. For the purposes of this analysis, a baseline marginal cost covering consumables and capital equipment of £3.60, ranging between £0 and £7, is used for generic liquid-based cytology techniques.

TABLE 15 *Marginal costs per sample for liquid-based cytology techniques*

	ThinPrep 2000	AutoCytePrep
Cost of test consumables	£3.50	£3.00
Capital cost	£30,000	£45,000[a]
Annual maintenance cost		£3000
Life-span (years)	6	6
Annual capacity[b]	50,000	60,000
Unit capital cost	£0.10	£0.13
Marginal cost per sample	£3.60	£3.13

[a] *Additional savings may be if made if a slide-staining machine is no longer required*

[b] *Based on single shift with 7/8-hour working day. These capacities are illustrative for the purpose of costings only (particularly the dispersal of capital cost). They are not intended to indicate the actual capacities of the systems in laboratory practice, which may vary, as may the lifespan of the equipment*

Colposcopy is routinely undertaken in a gynaecology outpatient setting. Practice may vary between individual hospitals, though increasingly, colposcopy and treatment by cervical 'conization' of any abnormalities is undertaken within 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 grade of cancer at diagnosis. Recommended procedures in detection, diagnosis and evaluation of cervical carcinoma are detailed by Obralic and co-workers[116] under the International Federation of Gynecology and Obstetrics 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 conization, 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 conization is increasingly being adopted for stage IA1 carcinomas. A baseline of 30% of screen-detected cancers is assumed in the model. These procedures include the cost for conization identified above.

In terms of resource utilisation, the hysterectomies are classified as Health Resource Group (HRG) 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 costs of subsequent radiation therapy, costs of palliative care and long-term support cost. This cost is also assumed to apply to those patients who die from cervical cancer. Thus, this cost is almost certainly an under-estimate of the costs associated with treating invasive cancer, and this will introduce a bias against screening policies and, specifically, screening developments aimed at improving screen test characteristics.

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 quality-adjusted life-year.

Parameter values used within the model

Table 16 presents all the parameter values used in the model, together with ranges and sources.

Assumptions within the model

- In the absence of any intervention, the disease is assumed to progress through each pre-invasive stage and from CIN3 to invasive cancer, with the proviso that regression to a disease-free state may occur from CIN1 only.
- The model assumes a constant incidence between the ages of 18 and 64 years. No further incident cases of CIN1 are assumed to arise after the age of 64 years.
- Disease progression and the proportion of fast-growing cancers are assumed not to be age-specific.
- Pre-invasive 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 assumed to be taken up by a certain percentage of women in this cohort.
- Women are assumed either to attend screening at the regular intervals or not at all.
- For the purposes of this model, inadequate slides are simply assumed to require an immediate re-screen; 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.

TABLE 16 *Description of parameters used in the model*

	Baseline	Minimum	Maximum	Reference
Management variables				
Female population	100,000	–	–	–
Start age (years)	18	–	–	–
First screen at age (years)	21	–	–	–
Last screen at age (years)	64	–	–	–
Policy	B[a]	–	–	–
Screening interval (years)	3	2	5	–
Discount rates				
Costs	6%	0%	10%	–
Health benefits	1.5%	0%	10%	–
Disease natural history and treatment				
6-month progression rates				
Progression rates from clear to CIN1	0.12%	–	–	97
Regression rates from CIN1 to clear	2.0%	–	–	97
Progression rates from CIN1 to CIN2	6.0%	–	–	97
Progression rates from CIN1 to CIN3	2.5%	–	–	97
Progression rates from CIN2 to CIN3	15%	–	–	97
Progression rates from CIN3 to invasive cancer	1.0%	–	–	97
Progression factor[b] (for sensitivity analysis)	100%	50%	150%	–
Incidence factor[c] (for sensitivity analysis)	100%	75%	125%	–
Effectiveness and mortality				
Effectiveness of cervical conisation	90%	80%	100%	115,116
Effectiveness of hysterectomy	85%	75%	95%	115
Screen-detected cancers suitable for conization – Stage IA1 carcinomas	30%	10%	50%	([d])
6-month mortality rates associated with invasive cancer	2%	0%	4%	83,115
Test characteristics				
Conventional smear test results				
Specificity of test	98%	96%	100%	97
False borderline/mild test result	1.8%	0.9%	2.7%	97
False moderate/severe test result	0.2%	0.1%	0.3%	97
Proportion of CIN1 lesions that give:				
negative test result	57%	42%	72%	97
borderline/mild test result	39%	24%	54%	97
moderate/severe test result	4%	2%	6%	97
Proportion of CIN2 lesions that give:				
negative test result	63%	50%	76%	97
borderline/mild test result	22%	10%	34%	97
moderate/severe test result	15%	10%	20%	97
Proportion of CIN3 lesions that give:				
borderline/mild test result	50%	40%	60%	97
moderate/severe test result	50%	40%	60%	97

[a] *Policy B – immediate colposcopy for women with a moderate/severe test result; re-screen at 6 months for women with borderline/mild result and colposcopy for those with any persistent abnormality*

[b] *Progression factor – for the purpose of the sensitivity analysis, all progression rates are increased/decreased by the same factor*

[c] *Incidence factor – for the purpose of the sensitivity analysis, incidence of CIN1 has been investigated over this range*

[d] *Personal communication – E McGoogan*

continued

TABLE 30 contd *Description of parameters used in the model*

	Baseline	Minimum	Maximum	Reference
Test characteristics				
Conventional smear test results contd				
Proportion of invasive cancers that give:				
borderline/mild test result	60%	50%	70%	97
moderate/severe test result	40%	30%	50%	97
Other test characteristics				
Inadequate conventional smear slides	9%	7%	11%	2
Inadequate liquid-based cytology samples	3%	1%	5%	([e])
CIN1/CIN2 – sensitivity improvement with liquid-based cytology	15%	5%	25%	([e])
CIN3/IC – sensitivity improvement with liquid-based cytology	2%	0%	4%	([e])
Improvement in specificity with liquid-based techniques	0%	-1%	1%	([e])
Percentage of women who take up screening	85%	80%	90%	2
Costs				
Cost per conventional smear	£55	£35	£75	118
Marginal cost for a liquid-cytology sample	£3.50	£0	£7.00	([e])
Cost of colposcopy and conization	£185	£135	£235	([f])
Cost of surgical treatment of invasive cancer	£1700	£1000	£2400	121

[e] *See text*

[f] *Personal communication typical NHS Trust*

- 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 more advanced than stage IA1. This HRG cost, however, does not take into account costs of subsequent radiation therapy, costs of palliative care and long-term support cost. This cost is also assumed to apply to those patients who die from cervical cancer.
- Incidence of CIN1 is assumed to be constant between the ages of 18 and 64 years. As the incidence is likely to be higher in the early years, this may mean that the peak prevalence of lesions is underestimated. This would lead to the effects of screening strategies potentially being underestimated.

Model validation

Overall incidence of invasive cancers

The model described here is based closely on the model of Sherlaw-Johnson and co-workers.[97] The overall incidence of invasive cancer in women over the age of 18 years in an unscreened population predicted by the UK model is 61 per 100,000 per annum compared with a figure of 59 per 100,000 per annum in the Sherlaw-Johnson model. With 70% coverage, triennial screening, and a policy of immediate colposcopy following all abnormal smears (Policy A), the UK model predicts an annual incidence of 21 compared with 20 under the Sherlaw-Johnson model. Under a policy of immediate colposcopy for those women with a moderate or severe smear test results, re-screening at 6 months for those women with a borderline or mild smear, followed by colposcopy for all persistent abnormalities (Policy B), the UK model predicts an annual incidence of 23 per 100,000 per annum compared with 21 in the Sherlaw-Johnson model. From these comparisons, it can be concluded that the model presented here closely reflects the earlier model.

The baseline coverage of screening in the Sherlaw-Johnson model is 70%, in the UK model a baseline of 85% is used in line with recently reported coverage.[2] With this amendment, the over 18 incidence is 14 per 100,000 per annum. When all ages are taken into account, the predicted incidence of invasive cancer from the UK model is 11 per 100,000 per annum, this compares very closely with a reported actual incidence in all ages of 12 per 100,000 per annum.[119]

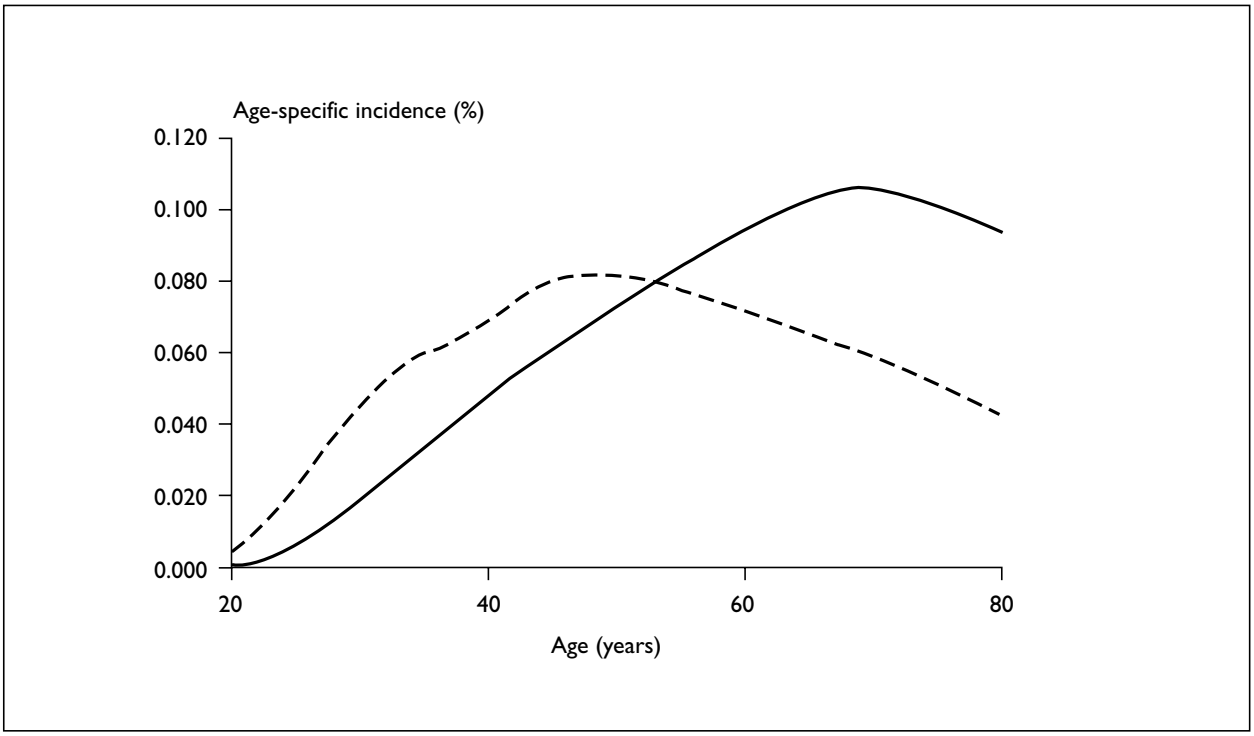

FIGURE 1 *Age-specific incidence of invasive cancer predicted by the UK model and the AHCPR model in the absence of screening (– – –, AHCPR model; ——, UK model)*

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 1*.

The initial rate of increase of incidence by age is slower in the model presented here than in the AHCPR model. The rate of increase, however, continues for longer giving a higher peak incidence at an older age than the AHCPR. The rate of decline of incidence in the two models is roughly equal but starts later in the UK model described here. This is as expected with the use of the constant incidence of CINI as compared with the age-specific incidence of the AHCPR model.

Age-specific incidence with a policy of screening every 3 years

The age-specific incidence figures for cervical cancer under a policy of screening every 3 years predicted by the model are compared with the equivalent actual figures from the Trent Cancer Registry for 1993.[119] These incidence figures are shown in *Figure 2*.

Rather than settle to a constant level, the age-specific incidence rises gradually over time. There is a similar rise and subsequent decline of 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 actual reported distribution as reported by the NHS CSP,[2] and the results are shown in *Table 17*. 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 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) though the costs associated with smear tests and colposcopies will rise. However, as there is little strong evidence

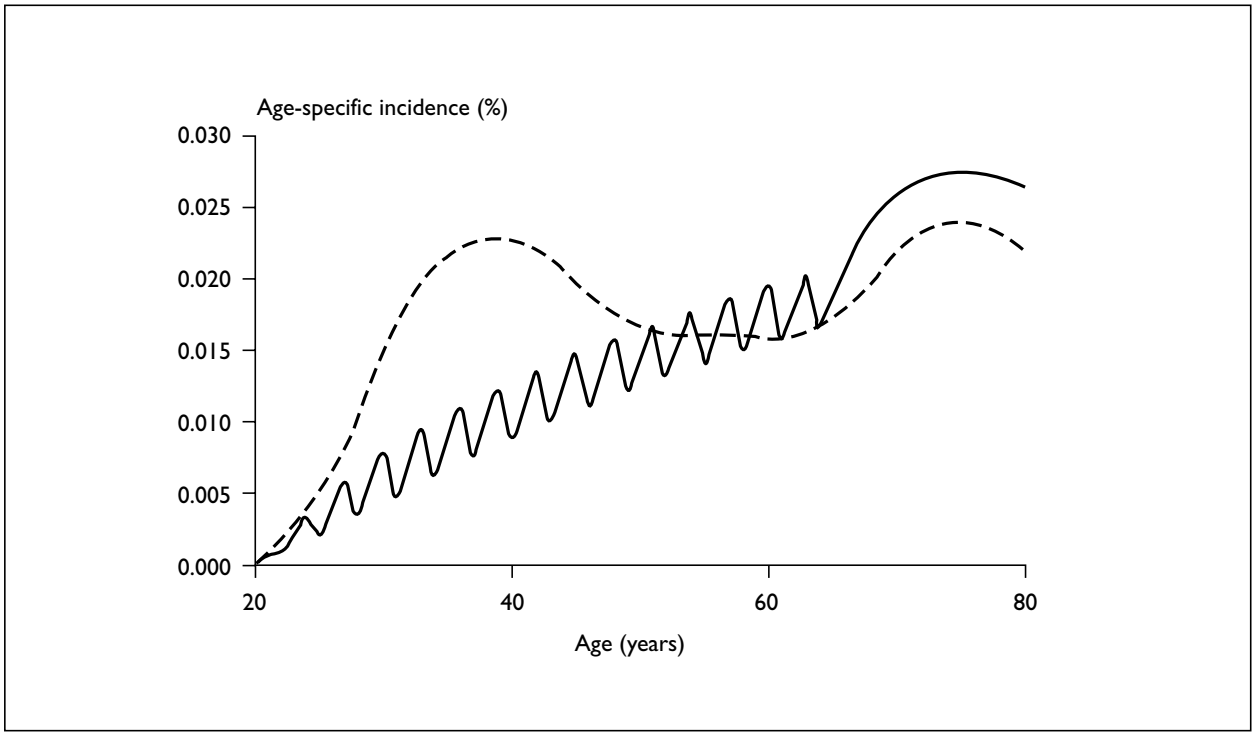

FIGURE 2 *Age-specific incidence of invasive cancer predicted by the UK model under a 3-year screening policy and current reported incidence (——, UK model; – – –, Cancer Registry)*

TABLE 17 *Predicted versus actual distribution of test results*

	Specificity	Negative	Bordeline/mild	Moderate/severe
NHS CSP statistics	?	93.0%	5.5%	1.5%
UK model	Baseline 98%	96.9%	2.6%	0.6%
Revised UK model	94%	93.0%	5.2%	1.8%

to suggest that the specificity of liquid-based testing is improved compared with conventional screening (whatever level is set), the impact on the relative costs and cost-effectiveness of liquid cytology versus conventional screening is small.

UK modelling 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. Note that the incremental analyses should be treated with some caution due to the high level of uncertainty in the analysis compared with the potentially small differential gains.

Conventional screening at 3–5 years is predicted to reduce the annual incidence of cervical cancer from approximately 60 per 100,000 women per annum to between 14 and 18 per 100,000 per annum. This prediction compares well with the actual incidence currently recorded. The introduction of liquid-based cytology techniques has the potential to reduce this incidence to between 13 and 16 per 100,000 women per annum.

Liquid-based 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 to arise from moving from a 5-year to a 3-year screening interval with conventional screening.

Conventional screening at a 5-year interval is estimated to increase the life expectancy of the

TABLE 18 *Key health outcomes arising from the introduction of liquid-based cytology*

		Annual incidence of invasive cancer	% of women who have invasive cancer	% of all deaths from cancer	Incremental life-days gained	Incremental life-days gained (discounted)
No screening		0.061%	3.75	1.71	–	–
Screening at 5 years	Conventional	0.018%	1.10	0.12	107.88	49.09
	Liquid-based	0.016%	1.00	0.10	1.15	0.51
Screening at 3 years	Conventional	0.014%	0.88	0.07	2.22	1.04
	Liquid-based	0.013%	0.79	0.05	0.78	0.33
Screening 2 years	Conventional	0.013%	0.79	0.05	0.16	0.12
	Liquid-based	0.012%	0.72	0.04	0.63	0.26

TABLE 19 *Average lifetime resource usage per woman*

		No. of smear tests	No. of colposcopies
No screening		–	–
Screening at 5 years	Conventional	8.4	0.086
	Liquid-based	7.9	0.091
Screening at 3 years	Conventional	13.9	0.104
	Liquid-based	13.1	0.110

TABLE 20 *Incremental cost per invasive cancer avoided*

		% with invasive cancer	Incremental % with invasive cancer avoided	Incremental cost per invasive cancer avoided (£)
No screening		3.748	–	–
Screening at 5 years	Conventional	1.096	2.652	6072
	Liquid-based	0.999	0.097	1581
Screening at 3 years	Conventional	0.876	0.123	73,011
	Liquid-based	0.791	0.084	2723

average 18-year-old women by around 110 days. The incremental gain in life expectancy through the introduction of liquid-based cytology techniques is estimated at between a 0.75 days and 1.25 days. If this gain in life days is discounted at a baseline rate of 1.5% then the gain reduces to between a third and half a day.

Resource usage

Liquid-based cytology techniques reduce the lifetime average number of smear tests for a woman primarily from the reduction in inadequate slide production and consequential reduction in re-screening. The average number of colposcopies is, however, 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 women. Note that this presents a health commissioning perspective and therefore includes the whole population, not just individuals who attend screening.

The change in the pattern of resource usage associated with the introduction of liquid-based cytology techniques leads to an offset of the increased unit costs per test. Thus, for example, the 7% increase in unit cost per test is offset by a 5% reduction in the number of smears.

Health economic outcomes

The incremental costs per invasive cancer avoided for the primary screening options under consideration are presented in *Table 20.*

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 average lifetime costs, both undiscounted and discounted at 6%, increase as the benefits increase, therefore, no option is dominated. As with the health economic outcomes presented earlier, due to the small differences in health benefit and the large uncertainties in the analysis, the marginal analysis may be misleading.

Screening at an interval of 2 years or more frequently is clearly not likely to be regarded as cost-effective under the assumptions of this analysis either with liquid-based cytology or conventional screening techniques. Screening at a regular interval of 3 years is estimated to be of borderline cost-effectiveness, with the above provisos concerning the level of uncertainty within the analysis. If 3-year screening is assessed as cost-effective then the baseline incremental cost-effectiveness of liquid-based cytology looks relatively favourable.

Finally, in considering the differences between 3- and 5-year screening it is important to recognise that screening in practice never occurs at precisely these time intervals. Women recalled at 3 years are unlikely to have their screening test until about $3\frac{1}{2}$ years, once letters have been sent out and appointments made. To be screened by 5 years, women must be recalled at $4\frac{1}{2}$ years at the latest after the previous test. Thus, the difference between 3- and 5-year policies may be exaggerated.

Sensitivity analysis

Disease natural history

There is no direct, and little indirect evidence regarding the natural history of cervical cancer in terms of the progression rates between pre-invasive 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 upon a hypothesised course for the disease. The impact of doubling and halving the disease progression rates is examined in *Table 22*.

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

		Marginal discounted life-days gained compared with no screening	Incremental life-days gained	Average discounted lifetime cost per woman (£)	Incremental discounted lifetime cost (£)	Incremental cost per life-year gained (£)
No screening		–	–	2.95	–	–
Screening at 5 years	Conventional	49.09	49.09	164.02	161.07	1197
	Liquid-based	49.61	0.51	165.56	1.53	1095
Screening at 3 years	Conventional	50.65	1.04	255.36	89.80	31,519
	Liquid-based	50.98	0.33	257.66	2.30	2522
Screening at 2 years	Conventional	51.10	0.12	368.20	110.54	342,358
	Liquid-based	51.36	0.26	371.35	3.15	4446

TABLE 22 *Sensitivity analysis for disease progression rates*

		Incremental cost per life-year gained		
Disease progression		**50%**	**Baseline**	**200%**
No screening		–	–	–
Screening at 5 years	Conventional	£5882	£1197	£317
	Liquid-based	£3684	£1095	£340
Screening at 3 years	Conventional	£196,995	£31,519	£6257
	Liquid-based	£8865	£2522	£855
Screening at 2 years	Conventional	£14,859,230	£342,358	£39,350
	Liquid-based	£16,515	£4446	£1569

Sensitivity analysis for test characteristics

The impact of uncertainty concerning the improvements in test sensitivity obtained from liquid-based cytology-based screening is presented in *Table 23*.

The impact of uncertainty concerning improvements in the rate of inadequate cervical smears is presented in *Table 24*.

Sensitivity analysis for costs

The impact of uncertainty concerning the increase in marginal costs arising from the introduction of liquid-based cytology is presented in *Table 25*.

Sensitivity analysis for discounting of costs and life-years gained

The impact of different assumptions concerning the discounting of costs and life-years gained

TABLE 23 *Sensitivity analysis for improvement in test sensitivity*

		Incremental cost per life-year gained		
Sensitivity improvement			Baseline	
CIN1/CIN2		5%	15%	20%
CIN3/invasive cancer		0%	1%	2%
No screening		–	–	–
Screening at 5 years	Conventional	£1197	£1197	£1197
	Liquid-based	£3604	£1095	£918
Screening at 3 years	Conventional	£23,089	£31,519	£36,765
	Liquid-based	£8075	£2522	£2125
Screening at 2 years	Conventional	£111,704	£342,358	£1,353,724
	Liquid-based	£13,896	£4446	£3750

TABLE 24 *Sensitivity analysis for improvement in test adequacy*

		Incremental cost per life-year gained	
Absolute improvement in inadequacy rate		0%	Baseline 6%
No screening		–	–
Screening at 5 years	Conventional	£1133	£1197
	Liquid-based	£7305	£1095
Screening at 3 years	Conventional	£26,712	£31,519
	Liquid-based	£17,536	£2522
Screening at 2 years	Conventional	£280,863	£342,358
	Liquid-based	£32,470	£4446

TABLE 25 *Sensitivity analysis for marginal sample cost for liquid-based cytology*

		Incremental cost per life-year gained		
Marginal cost of liquid-based cytology		Baseline £3.50	£7.00	£10.00
No screening		–	–	–
Screening at 5 years	Conventional	£1197	£1197	£1197
	Liquid-based	£1095	£7729	£13,584
Screening at 3 years	Conventional	£31,519	£28,253	£25,372
	Liquid-based	£2522	£18,558	£32,708
Screening at 2 years	Conventional	£342,358	£297,055	£257,082
	Liquid-based	£4446	£34,371	£60,775

are presented in *Table 26*. It can be seen that discounting assumptions, particularly regarding the discounting of life-years gained, have a marked impact on the potential cost-effectiveness of both conventional and liquid-based cytology techniques. Nevertheless, liquid-based cytology at a screening interval of 5 years still remains a cost-effective option under all but the 10% discounting option. The importance of the discounting assumptions arises from the fact that most benefits are distant in the future compared with the incurring of screening costs. This is particularly true when estimating the expected life costs at the age of 18 years. The impact of discounting would be expected to lessen as you estimated the remaining life benefits at increasing ages. This would tend to increase the relative benefits to be obtained from screening at reduced interval at ages where incidence of pre-invasive disease is highest.

Sensitivity analysis for costs and discounting

A two-way sensitivity analysis for the marginal costs arising from the introduction of liquid-based cytology and discounting assumptions is presented in *Table 27*. Note that the cost-effectiveness is very sensitive to joint increases in the marginal cost and to variation in the discounting assumptions, particularly concerning the discounting of life-years gained. Where the health benefits are discounted at the same rate as costs, the cost-effectiveness of liquid-based cytology becomes very poor. The scenario outlined in *Table 27* shows an incremental cost per life-year gained of over £100,000 even at a 5-year screening interval when compared with conventional screening at the same interval with a marginal cost of £10 per slide. In addition, the discounting rates used by the AHCPR, together with a £7 per slide marginal cost give a cost-effectiveness of approximately £25,000 per life-year gained.

TABLE 26 *Sensitivity analysis for discount rates*

		Incremental cost per life-year gained			
Discount factors					
Cost		0%	6%	6%	10%
Life-years		0%	1.5%	6%	10%
No screening		–	–	–	–
Screening at 5 years	Conventional	£1519	£1197	£9557	£27,428
	Liquid-based	£1142	£1095	£8315	£21,254
Screening at 3 years	Conventional	£49,222	£31,519	£206,300	£409,474
	Liquid-based	£2871	£2522	£21,156	£53,444
Screening at 2 years	Conventional	£799,339	£342,358	£1,129,371	£1,771,825
	Liquid-based	£5085	£4446	£43,238	£116,924

TABLE 27 *Sensitivity analysis for cost and discounting*

		Incremental cost per life-year gained		
Cost discount		6%	3%	6%
Life-years discount		6%	3%	1.5%
Marginal cost		£10.00	£7.00	£3.60
No screening		–	–	–
Screening at 5 years	Conventional	£9557	£3935	£1197
	Liquid-based	£103,191	£25,454	£1095
Screening at 3 years	Conventional	£166,071	£25,454	£31,519
	Liquid-based	£274,392	£25,454	£2522
Screening at 2 years	Conventional	£848,063	£157,795	£342,358
	Liquid-based	£591,017	£128,234	£4446

Conclusions of UK modelling

There are multiple sources of bias within this analysis. The use of a constant incidence for pre-invasive lesions and constant progression between stages across all ages means that the underlying peak prevalences (CIN1, CIN2, CIN3, and invasive cancer) of disease are likely to be underestimated. As the positive predictive value of the tests is dependent on the disease prevalence, the effectiveness of screening at the peak ages may be underestimated. This would introduce a small negative bias against tests with improved sensitivity in the analysis. Assumptions regarding the specificity of conventional screening[97] may also introduce bias into the assessment; evidence from subsequent research[120] together with the model validation results presented in chapter 4 (*Test programme characteristics*) indicate that true rates may be lower. However, as discussed in the *Supplementary economic analysis* (see appendix 4), it is the relative specificity between the two tests that is economically important; the data used within the model here are referenced and are based on information summarised in the main report. Notwithstanding the weaknesses in the evidence for test specificity a lower conventional rate may 'leave more room for improvement' from liquid-based techniques. Any underestimates of improvements in test specificity would lead to a negative bias against the improved screening techniques.

Morbidity and mortality associated with invasive cancer have been modelled crudely; specifically the costs are underestimated and survival overestimated for the highest grade cancers. Again this would introduce a negative bias (though probably small) against improved screening techniques.

While the estimated marginal cost per slide associated with the new screening techniques has been based on available information these costs are probably underestimated, as issues such as training, storage and transportation are not addressed. This would lead to a bias in favour of improved screening techniques. The sensitivity analysis indicates that the economic results are highly sensitive to marginal costs.

Furthermore, it is recognised that in so far as liquid-based cytology techniques may reduce additional recalls and false-positive test results there may be some impact on indirect benefits; direct benefits alone are therefore likely to underestimate total benefits.

Conventional screening at 5-year intervals (compared with no screening) prevents cervical cancer mortality at a cost-effectiveness ratio usually considered as appropriate within the NHS.

Liquid-based screening, compared with conventional smears at 5 years, is estimated to have an incremental cost-effectiveness ratio of less than £10,000 per life-year gained. The conditions where this may not be true are under different assumptions regarding the marginal costs and discounting of life-years gained. This is particularly true where health benefits are discounted at the same rate as costs. In such circumstances, liquid-based cytology becomes very much more expensive per life-year gained.

The cost per life-year gained of conventional screening at 3 years compared with liquid-based screening at 5 years is, however, likely to be considerably higher. Change to liquid-based cytology from conventional smears at 3-year screening intervals may be within an acceptable range of cost-effectiveness (but estimates depend highly on the approach to discounting costs and benefits).

Screening at intervals of less than 3 years is, under most assumptions and irrespective of technology used, very expensive in relation to the benefits obtained (over £100,000 per life-year gained compared with 3-year screening).

Finally, it is important to bear in mind that the introduction of other methods of reducing the burden of invasive cancer, such as improving coverage or the use of more effective specimen taking devices, may result in liquid-based cytology having a reduced impact. It has not been within the scope of this report to consider the relative impact of these other possible developments.

Chapter 5
Conclusions

Implications of screening tests

Financial impact for patient and others
The potential benefits to the women screened, in addition to potential reduction of invasive cancer and of 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 types of benefits in this report.

Social and legal implications
Problems in relation to cervical screening have resulted in litigation. While there is a potential to reduce payments for damages and associated litigation costs if false-negative results are reduced, there is said to be inadequate appreciation of the propensity of all screening tests to have a sensitivity lower than 100%. Liquid-based cervical cytology is no different, and will also have a sensitivity that is not perfect, so false-negative results will still occur. There has been no attempt here to quantify these issues in respect of litigation-related costs and savings.

Health targets
Reduction in cancer mortality is a key target in respect of the *Our Healthier Nation* initiative.[122]

Fair access and equity issues
The uptake of cervical cytology 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 make the 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 liquid-based cytology if it is decided to introduce it. However, it is acknowledged that such a plan would be needed and it would need to consider aspects like training, workforce planning, quality management, and relevant logistics such as storage space.

Recommendations for research

A full cost-effectiveness study of liquid-based cytology based on a trial of its introduction in a low-prevalence population would provide more definitive information than is possible by modelling studies. It is not clear that such a study is needed at this stage given what is already known about the technique. However, an assessment of the uncertainties about the values and assumptions used in the economic model indicate that the key areas for further research are:

- the marginal cost per sample of the new technologies compared with conventional screening methods
- the improvement in the rate of inadequate samples and the relative specificity of the liquid-based cytology techniques.

Expiry date
No systematic search was carried out to find significant trials in progress which are expected to report soon, although none came to the attention of the authors. However, it is recommended that the conclusions from this report are revisited in July 2001 or earlier if new trials and technologies do emerge before then.

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Appendix 1

Search strategy

Clinical effectiveness

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

Cost-effectiveness

1 Vaginal smears/
2 Cervix neoplasms/
3 Cervical intraepithelial neoplasia/
4 Cervix dysplasia/
5 or/2-4
6 di.fs.
7 exp Diagnosis/
8 6 or 7
9 5 and 8
10 1 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

Modelling

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 8 or 9 or 10 or 11
13 7 and 12

Appendix 2

Summary of objectives and modelling methodologies used in evaluations of cervical cytology screening

TABLE 28

Study/country	Study objectives	Outcomes generated	Does the paper describe an original model?	Is the model cross-referenced to related work?	Reference details for original model
Brown & Garber, 1999[77] USA	Estimate the cost-effectiveness of new technological enhancements to the conventional smear test: ThinPrep, AutoPap™, Papnet™	Life-years gained Lifetime chance of developing cancer Cost per woman screened Cost per life-year gained	No	Yes	Eddy,[83–87]
van Oortmarssen *et al.*, 1995[78] n/a	Review of modelling issues. Note: general cancer not cervical cancer specifically				
Parkin, 1985[79] UK	Development of model to aid in policy planning	Incidence of clinically diagnosed cancer No. of deaths from cervical cancer Life-years gained	Yes	No	
Gustafsson & Adami, 1991[80] Sweden	Evaluation of screening programme	Incidence of clinically diagnosed cancer *in situ* Cervical cancer mortality rates	Yes	No	
van Oortmarssen *et al.*, 1991[81] The Netherlands and British Columbia	Hypothesis testing about natural history of cervical cancer. Particularly progression and regression of pre-clinical lesions	Age-dependent regression rates Average duration of dysplasia Sensitivity of conventional smear	Yes		
Noorani *et al.*, 1997[20] Canada	Health technology assessment of automated re-screening strategies. Note: economics of liquid cytology not explicitly addressed		Yes		
Australian Health Technology Advisory Committee, 1998[6] Australia	Health technology assessment of automated and semi-automated cervical screening devices	Cost per cancer prevented	Yes		
Bastian *et al.*, 1999[21] USA	Health technology assessment of new technologies focused on optimising conventional test false-negative rates. (Summary and main report)				
Brookmeyer & Day, 1987[82] USA	Examination of natural history of disease	Transition, regression and duration properties	Yes	No	

AutoPap, Neopath Inc., Redmond, WA
Papnet, Neuromedical Systems Inc., Suffern, NY

continued

TABLE 28 contd

Study/country	Study objectives	Outcomes generated	Does the paper describe an original model?	Is the model cross-referenced to related work?	Reference details for original model
Zelen, 1993[83] USA	Evaluation of clinical management policies in cervical cancer screening. Focuses on screen scheduling. Note: not necessarily regular	Equations for finding optimal screening schedules	Yes	No	
van Oortmarssen *et al.*, 1992[88] Sweden	Evaluation of clinical management policies in cervical cancer screening. Focuses on predicting mortality following negative screen tests	Mortality from invasive cancer Incidence of invasive cancer	No	Yes	van Oortmarssen & Habbema[81]
Parkin & Moss, 1986[89] UK (IARC)	Evaluation of clinical management policies in cervical cancer screening	Cervical cancer mortality Life-years gained	No	Yes	Parkin[79]
Prorock *et al.*,[90] USA	Review of the mathematical models in cervical cancer screening and their implications for disease natural history	Transition and duration properties of pre-clinical stages of cervical cancer	No	Yes	
Koopmanschap *et al.*, 1990[91] The Netherlands	Cost-effectiveness analysis of cervical cancer screening	Costs of screening Costs of diagnosis and treatment Cost per life-year gained	No	Yes	Habbema *et al.*[95]; Gustafsson *et al.*[98]
Sherlaw-Johnson *et al.*, 1999[92] UK	Evaluation of clinical management policies in cervical cancer screening. Focuses on withdrawing low-risk women from screening programme	Annual incidence of invasive cancer No. of smears/colposcopies	No	Yes	Sherlaw-Johnson *et al.*[97]; Jenkins *et al.*[94]
Matsunaga *et al.*, 1997[93] Japan	Cost-effectiveness analysis cervical screening	Cost per life-year gained	Yes		
Jenkins *et al.*, 1996[94] UK	Evaluation of the impact of HPV on cervical cancer screening	Annual incidence of invasive cancer Resource usage: smears, HPV tests, colposcopies	Yes	Yes	Sherlaw-Johnson *et al.*[97]
Eddy, 1990[84] USA	Evaluation of clinical management policies in cervical cancer screening	Lifetime probability of invasive cancer Mortality from invasive cancer Life-years gained	No		
Habbema *et al.*, 1984[95] The Netherlands	Evaluation of clinical management policies in cervical cancer screening	Outcomes defined but not quantified	Yes		
Benneyan & Kaminsky, 1996[96] USA	Evaluation of laboratory screening policies. Estimation of screen process sensitivity and specificity	Overall system sensitivity Overall system specificity Total cost of laboratory screening policy	Yes		
Sherlaw-Johnson *et al.*, 1994[97] UK	Evaluation of clinical management policies in cervical cancer screening	Incidence of invasive cervical cancer No. of smears/colposcopies Total cost of laboratory screening policy	Yes		
Gyrd-Hansen *et al.*, 1995[99] Denmark	Cost-effectiveness analysis of cervical cancer screening	Cost per life-years gained	No	Yes	Gyrd-Hanson[106]
Spiegelhalter *et al.*, 1998[100] UK	Uses cervical cancer screening as a case study for the formal development of Bayesian graphical modelling		Yes	No	

continued

TABLE 28 contd

Study/country	Study objectives	Outcomes generated	Does the paper describe an original model?	Is the model cross-referenced to related work?	Reference details for original model
van Oortmarssen & Habbema, 1995[101] The Netherlands	Estimation of the duration of pre-clinical cervical cancer following negative conventional smears	Relative risk of invasive cancer following negative screening tests	No	Yes	van Oortmarssen & Habbema[81]
Gustafsson & Adami, 1992[102] Sweden	Evaluation of clinical management policies in cervical cancer screening. Focuses on optimal scheduling of a given no. of screens	Estimated age-specific prevalence rates Lifetime probability of developing invasive cervical cancer Optimal screening strategies by screen efficiency	No	Yes	Gustafsson & Adami[98]
Kaminsky *et al.*, 1995[103] USA	Evaluation of laboratory screening policies. Estimation of screen process specificity	Process specificity Cost per screen	Yes	No	
Frame & Sutherland-Frame, 1998[104] USA	Evaluation of clinical management policies in cervical cancer screening. Focuses on screening interval	Percentage of invasive cancers prevented by frequency/sensitivity	Yes	No	
Kaminsky *et al.*, 1997[105] USA	Evaluation of automated re-screening. Estimation of screen process sensitivity, specificity and cost	Overall process sensitivity/specificity Cost per smear	Yes	No	
McGoogan & Reith, 1996[55] UK	Comparison of operational characteristics of conventional smear test and monolayer preparations. CytoRich, ThinPrep	Cytologic quality Diagnostic accuracy Screening times Costs (consumables)			
Bur *et al.*, 1995[45] USA	Comparison of conventional smear test and ThinPrep preparations	Cytologic quality Diagnostic accuracy Screening times Costs			
Fahey *et al.*, 1995[7] n/a	Meta-analysis of conventional smear test accuracy	Sensitivity Specificity Receiver operator characteristics			
Martin-Hirsch *et al.*, 1999[76] UK	Efficacy of cervical smear collection devices				
DoH, 1999[2] UK	CSP statistical bulletin				
Melamed *et al.*, 1998[107] USA	Summary of issues in cost–benefit analysis of new technologies				
Charny *et al.*, 1987[107] UK	Estimation of the cost-effectiveness of cervical cytology screening	Cost per life saved Smears/biopsies per death averted Cost of service			
Linder, 1997[109] USA	Review of screening developments				
Waugh & Robertson, 1996[110] UK (Scotland)	Evaluation of clinical management policies in cervical cancer screening. Focuses on estimating cost-effectiveness of reduction in screening interval	Cost per life saved Cost per life-year gained	Yes	No	

continued

TABLE 28 contd

Study/country	Study objectives	Outcomes generated	Does the paper describe an original model?	Is the model cross-referenced to related work?	Reference details for original model
Braly & Kinney, 1999[111] USA	Review of AHCPR report				
Brookmeyer & Day, 1987[82] USA	Principles of operation and practical aspects of automating screening machines				
Ettler *et al*., 1999[112] Canada	Cytohistological evaluation				
Mitchell & Medley, 1995[113] Australia	Cytohistological evaluation				
Giard & Hermans[114] The Netherlands	Evaluation of cervical cytology				

Appendix 3

Systematic review of economic evaluations of liquid-based cytology techniques

TABLE 29

Study	Brown & Garber, 1999[77]	AHCPR, 1999[21]	Australian Health Technology Advisory Committee, 1998[6]
Title	Cost-effectiveness of three methods to enhance the sensitivity of Papanicolaou testing	Evaluation of cervical cytology	Review of automated and semi-automated cervical screening devices
Modelling assessments should include:			
1 A statement of the problem	Evaluation of cost-effectiveness of ThinPrep, AutoPap, Papnet	The initial objective of the modelling element of this study was to answer the question: "What are the effects on total healthcare costs, morbidity and mortality of regular cervical cytology screening using thin-layer cytology or computer re-screening compared with conventional smear in women participating in a screening programme?" for the three technologies: ThinPrep, AutoPap and Papnet. In the light of the high level of uncertainty the question was reframed to: "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% re-screening at improved sensitivity	To provide an estimate of the potential additional costs and benefits of the use of the automated and semi-automated technologies applied to additional potential cancers in a 2-year screening cycle. Though the evaluation is aimed at both slide preparation and automated re-screening devices, these technologies 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
2 A discussion of the need for modelling versus alternative methodologies	Implied by the lack of empirical economic evidence though not stated directly	Systematic search undertaken for economic evidence	A dearth of health economic evidence for the monolayer technologies identified through a systematic search
3 A description of the relevant factors and outcomes	Factors included: disease incidence and progression, age-dependent; regression of pre-invasive lesions; test characteristics; success of treatment for diagnosed abnormalities, stage-dependent; all-cause mortality; costs of screening and treatment	Factors included: HPV infection and regression; disease incidence and progression, age-dependent; regression of pre-invasive lesions; test characteristics; success of treatment for diagnosed abnormalities, stage-dependent; all-cause mortality; costs of screening, diagnosis and treatment	Health benefits are measured in terms of 'additional cancer cases detected'. This is estimated from the increase in low- and high-grade abnormalities detected. 1% of low- and 12% of high-grade lesions are assumed to progress to true invasive cancer

continued

TABLE 29 contd

Study	Brown & Garber, 1999[77]	AHCPR, 1999[21]	Australian Health Technology Advisory Committee, 1998[6]
Title	Cost-effectiveness of three methods to enhance the sensitivity of Papanicolaou testing	Evaluation of cervical cytology	Review of automated and semi-automated cervical screening devices
Modelling assessments should include (*contd*):			
4 A description of the model including reasons for this type of model and a specification of the scope including: time frame, perspective, comparators and setting	Nine-state, time varying state transition model is used to model the life experience of cohort of women aged 20 to 65 years A societal perspective is used to analyse costs A rate of 3% (0–5%) is used to discount both health benefits and costs. The model used is not fully described but is attributed to Eddy[84,86] All techniques are compared with no screening and incrementally each other. Dominant strategies are identified	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 from age 15 to 85 years A direct healthcare perspective is used to analyse costs. Though, in line with the revised scope of the assessment the costs of the individual technologies are not directly included. Rather a generic range of incremental costs is used. A rate of 3% (0–5%) is used to discount both health benefits and costs	A simple model for estimated the no. of cancer cases potentially avoided is described
5 A description of data sources (including subjective estimates), with a description of the strengths and weaknesses of each source, with reference to a specific classification or hierarchy of evidence	The test characteristics for the three techniques have been obtained from a systematic search and review. The search considered MEDLINE as the only publications database, though key journals were handsearched and the equipment suppliers were contacted for unpublished evidence The cytologic classification used to describe disease progression is not reported, though this is referenced to Eddy[84] and claimed to be similar to the Bethesda system. Disease progression rates are not given but again referenced to Eddy All direct costs of screening are 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$0.25 per slide and equal for all technologies. References included[55,40] Costs of care figures from Eddy[84] updated to 1996 US$. Marginal consumable cost of ThinPrep $9.75	The test characteristics for the three techniques have been obtained from a systematic search and review. The search covered MEDLINE, CancerLit, HealthSTAR, CINAHL, EMBASE and EconLit databases. Recently published journals were handsearched and web resources were consulted. Full inclusion/exclusion criteria and results are reported and estimates of test characteristics are made. In line with the revised scope of the modelling study a threshold type analysis is undertaken with a wide range of potential effectiveness Pre-cancerous lesions are classified according to the Bethesda system, invasive cancer is staged according to the International Federation of Gynecology and Obstetrics classification system Costs of screening, diagnosing and treating cervical cancer were estimated using private insurance claims, Medicare fee schedules and secondary data sources Costs were adjusted to 1997 US$	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

continued

TABLE 29 contd

Study	Brown & Garber, 1999[77]	AHCPR, 1999[21]	Australian Health Technology Advisory Committee, 1998[6]
Title	Cost-effectiveness of three methods to enhance the sensitivity of Papanicolaou testing	Evaluation of cervical cytology	Review of automated and semi-automated cervical screening devices
Modelling assessments should include (*contd*):			
6 A list of assumptions pertaining to: the structure of the model (e.g. factors included, relationships, and distributions) and the data	A full detailing of assumptions within the modelling exercise is not presented The test characteristics, that is 'true-positive' and 'true-negative' rates are defined in terms of LSIL+. Sensitivity and specificity are therefore not differentiated between the higher disease states	Assumptions within the modelling exercise are systematically reported Sensitivity and specificity are not differentiated between the higher disease states	
7 A list of parameter values that will be used for a base case analysis, and a list of the ranges in those values that represent appropriate confidence limits and that will be used in a sensitivity analysis	Base case values are given for: treatment success rates and costs (point estimates); screen test characteristics (range given). Disease progression rates not given but source referenced[83]	All parameter estimates are systematically reported, sourced and ranges are given	
8 The results derived from applying the model for the base case	Summarised		
9 The results of the sensitivity analyses; unidimensional; best/worst case; multi-dimensional (Monte Carlo/ parametric); threshold	Restricted to scenario-based sensitivity analysis on: population/disease characteristics; cost and true-positive rate of conventional test; cost and true-positive rate of new technologies. These analyses constitute a unidimensional sensitivity analyses	Threshold analyses are undertaken focusing on improvements to sensitivity and decline of specificity and incremental costs. Univariate sensitivity analyses are undertaken on policies that had a potential baseline cost per life-year of less than $50,000. Furthermore in the absence of credible range estimates for many parameters, a set of tables is presented that allow cost-effectiveness to be predicted under a wide range of assumptions	
10 A discussion of how the modelling assumptions might affect the results, indicating both the direction of the bias and the approximate magnitude of the effect	Discussion based on sensitivity analyses given	Discussion based on sensitivity analyses given	
11 A description of the validation undertaken including: concurrence of experts; internal consistency; external consistency; predictive validity	No validation of the model is described here, though the original model by Eddy has been validated in prior studies	The model was validated against two type of external data: epidemiological data and previously published models of cervical cytology screening	

continued

TABLE 29 contd

Study	Brown & Garber, 1999 [77]	AHCPR, 1999 [21]	Australian Health Technology Advisory Committee, 1998 [6]
Title	Cost-effectiveness of three methods to enhance the sensitivity of Papanicolaou testing	Evaluation of cervical cytology	Review of automated and semi-automated cervical screening devices
Modelling assessments should include (*contd*):			
12 A description of the settings to which the results of the analysis can be applied and a list of factors that could limit the applicability of the results		Settings are completely described	
13 A description of research in progress that could yield new data that could alter the results of the analysis	Discussion of new technological developments and ongoing trials is given	A need for further studies to provide more precise estimates of costs and effectiveness of specific technologies is identified	

Appendix 4

Supplementary economic analysis: liquid-based cytology in cervical screening

Introduction

This report presents supplementary economic analyses of liquid cytology techniques compared with conventional screening methods. These analyses use the model described in the main report and focus upon more rigorous sensitivity analyses of the uncertainties within the model.

The parameter values used in the analysis are reviewed. The overall uncertainty in the cost-effectiveness of the new technologies is described, key uncertainties are identified through an analysis of the expected value of perfect information for each parameter within the model.

The analysis of the uncertainty in cost-effectiveness of the new technologies is based on a strategy of screening every 3 years between the ages of 18 and 64 years.

Parameter values used in the analysis

Table 16 presented the parameter values used within this analysis together with ranges and sources. For simplicity, triangular distributions have been assumed between the range endpoints in the sensitivity analyses.

Overall cost per life-year gained

The sensitivity analysis presented here focuses upon the cost per life-year gained of liquid-based cytology techniques with conventional screening under a policy of triennial screening between the ages of 18 and 64 years. Three different assumptions concerning discounting are analysed:

- discounting costs at 6% and life-years at 1.5%
- discounting costs at 3% and life-years at 3%, and
- discounting costs at 6% and life-years at 6%.

A multi-way sensitivity analysis has been undertaken using a Monte Carlo methodology, varying all parameters (not including management variables) between the ranges shown in *Table 16* and according to the triangular distributions assumed. The overall variation in cost-effectiveness estimates is presented in *Figure 3*. This figure shows the probability of having a cost-effectiveness at least as good as the given cost per life-year gained. The impact of three different assumptions regarding the discounting of costs and benefits is presented.

The positive probability at £0 per life-year saved indicates that under the assumptions used in this analysis and under all discounting options the technology may well be either cost neutral or cost saving.

Using a discount rate of 6% for costs and 1.5% for life-years gained, the cost-effectiveness of liquid-based technologies is robust with a high probability of the cost-effectiveness being better than £10,000 per life-year gained.

Using common discount rates for both costs and benefits of 3%, as used by the AHCPR, and 6%, the cost-effectiveness of liquid compared with conventional techniques deteriorates and is prone to greater uncertainty. There is a high probability for both 3% and 6% that the cost per life-year gained will exceed £20,000.

Expected value of further information

An analysis of the expected value of perfect information regarding each of the parameters within the model is undertaken using the decision analytic methodology described by Raiffa,[123] Phelps and Mushlin[124] and Claxton and Posnett.[125]

In this methodology a strict rule for commissioning interventions is proposed based on the expected cost-effectiveness. Consider a threshold cost-effectiveness defined such that if the expected cost-effectiveness of a new technology is better than this threshold then the decision is to commission the novel technology; conversely if the

expected cost-effectiveness is worse than the threshold then the conventional technology is commissioned. Notice that this decision is based purely on the expected cost-effectiveness and is not affected by the uncertainty in that estimate.

Uncertainty in the estimated cost-effectiveness gives rise to the possibility of making the wrong decision. There are two types of commissioning decision error that may be made:

- deciding to commission a novel technology when current information implies an attractive expected cost-effectiveness when, in fact, the real underlying cost-effectiveness is worse than the decision-making threshold, or
- deciding to not commission a novel technology when current information implies an unattractive expected cost-effectiveness when, in fact, the real underlying cost-effectiveness is better than the decision-making threshold.

These 'wrong decisions' will be associated with an opportunity loss, either financial or in lost health benefit. This opportunity loss can be measured in financial terms or in health benefit terms, with the 'exchange rate' being the decision-making threshold cost-effectiveness defined at the outset.

The opportunity loss can be estimated for an individual or for a cohort of individuals over any period.

The expected opportunity loss under the current state of knowledge reflected in the parameter estimates and ranges can be calculated by repeated calculation of cost-effectiveness while letting all parameters vary concurrently (see *Figure 3*). The value of perfect knowledge concerning any parameter can then be estimated by fixing that parameter (over its range) and letting all other parameters vary, the value of perfect knowledge concerning that parameter is then the reduction in expected opportunity loss. The relative importance of the uncertainty in each parameter can then be obtained by ranking the parameters in order of a decreasing value of perfect information.

Figure 4 shows the estimated opportunity loss against the minimum acceptable cost per life-year gained. The opportunity losses are assessed for 100,000 new women joining the screening programme at age 18 each year for the next 5 years. The opportunity losses are shown for two discounting scenarios: 6% costs and 1.5% life-years; and 6% costs and 6% life-years.

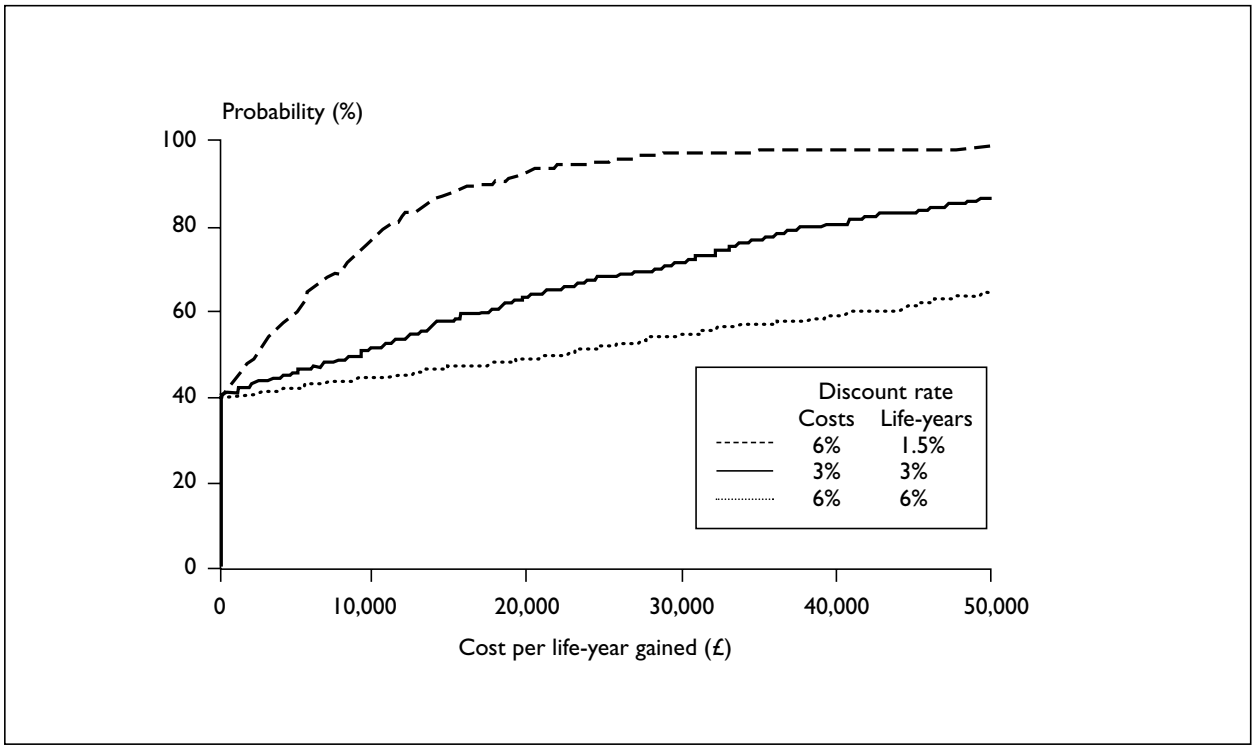

FIGURE 3 *Cumulative probability for cost-effectiveness of liquid-cytology techniques compared with conventional smears under different discounting assumptions*

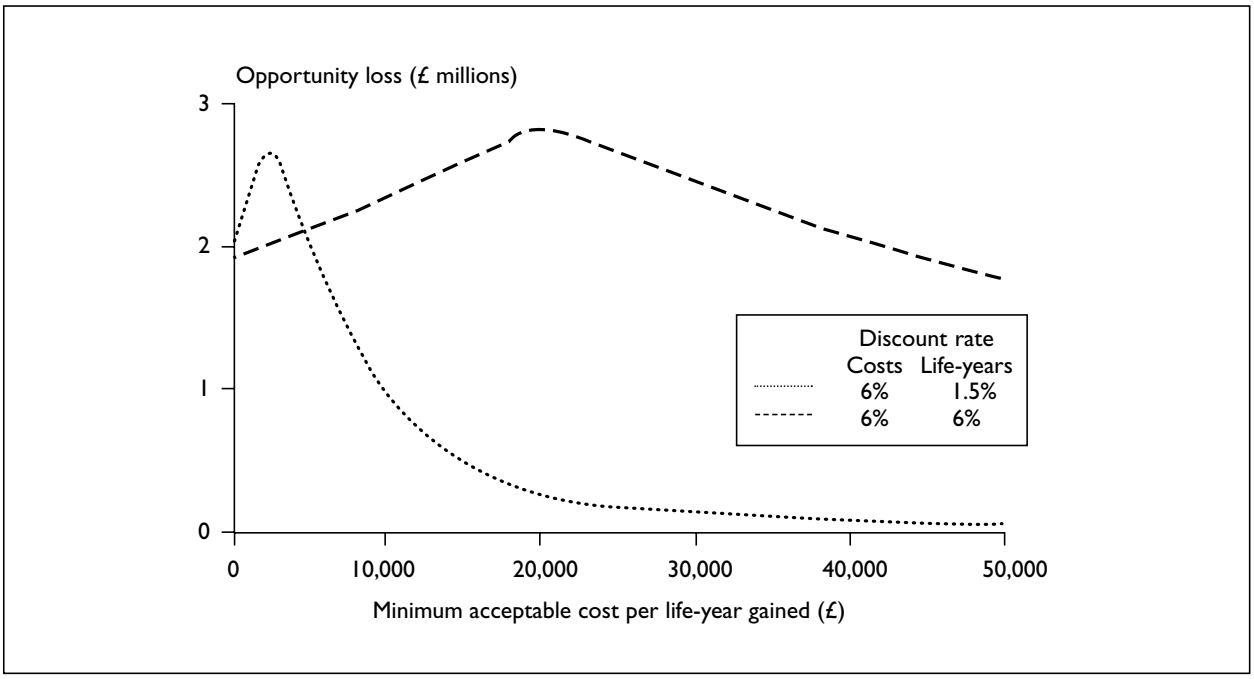

FIGURE 4 *Opportunity loss associated with decision making on current evidence against difference cost per life-year saved thresholds and discounting assumptions*

Using a discount rate of 6% for costs and 1.5% for life-years gained, the cost-effectiveness of the liquid-cytology techniques is good. From *Figure 4* it can be seen that at a threshold of £20,000 per life-year saved the expected opportunity loss is small, in the region of £200,000 per 100,000 new women aged 18 years joining the screening programme annually over the next 5 years. This indicates that while further information may be of use in considering clinical effectiveness, it would not add greatly to the health economic evidence for this technology.

In contrast, if both costs and life-years are discounted at 6% then the expected cost-effectiveness of liquid-cytology techniques is just over £20,000 per life-year. In this context a threshold of £20,000 would indicate not commissioning the liquid-based technology; however, the expected opportunity loss associated with this decision (and equally with a decision to commission associated with a slightly higher threshold) would be large, in the region of £2 million pounds per 100,000 new women entering the screening programme annually for 5 years.

Table 30 presents the expected opportunity loss, and expected value of perfect information for all parameters in the model ranked into reducing

TABLE 30 *Expected opportunity loss and value of perfect information for key parameters*

Parameter	Expected opportunity loss	Expected value of perfect information
All parameters varying	£2,824,000	–
Marginal cost for a liquid-cytology sample	£410,000	£2,414,000
Cost per conventional smear	£1,761,000	£1,063,000
Inadequate liquid-based cytology samples	£1,922,000	£902,000
Inadequate conventional smear slides	£2,025,000	£799,000
Change in specificity liquid-based techniques	£2,221,000	£603,000
% Clear with moderate/severe test result	£2,266,000	£558,000
Mortality rate associated with invasive cancer	£2,318,000	£506,000
All other factors	–	< £500,000

value of information. These figures are for a discounting rate of 6% for costs and benefits and a threshold cost-effectiveness of £20,000. The value of further information for the key parameters against the minimum acceptable cost per life-year gained is shown in *Figure 5*.

Marginal cost of liquid-cytology techniques

Figure 6 presents the expected cost per life-year gained of the liquid-based cytology techniques compared with conventional screening against the marginal cost per sample of the liquid-based techniques.

This confirms that the cost-effectiveness of the novel techniques is very sensitive to this marginal cost. At a marginal cost of under £3.00 per slide, the novel techniques would be estimated to both cost less and be more effective than conventional screening. However, the best estimate of increased consumable costs, not including increased costs of transport, storage and training are in the region of £3.50 per sample. If, however, a marginal cost of £5 per slide is assumed then with costs discounted at 6% and benefits at 1.5%, the expected cost per life-year gained is approximately £10,000, with both costs and benefits discounted at 6% the cost per life-year gained is £80,000.

Conclusions

The limitations and assumptions associated with the economic model are discussed in the main report, subject to these same provisos the following conclusions may be drawn from this analysis.

Using a discount rate of 6% for costs and 1.5% for life-years gained the expected cost-effectiveness of the liquid-cytology techniques compared with conventional screening is good, under £10,000 per life-year gained. This estimate of cost-effectiveness is robust under the ranges for parameters used in the sensitivity analysis, and is under £20,000 per life-year gained for all circumstances considered. The expected opportunity loss associated with making a decision to commission this technology is small, and while further information, gained through further analytical or research work, may be of use in considering clinical effectiveness it would not add greatly to the health economic evidence for this technology.

If both costs and life-years are discounted at the same rate of 3% or 6% then the expected cost-

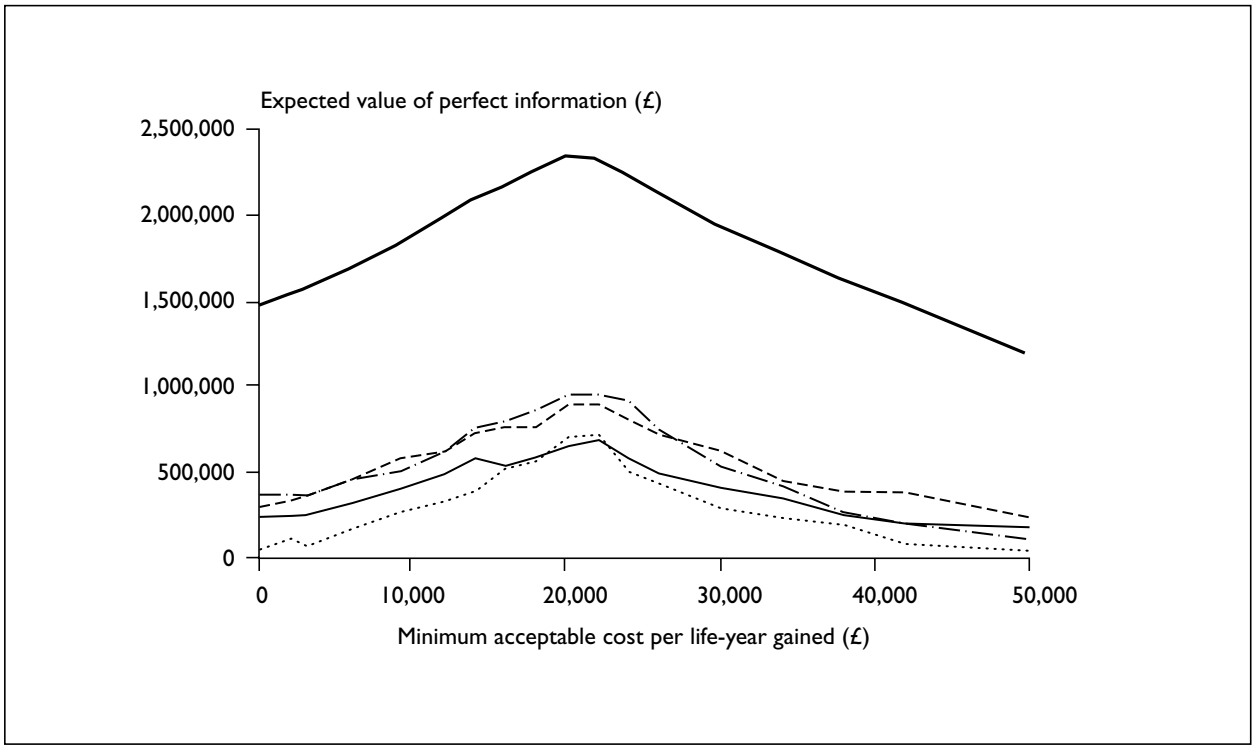

FIGURE 5 *Expected value of perfect information for the key parameters against the minimum acceptable cost per life-year gained threshold (key parameters: ——, liquid costs; — · — ·, conventional costs; ·····, liquid inadequacy rate; – – –, conventional inadequacy rate; ——, change in specificity)*

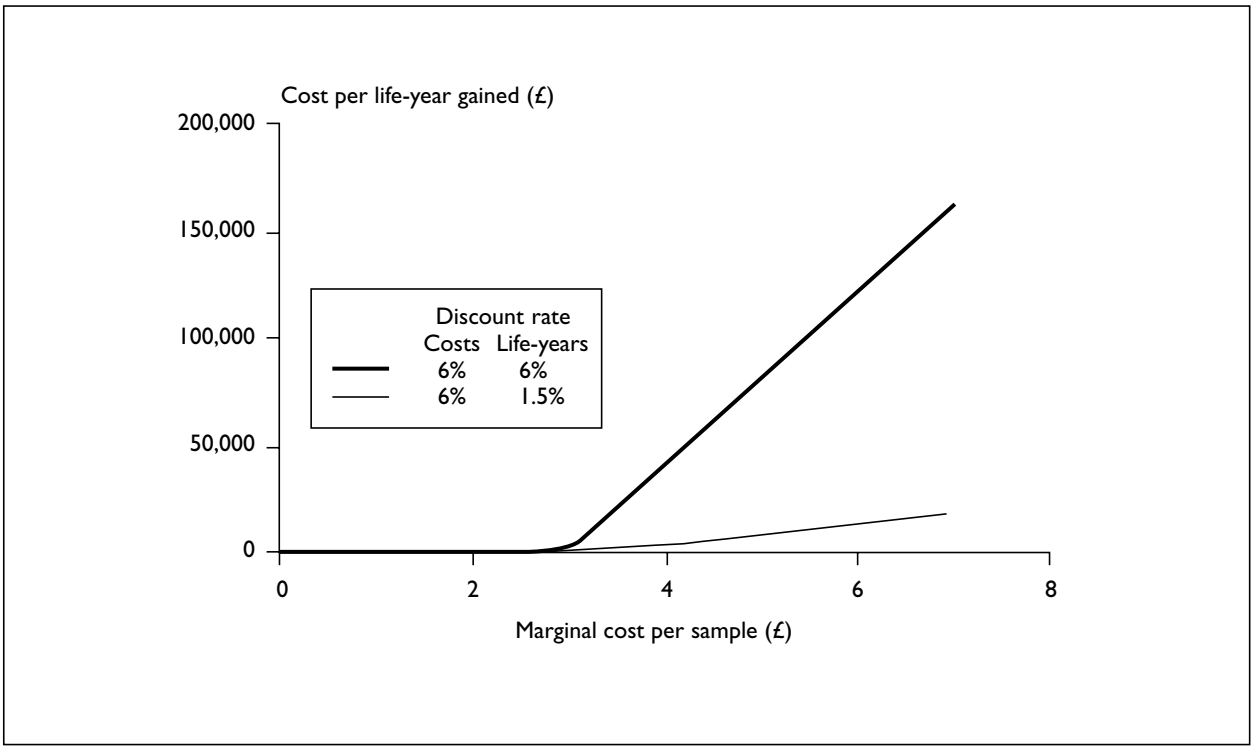

FIGURE 6 *Cost per life-year gained of liquid-based cytology techniques compared with conventional screening against marginal cost per sample*

effectiveness of liquid-cytology techniques deteriorates and the associated uncertainty increases. For a discounting rate of 6% the cost per life-year gained for liquid cytology is just over £20,000, if a commissioning threshold in the region of £20,000 to £30,000 is applied, this implies a large expected opportunity loss associated with either a decision to commission or not to commission.

The key uncertainty is the marginal cost per sample between the two technologies. At a marginal cost of up to £3 per sample, the novel technologies would be expected to be cost saving, current estimates of consumable cost are in the region of £3.50 per slide, elements not included are storage, transport and training. In addition other key uncertainties include the cost of the conventional smear test and the improvement in the rate of inadequate smears achieved with liquid cytology.

The key clinical uncertainty impacting on the cost-effectiveness is the achieved specificity of the liquid-cytology test, where a small change will have a marked affect on the costs and cost-effectiveness of the technology.

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We look forward to hearing from you.

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