Technology *Report*

Issue 40 November 2003

Liquid-Based Cytology and Human Papillomavirus Testing in Cervical Cancer Screening

Publications can be requested from:

CCOHTA
600-865 Carling Avenue
Ottawa, Ontario, Canada K1S 5S8
Tel. (613) 226-2553
Fax. (613) 226-5392
Email: pubs@ccohta.ca

or download from CCOHTA's web site:
http://www.ccohta.ca

Cite as: Noorani HZ, Brown A, Skidmore B, Stuart GCE. **Liquid-based cytology and human papillomavirus testing in cervical cancer screening.** Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2003. Technology report no 40.

CCOHTA is a non-profit organization funded by the federal, provincial and territorial governments.

Legal Deposit – 2003
National Library of Canada
ISBN: 1-894978-07-2 (print)
ISBN: 1-894978-08-0 (electronic version)

Publications Mail Agreement Number: 40026386

Canadian Coordinating Office for Health Technology Assessment

Liquid-Based Cytology and Human Papillomavirus Testing in Cervical Cancer Screening

Hussein Z. Noorani MSc[1]
Allan Brown BSc MBA MA[1]
Becky Skidmore MLS[1]
Gavin C.E. Stuart MD[2]

November 2003

[1] Canadian Coordinating Office for Health Technology Assessment (CCOHTA), Ottawa, Ontario, Canada
[2] Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada

Reviewers

These individuals kindly provided comments on this report.

External Reviewers

Andrew Coldman, PhD
Head, Population and Preventive Oncology
British Columbia Cancer Agency
Vancouver, British Columbia

Terence J. Colgan, MD FRCPC
FCAP MIAC
Head of Gynaecological Pathology, Pathology and Laboratory Medicine
Mount Sinai Hospital
Toronto, Ontario

Eduardo L. Franco, MPH DrPH
Professor and Director
Division of Cancer Epidemiology
McGill University
Montreal, Quebec

C. Meg McLachlin, MD
Medical Leader, Cytopathology
London Health Sciences Centre
London, Ontario

Brent W. Zanke, MD PhD FRCPC
Systemic Therapy, Provincial Head
Cancer Care Ontario
Toronto, Ontario

CCOHTA Scientific Advisory Panel Reviewers

Kenneth Marshall, BA MSc MD
FRCPC FCFP
Professor of Family Medicine (Retired)
University of Western Ontario
London, Ontario

David Persaud, MSc MHSA PhD
Assistant Professor
School of Health Services Administration
Dalhousie University
Halifax, Nova Scotia

This report is a review of existing public literature, studies, materials and other information and documentation (collectively the "source documentation") which are available to CCOHTA. The accuracy of the contents of the source documentation on which this report is based is not warranted, assured or represented in any way by CCOHTA and CCOHTA does not assume responsibility for the quality, propriety, inaccuracies or reasonableness of any statements, information or conclusions contained in the source documentation.

CCOHTA takes sole responsibility for the final form and content of this report. The statements and conclusions in this report are those of CCOHTA and not of its Panel members or reviewers.

Authorship

All authors participated in planning the project.

Hussein Z. Noorani is a Research Officer at CCOHTA. He reviewed the clinical and economic literature; composed drafts of the executive summary, introduction, clinical review, overall discussion, and conclusions; and revised manuscript drafts.

Allan Brown is a Health Economist at CCOHTA. He reviewed the clinical and economic literature; composed the economic review; and revised manuscript drafts.

Becky Skidmore is an Information Specialist at CCOHTA. She designed and executed the literature search strategies; wrote the methods section and associated appendix on literature searching; and verified and formatted references.

Gavin C.E. Stuart is the Dean of Medicine at the University of British Columbia. He assisted in drafting the introduction and overall discussion; and revised manuscript drafts.

Conflicts of Interest

Hussein Z. Noorani, Allan Brown, Becky Skidmore and Gavin C.E. Stuart disclosed no conflicts.

REPORT *IN BRIEF*

November 2003

HPV Testing and Liquid-based Techniques for Cervical Cancer Screening

Technology Name
Tests for the human papillomavirus (HPV)
Liquid-based cytology (LBC)

Disease/Condition
Cervical cancer is mainly caused by the sexually transmitted human papillomavirus (HPV). Among high grade precancerous lesions, 75% to 95% test positive for HPV infection. In 2003, an estimated 1,400 women in Canada will develop invasive cervical cancer and 420 women will die from this preventable disease. Precancerous lesions can be detected through screening and treated before they develop into invasive cervical cancer.

Technology Description
In LBC, which is a variation of conventional cytology, cells collected from the cervix are immediately preserved and spread in a monolayer on a glass slide for viewing under a microscope. The intent of the immediate fixation and the uniform spread of cells is to reduce sampling errors. Tests for HPV involve detecting and identifying the genetic material of the virus which exists as many strains.

The Issue
The Pap smear is the most common screening method used to detect precancerous changes in cervical cells. Several new technologies are being evaluated to determine their ability to detect cervical cancer and its precursor stages. LBC and HPV testing may offer advantages over the Pap smear.

Objectives
- To evaluate the diagnostic accuracy of LBC and HPV testing to detect precancerous or malignant cervical lesions
- To evaluate the comparative cost and cost-effectiveness of LBC and HPV testing

Methods
The literature was searched between January 1997 and July 2003 for comparative trials that examined the diagnostic accuracy of LBC and HPV testing and Pap smears. The outcomes were estimates of test sensitivity and specificity. Economic evaluations or cost studies of LBC and HPV testing were identified through a literature search. The outcomes examined were average costs per patient, life days saved and incremental cost per life year saved relative to those for Pap smears.

Conclusions
- For women with an ordinary risk of cervical cancer, but not for women at high risk, LBC is more sensitive than the Pap smear.
- LBC produces a lower rate of unusable samples of cervical cells.
- HPV testing, alone or with cytology, is more sensitive than the Pap smear but less specific for primary screening and triage.
- LBC screening every three years or longer may be as cost-effective relative to the Pap smear.
- Economic modelling based on the use of LBC in a Canadian context is needed before conclusions can be made about the cost-effectiveness of HPV testing.

This summary is based on a comprehensive health technology assessment report available from CCOHTA's web site (www.ccohta.ca): Noorani HZ, Brown A, Skidmore B, Stuart GCE. **Liquid-based cytology and human papillomavirus testing in cervical cancer screening.**

Canadian Coordinating Office For Health Technology Assessment (CCOHTA)
600-865 Carling Avenue, Ottawa, ON, Canada K1S 5S8 Tel: 613-226-2553 Fax: 613-226-5392 www.ccohta.ca

***CCOHTA** is an independent, non-profit health research agency funded by the federal, provincial and territorial governments.*

EXECUTIVE SUMMARY

The Issue

Cervical cancer is a largely preventable disease, which remains the 12th most common cancer among women in Canada. In 2003, an estimated 1,400 women in Canada will develop invasive cervical cancer and 420 women will die from the disease. The Papanicolaou (Pap) smear is the most common screening method used to detect precancerous changes. Pap smears, however, are associated with variable false-positive and false-negative rates. Several new technologies have been evaluated to determine their effectiveness in detecting cervical cancer and its precursors. One test involves liquid-based cytology (LBC), which is designed to improve the quality of Pap smears. Because human papillomavirus (HPV) is the central cause of cervical cancer, new HPV testing methods have also been developed.

Objectives

The aim of this report is 1) to evaluate the diagnostic accuracy of detecting precancerous or malignant cervical lesions by LBC and HPV testing, compared to that of Pap smears; and 2) to evaluate the comparative cost and cost-effectiveness of LBC and HPV testing.

Review of Diagnostic Accuracy

Methods: To update a previous Canadian Coordinating Office for Health Technology Assessment (CCOHTA) review, literature between January 1997 and July 2003 was identified by searching databases using DIALOG® and other bibliographic systems. Full reports and abstracts of comparative trials focusing on the diagnostic accuracy of LBC versus Pap smears and HPV testing versus Pap smears were included. The primary outcomes were estimates of test sensitivity and specificity. For the comparison of LBC versus Pap smears, a secondary outcome was the proportion of unsatisfactory specimens used for evaluation. The quality of a report was assessed in terms of the method of recruitment, verification bias, reference standard (histology or cytology review), blinding of outcome assessment and level of industry funding for research. Pooled estimates across trials were expressed as relative risks [RR; with 95% confidence intervals (CI)].

Results: In none of these trials are participants randomized to have their cervical samples analyzed by either of the new tests and Pap smears. Thirteen trials meet the selection criteria for the comparison of LBC versus Pap smears (in nine countries, with one multi-centre trial recruiting some women from Canada). Ten trials (77%) use a split-sample design where the cervical specimen is split to make a conventional smear and a sample to be used in a liquid-based method. Eight trials (61.5%) are funded partially or completely by manufacturers of LBC technologies. Eleven trials (n=4,406 test samples) are included in a meta-analysis of sensitivity at a threshold of low-grade squamous intraepithelial lesions. Sensitivity rates are higher for LBC (range 53% to 96%) than for Pap smears (34.5% to 94%). LBC is a superior screening technology for ordinary populations (RR 1.17 95% CI 1.02; 1.35), but not for high risk populations (RR 1.07 95% CI 0.97; 1.18). There is no significant difference in specificity rates between LBC (45% to 99.5%) and Pap smears (17% to 99.7%; RR 1.35 95% CI 0.82; 2.23).

Eight trials (n=131,407 samples) report on the rate of unsatisfactory specimens used for evaluation. LBC has a lower rate of unsatisfactory specimens (0.1% to 1%) than Pap smears (0.1% to 12%; RR 0.34 95% CI 0.20; 0.59).

Twelve trials meet the selection criteria for HPV testing as a primary screening test (in 11 countries, with one Canadian trial), nine trials as a triage of women with borderline or low-grade cytologic abnormalities (in six countries, with two Canadian trials) and two international trials as surveillance post-treatment. For trials on primary screening and triage, the mean age of participants is 36 years and the reference standard is a histological outcome of high-grade cervical intraepithelial neoplasia. In most trials, HPV testing used alone is more sensitive (range 68% to 100% for primary screening; 66% to 96% for triage) than Pap smears (20% to 89%; 35% to 93%). Specificity is lower with HPV testing (16% to 97% for primary screening; 35% to 67% for triage) in comparison to Pap smears (87% to 99%; 31% to 92%). Adjunctive HPV testing with Pap smears has higher sensitivity but lower specificity than Pap smears alone. There is insufficient evidence on the diagnostic accuracy of HPV testing for surveillance.

Economic Review

Methods: A literature search identified economic evaluations or cost studies pertaining to LBC and HPV testing. Information on study characteristics, average costs per patient, life days saved and incremental cost per life year saved relative to Pap smears were summarized.

Results: Thirteen studies meet the selection criteria. These studies come from seven developed and developing nations. Seven studies are on LBC (six economic evaluations and one cost study) and six are on HPV testing (all economic evaluations: four for primary screening and two for triage). For LBC, results suggest that screening with a frequency of every three years or longer may be cost-effective, while screening annually or every two years may not. For HPV, results are less clear-cut. US-based models suggest that HPV testing for primary screening at a frequency of every three years or longer is cost-effective relative to Pap smears. Evidence from an Australian-based triage model suggests that HPV testing of women with low-grade cytologic abnormalities is more expensive and less effective than Pap smear testing. Determination of the incremental cost-effectiveness of LBC and HPV testing can be problematic given the uncertainty about key parameters, such as comparative sensitivity and specificity relative to current programs based on Pap smear screening.

Conclusions

The evidence shows that the LBC technique reduces the number of false-negative results as compared with the Pap smear for ordinary populations of women, although not for high risk populations. LBC also reduces the proportion of unsatisfactory specimens compared with Pap smears. The evidence shows that HPV testing, alone or with cytology, is more sensitive but less specific than Pap smears for primary screening and triage. The failure of some trials to meet several validity criteria, including the limitation of not having all women receive the reference test, hampers the interpretation of the results. The economic evidence suggests that LBC screening every three years or longer may be cost-effective relative to Pap smear screening. Economic modelling based on the use of LBC in a Canadian context is needed before cost-effectiveness conclusions can be reached about the use of HPV testing.

TABLE OF CONTENTS

ABBREVIATIONS

ASCUS	atypical squamous cells of undetermined significance
ASCUS+	atypical squamous cells of undetermined significance and higher grade lesions
CCPN	Cervical Cancer Prevention Network
CIN	cervical intraepithelial neoplasia
CI	confidence interval
CCOHTA	Canadian Coordinating Office for Health Technology Assessment
FDA	The United States Food and Drug Administration
HC-II	hybrid capture-II test
HPV	human papilloma virus
HSIL	high-grade squamous intraepithelial lesion
HSIL+	high-grade squamous intraepithelial lesion and squamous cell carcinoma
LBC	liquid-based cytology
LSIL	low-grade squamous intraepithelial lesion
LSIL+	low-grade squamous intraepithelial lesion and higher grade lesions
MSAC	The Australian Medical Services Advisory Committee
NICE	The United Kingdom National Institute for Clinical Excellence
PCR	polymerase chain reaction
QALY	quality adjusted life year
RR	relative risk
UK	United Kingdom
US	United States

GLOSSARY*

Confidence interval (CI): The range in which the "true" value of the effect of an intervention is expected to lie with a given degree of certainty, a confidence interval represents the distribution probability of random errors, but not systematic errors (bias).

Fixed effects model: This is a mathematical model for combining the results of studies. It assumes that the effect is truly constant in all populations studied. Thus, only within-study variation is taken to influence the uncertainty of results and it produces narrower confidence intervals than the random effects model.

Forest plot: This presents the individual study effects with their confidence intervals as horizontal lines, the box in the middle of the horizontal line representing the mean effect. When using relative risk (or odds ratio) as the effect measure, the effects are usually plotted on a log scale to introduce symmetry. The vertical line drawn at a relative risk of one (unity) represents "no effect" and a confidence interval overlapping this vertical line represents the lack of a statistically significant effect. Different sized boxes may be plotted for each study. The size of the box increases with the weight that the study takes in the analysis.

Funnel plot: This is a statistical method that displays publication bias. Funnel plots show the distribution of effect sizes according to sample sizes (or inverse of variance). It is expected that points (each representing an effect size) will fill a funnel shape. More variability in reported effect sizes would occur in smaller studies. Large gaps in the funnel indicate that a group of publications may be "missing."

Heterogeneity: This is the variability or difference between studies in terms of key characteristics (clinical heterogeneity), quality (methodological heterogeneity) and effects (heterogeneity of results). Statistical tests of heterogeneity may be used to assess whether the observed variability in study results (effect sizes) is greater than that expected to occur by chance.

Publication bias: This term refers to a bias in the literature where the likelihood of publication of a study is influenced by the significance of its results. For example, studies in which an intervention is not found to be effective may be less likely to be published. Systematic reviews that fail to identify such studies may overestimate the true effect of an intervention by disproportionately reporting on studies where the intervention was found to be effective.

Random effects model: This mathematical model for combining the results of studies allows for variation in the effect among the population studied. Thus, within-study variation and between-study variation are included in the assessment of the uncertainty of results.

Sensitivity (true positives): This is the proportion of those people who have the disease and who are correctly identified as having the disease.

* Adapted in part from Khan (2001)[26]

Sensitivity analysis: This analysis is used to determine how the results of a study change because of variations arising from uncertain decisions or assumptions about the data and the methods used.

Specificity (true negatives): This is the proportion of those people who do not have the disease and who are correctly identified as being without the disease.

Relative Risk (RR): The ratio of risk in the intervention group to the risk in the control group. An RR of one indicates that there is no difference between comparison groups. For undesirable outcomes, an RR of less than one indicates that the intervention is effective in reducing the risk of that outcome.

1 INTRODUCTION

1.1 Background

1.1.1 Cervical cancer

In Canada, the incidence of cervical cancer and its associated mortality has steadily declined since the late 1950s. Cervical cancer, however, remains the 12th most common cancer among women in Canada.[1] In 2003, an estimated 1,400 women will develop invasive cervical cancer and 420 women will die from the disease, resulting in an estimated age-standardized incidence rate in Canada of 8.0 per 100,000.[1]

The decline in the incidence and mortality of cervical cancer is almost exclusively due to a decreased incidence of squamous cell carcinoma.[2] As squamous cell carcinoma occurs in the junctional region of the endocervical columnar epithelium and the ectocervical squamous epithelium, visual inspection and routine non-invasive cytologic testing are possible. Moreover, the anatomical and histological features facilitate the graded, local, non-invasive treatment of dysplasia and microscopic invasion.

Infection with human papillomavirus (HPV) is the central cause of cervical cancer.[3-6] The results of modern tests show that over 95% of all cervical cancers are HPV-positive and that 75% to 95% of high-grade precancerous lesions are associated with a positive HPV test on exfoliated cells.[4] The World Health Organization and the International Agency for Research on Cancer officially designated HPV types 16 and 18 as carcinogenic agents.[5] Several other HPV types are also considered carcinogenic.[3]

1.1.2 Cervical screening in Canada

Since the late 1950s, Canada has made a commitment to the secondary prevention of cervical cancer through provincial screening, consensus workshops and guideline documents. It has been agreed that the desirable goal is a comprehensive program of organized screening. To date, however, none of the provinces or territories have implemented a comprehensive screening program in Canada, despite the fact that several provinces have programs with many of the required elements.[7]

In 1976, the Walton Report on Cervical Cancer Screening Programs supported the implementation of provincial screening programs with appropriate recruitment, quality assurance and recall.[8] A follow-up report in 1982 provided more details about quality assurance and recall.[9] In 1982, British Columbia was the only province where elements of an organized program were in place. In 1991, the recommendations of a national workshop on screening for cancer of the cervix were published.[10] These recommendations emphasized the need for a broad based organized program. Details were provided regarding the frequency and initiation of screening and the management of abnormalities.[10]

During the late 1980s and early 1990s, several reports from provinces across Canada documented that the major characteristic of women presenting with invasive cervical cancer was that they had never been screened or had not been screened within the past five years; the rate of inadequate screening was over 60%.[11-15] These reports were consistent across Canada.

Several national workshops were convened during the 1990s to advance the implementation of organized screening programs. Interchange '95, a Canadian forum of collaboration on cervical cancer screening program implementation strategies, was convened to identify the factors that were adversely affecting implementation.[16] Three working groups were established, including the creation of the Cervical Cancer Prevention Network (CCPN). The CCPN convened a workshop in 1998.[17] During this worskshop, three working groups were formed. The Quality Management Working Group produced a document entitled "Programmatic Guidelines for Screening for Cancer of the Cervix in Canada" in 1998. The Information Systems Working Group defined a minimal data set for an organized screening program and the electronic platforms with a capacity to handle the data. The Recruitment Working Group worked with others, including a workshop sponsored by the National Cancer Institute of Canada and the Canadian Cancer Society, to review existing strategies.

In 1997, the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) published a report called "Assessment of Techniques for Cervical Cancer Screening."[18] This report examined the effectiveness of the conventional Pap test and the cost-effectiveness of automated rescreening strategies. The CCOHTA report recommended that a focus on recruitment into existing programs and quality assurance were priorities. The potential role of liquid-based cytology (LBC) and HPV testing remained to be determined.[18]

To date, no province or territory has implemented a comprehensive population-based screening program for cervical cancer. Yet the key elements of such a program are present in most jurisdictions. This was confirmed in a recent survey of all 13 provincial and territorial jurisdictions (Dr. Gavin Stuart, Dean, Faculty of Medicine, University of British Columbia, Vancouver: personal communication, 2003 Oct). Inconsistencies remain, even in the reporting of terminology; although most use the 2001 Bethesda Reporting Classification (Appendix 1). In the absence of organized programs, the recommendations for screening practices have remained unclear. Most jurisdictions, however, support the recommendations of the 1991 national workshop.[10]

The new technologies that have been developed could have an impact on the delivery of cervical screening programs. In addition to LBC and HPV testing, these include automated cytology screening, primary vaccine programs and optical spectroscopy. Some of these new interventions will benefit an individual woman at risk for cervical cancer and others may benefit a population of women at risk for cervical cancer. This review is intended to assess the applicability of some of these technologies to the Canadian population at risk of this disease in the context of rational resource allocation.

1.2 Technology Overview

1.2.1 Papanicolaou (Pap) smear test

Invasive cervical cancer is largely preventable if precancerous lesions are detected by effective screening and then adequately treated. The Papanicolaou (Pap) smear is the most common screening method used to detect precancerous changes for squamous cervical cancer.[19,20] The Pap smear test involves the collection of cells from the cervix of an asymptomatic woman by a physician or nurse using a spatula or an endocervical brush. The collected cells are transferred to a microscope slide, stained and examined for abnormalities in a cytopathology laboratory. If the presence of an abnormality is suspected, then the woman is referred to a gynecologist, who examines the cervix with a magnifier called a colposcope to highlight any precancerous or cancerous areas. At this stage, a pathologist can confirm the diagnosis based on a biopsy and treatment designed to prevent invasive cervical cancer can be started.[19]

The Pap smear, similar to any test used in medicine, has measurable parameters, which are known as sensitivity and specificity. Sensitivity refers to the ability of the test to detect all those patients with the condition of interest. This is expressed in the more common concept of the false-negative rate. Specificity refers to the test's ability to only detect those patients without the condition of interest. This is expressed in the notion of a false-positive rate. The Pap smear test's parameters have been examined in studies and high quality systematic reviews.

In the most recent comprehensive review on the accuracy of conventional and new methods of Pap testing, it was found that false-negative rates for Pap smears range from 13% to 70% (sensitivity 87% to 30%).[21] Approximately two-thirds of false-negative results are caused by sampling error and the rest are caused by detection error (see section 1.1.4 below). False-positive rates range from 14% to 0% (specificity of 86% to 100%).[21] The wide range of Pap smear test parameters reflects differences in the patient population's baseline prevalence and the reference test to which the Pap smear is compared.

1.2.2 New technologies

Screening programs are investigating or using new technologies designed to detect cervical cancer and its precursors. There are three types of innovative technologies.

1) With technologies that are designed to improve the quality of cell collection procedures, the intent is to obtain a more representative sample from the squamo-columnar junction and to better preserve these cells for accurate histological examination. The goal is to reduce sampling error. The most common and widely tested innovation is LBC.

2) Computer-assisted methods have been developed to automate the cytologic interpretation process. The goal is to reduce the cost of technicians and to improve the replicability of Pap smear interpretation.[22,23] These methods, designed to reduce detection error, are not considered in this review.

3) The more radical third type of innovation involves the replacement of Pap smears as a screening tool with HPV testing. This innovation, which is considered in this systematic review, has become automated and standardized to the point where it has undergone population-based evaluation.

1.2.3 Liquid-based cytology (LBC)

LBC is a variation of conventional cytology. Cervical samples are collected in the same fashion, but using a brush-like device rather than a spatula. The US Food and Drug Administration (FDA) has approved two techniques: ThinPrep (Cytyc, Massachusetts) and AutoCyte Prep (also known as SurePath; TriPath Imaging, formerly Autocyte, North Carolina), which were approved in May 1996 and June 1999 respectively.[19,20] Initial trials with this technique were performed with the ThinPrep Processor Beta model, now replaced by the Food and Drug Administration-approved ThinPrep 2000 (T2000). ThinPrep provides a semi-automated (T2000) or fully automated (T3000) method of sample preparation.[24] Cervical samples are rinsed with proprietary PreservCyt transport medium into a vial, which is then processed using the T2000 or T3000 machine. The T2000 processes slides individually, while the T3000 can batch process up to 80 specimens per cycle. Subsequent staining and microscopic evaluation of the slides are done in a similar manner to the steps done for the conventional Pap smear.[24] The T2000 is used in most published trials on ThinPrep.

The AutoCyte PREP technique requires that the collection device be retained in the proprietary collection vial, which contains transport fluid, so that all collected cervical cells are sent to the cytopathology laboratory.[24] Vials are centrifuged by laboratory personnel; all subsequent preparation of the sample and slide is automated using the Prepstain machine, which processes 48 samples at a time.[24] Potential advantages of the LBC method include an improved means of slide preparation, producing more homogenous samples than the Pap smear.[20,24] It is claimed that these techniques reduce the proportion of specimens classified as technically unsatisfactory for evaluation. Another advantage is that the cell suspension in preservative can be retained and used for later testing with HPV and other molecular biological tests.[19,20]

1.2.4 HPV testing

HPV is a sexually transmitted viral infection. Many strains of the virus exist and many are asymptomatic. Some cause condyloma acuminata (venereal warts), while others are potentially oncogenic in women in whom the virus persists for prolonged periods.[4] Screening tests for HPV focus on the strains that are known to be oncogenic. A comprehensive review investigating HPV testing in a cervical cancer screening program compared HPV assay methods and concluded that two polymerase chain reaction (PCR)-based assays and the second-generation Hybrid Capture (HC-II) test (Digene Diagnostics, Maryland) were the methods of choice.[4] The HC test is the only method approved by the FDA.[25]

The HC-II test that became commercially available in 1997 is a nucleic acid hybridization assay with signal amplification for the quantitative detection in cervical specimens of HPV DNA of 13 high risk, cancer-associated types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68.[6,25] The HC-II test cannot determine the specific HPV type present, because detection is performed with a combined probe mix.[25] Samples for assay with HC-II technology can be collected with the

standard devices used for Pap smears, with or without LBC techniques or with the proprietary sampling and specimen transport medium included with the HC-II test. HC-II test results are expressed in relative light units, which are a measure of the light produced by the individual sample reaction divided by the mean level of light generated by three 1.0 pg/mL positive calibrators.[4] A reading of 1.0 relative light unit is equivalent to 1.0 pg/mL.[4]

1.3 Testing the Tests

Diagnostic accuracy is most commonly expressed as sensitivity and specificity.[26] In reports of diagnostic accuracy, results from one or more tests are compared with the results obtained with the reference standard on the same subjects. The Standards for Reporting of Diagnostic Accuracy (STARD) initiative improves the quality of reporting of trials of diagnostic accuracy.[27,28] Following the CONSORT (Consolidated Standards of Reporting Trials) initiative for the reporting of randomized trials, the STARD working group developed a checklist of items to be included in the report of a trial on diagnostic accuracy. Key methodological issues relevant to these trials in the context of cervical cancer screening include the use of appropriate study designs, the evaluation of the test in an appropriate spectrum of subjects, the use of a reference standard to verify diagnoses as accurate, the choice of thresholds for reporting positive diagnoses and the role of industry funding in the research.

1.3.1 Study designs

In the most valid design for diagnostic and screening tests, both tests are applied to the same woman and compared in a within-subjects analysis.[20,23] The advantage is that many characteristics are equivalent for both tests (including patient attributes, timing in the menstrual cycle and clinician factors). Within-subjects analysis is common in diagnostic accuracy studies for cervical cancer screening, because it is relatively simple to collect two samples during a pelvic examination. For automated screening studies, slides from the same woman can easily be screened again using a different test. There have been concerns, however, about the validity of the design when the split-sample technique is used to compare Pap smear test to LBC. With the split-sample design, the cervical specimen is used first to make a smear in the conventional manner.[20] Then, the rest of the specimen is used for LBC. Thus, two specimens are produced for each woman screened: a Pap smear and a liquid-based preparation. This technique has been reported as a disadvantage for the liquid-based smear. As fewer endocervical cells are left for the LBC analysis, there is an underestimate of its sensitivity.[20,23] It is also argued that in split-sample trials, the LBC is the "research" technique, in contrast to the Pap smear as the "standard" and that this in itself may introduce bias.[20]

An alternative sampling method is the two-cohort design used for between-subjects comparisons.[20,23] This involves the examination of two groups of women, usually during two time periods, whose cervical cytology specimens have been examined using either the conventional or liquid-based (but not both) slide preparation technique.[20] Although the two-cohort design does not have an in-built comparison mechanism, it might be a fairer assessment of improved sensitivity, provided that the two cohorts are large enough and genuinely comparable.[20,23] This can be achieved through random allocation of sufficiently large groups of women to test conditions. Without randomization, one cannot be confident that the spectrum of

diseases is equivalent between women receiving each test, as may be the case, for example, if the ages of the women in the two arms of the trial differ significantly. Random recruitment is reported as a quality criterion in evidence tables for appraised trials in this review, although such biases are difficult to control.

1.3.2 Spectrum of disease in study population

Regardless of whether the trial's design is within-subject or between-subjects, comparability between reports or between centres in a multi-centre trial requires a detailed description of the population from which the women are drawn.[22,23] Depending on the prevalence of the disease in a population, there may be more cases of higher grade abnormalities, such as high-grade squamous intraepithelial lesions (HSIL) and cancer (Appendix 1), which are the most important outcomes for a test to detect.[29,30] Test sensitivity is likely to be higher and specificity lower in populations with a high prevalence of disease.[22] Thus, test parameters must be qualified as to whether they are applied to a general population (ordinary risk populations) or to a population of women identified as being at increased risk of cervical cancer (high risk populations).

1.3.3 Reference standard

A reference standard is a test that provides an accurate or "truth" diagnosis.[22] It is an independently applied test that is compared to the screening test being evaluated to verify sensitivity and specificity. Without a verification of positive and negative diagnoses, one cannot be sure that all test results represent accurate diagnoses: (that is positives are "true positives" and negatives are "true negatives").[22,23] Some of these diagnoses may represent "false-positives" (test results are positive in the absence of cervical abnormality) and "false-negatives" (test results are negative in the presence of cervical abnormality).

Whilst it is accepted that a reference standard in evaluating screening tests is needed, there has been debate about what is a valid standard. Detection of invasive or metastatic cancer is considered to be the gold standard, but this would require the use of a longitudinal study involving many women tested repeatedly over many years. Because of the time, expense and difficulty involved with a longitudinal study, an acceptable surrogate is histology. A key reason for this is that whereas the Pap smear, LBC and HPV testing are screening tests, a clinical diagnosis is based on biopsy confirmation, which is also used to form most treatment decisions.[22,30]

The lack of histological verification of test negatives is a limitation of the research conducted in this area.[21-23] The evaluation of asymptomatic women with negative test results is considered to be invasive and costly and it raises ethical and practical concerns. As a result, the use of colposcopy and histological follow-up is limited to women with positive diagnoses identified by alternative screening tests. The verification of only those who test positive is susceptible to bias, as a high frequency of histological abnormalities is included in the sample verified.[21,25,31,32] This bias can lead to elevated estimates of sensitivity and lowered estimates of specificity. Thus, these estimates should be considered to be relative.[21,22,25]

In the absence of histological verification, a consensus cytology review by an independent panel of two or more cytologists is considered to be a methodologically acceptable reference standard

in comparative trials of Pap smears with LBC.[21,22] Verification of positive and negative diagnoses, a reference standard and blind verification of test results are reported as quality criteria in evidence tables for appraised trials in this review.

1.3.4 Thresholds for reporting positive diagnoses

Cervical screening tests detect degrees of abnormalities. The choice of threshold at which Pap smears or liquid-based smears (at this level of abnormality or higher) are reported as positive (which also determines the levels below which smears are negative) is of crucial importance.[22,29,30] The progression of lower grade abnormalities to cancer is significantly reduced when compared with high-grade lesions (Appendix 1). Efforts to increase sensitivity are likely to decrease specificity, leading to an increase in the reporting of low-grade change. This requires further investigation for relatively benign lesions. As a result, the diagnosis of lower grade lesions has economic implications for cervical screening programs, as repeat smears and in some cases, colposcopies may be required.[6,20,22,23] Low-grade lesions also have psychological implications, as they may raise women's anxieties and cause them inconvenience.[6,20] Such impacts are important given the relatively high numbers of low-grade lesions compared with high-grade lesions. This review reports outcomes at three cytology thresholds for positive diagnoses using the 2001 Bethesda system nomenclature (Appendix 1).[29]

1.3.5 Industry funding

A final methodological issue in comparing trials relates to the investigators involved and the potential biases affecting their work. The financial stakes are high.[22,23] Many investigators were involved in developing the technologies and continue to play roles in the companies. Given the pressures associated in profit making, concerns have been raised about manufacturers exaggerating the effectiveness of technologies.[22,23] Thus, trials conducted on behalf of manufacturers or with their financial support may not be truly independent and systematic biases may exist. Given these concerns, a quality criterion used in this review, as was done in previous systematic reviews, describes the level of industry funding for research.

1.3.6 Testing for HPV

The introduction of HPV testing, in contrast to that of LBC, is a larger change, because it involves a new form of primary screening and follow-up testing. Thus, the appropriate level of evidence used to determine acceptance of this innovation exceeds that used for an innovation such as LBC. At issue for HPV testing are program parameters such as invasive cancer rates and cervical cancer mortality.[4,6] It is naive to assume that simple sensitivity, in terms of cytologic or histologic (colposcopic) reference standards, is adequate. For example, while HPV and Pap smears may have similar sensitivity rates, this does not mean that the same women will be found when either is used. The ultimately invasive and fatal cancers could occur in a different portion of the false-negative group. As a result, HPV validation requires program evaluation.

The evaluation of HPV testing in terms of histologic reference points can proceed along the same lines as that for LBC, with the same study methodology and rigour. The interpretation of the diagnostic test parameters, however, differs for program planning. HPV testing could be important in cervical cancer screening programs, because of HPV's central role in the

pathogenesis of squamous cell cancer.[4,6] Because the presence of HPV is a necessary although insufficient condition for the development of squamous cell cancer, a negative HPV test could preclude the need for squamous cytology testing. Testing for HPV could have three roles.

1) HPV test could be a regular adjunctive primary screening test to the Pap smear used to assess a woman's risk of developing cervical cancer over her lifetime. HPV status could be used to determine an appropriate screening interval for her. For example, if a woman is consistently HPV negative, the screening interval may be extended without increasing her risk of developing invasive cancer. In March 2003, the FDA approved the use of HPV as an adjunctive primary screening test with cytology for women aged 30 years and over, but not for use as a viral test in isolation.[33]

   A methodological issue that should be considered in this context is the bias of false gains in sensitivity as a result of combined testing.[25,31,32] A nominal increase in the baseline sensitivity of cytology can occur by chance when using adjunctive testing with HPV or other methods, even if the results of new test were random with respect to the disease being evaluated. Even a gain in sensitivity from the adjunct screening tests can lead to an unacceptable cost in specificity.[25,31]

2) HPV testing could be used in triage to improve the management of women with cervical abnormalities detected through screening, i.e., to avoid colposcopy and excessive follow-up if the woman is HPV negative.

3) HPV testing could be used in surveillance to determine whether treatment for cervical cancer has been successful.

2 THE ISSUE

Most jurisdictions in Canada are considering whether to adopt these new technologies for cervical cancer screening. In June 2002, at the national meetings of the Canadian societies for colposcopy, cytology and gynecologic oncology, CCOHTA was asked to provide a systematic review of the scientific evidence. Specifically requested was a systematic review of the diagnostic accuracy and comparative cost and cost-effectiveness of LBC and HPV testing. CCOHTA and the Cervical Cancer Prevention Network (CCPN) of Canada subsequently developed a coordinated national approach.

The findings from this CCOHTA review are to be presented at a national conference on cervical cancer screening held in Ottawa in November 2003. The primary purpose of this conference is to provide evidence-based recommendations regarding cervical cancer screening.

3 OBJECTIVES

A research protocol, written *a priori*, identified two primary objectives:

1) to evaluate the diagnostic accuracy of detecting precancerous or malignant cervical lesions by LBC and HPV testing in comparison to Pap smears.

2) to evaluate the comparative cost and cost-effectiveness of LBC and HPV testing.

A secondary objective is to review the status of cervical screening initiatives in Canada.

4 CLINICAL REVIEW: DIAGNOSTIC ACCURACY

4.1 Methods

4.1.1 Literature search strategy

Published literature was identified by searching several databases (Appendix 2). To update references obtained for the previous CCOHTA review,[18] retrieval was limited to 1997 onwards and where possible, the human population. There were no language restrictions. BIOSIS Previews®, CANCERLIT®, EMBASE®, MEDLINE® and PASCAL were searched on DIALOG®, with regular alerts and updates received throughout the project. Parallel searches were run on PubMed. The CD-ROM version of The Cochrane Library was also searched and updated as new issues arrived.

Grey literature was obtained through searching the web sites of health technology assessment and related agencies and their associated databases. Clinical trial registries were searched for information on completed and ongoing trials. The National Health Service's Cervical Cancer Screening Literature Database was also searched. Google™ and other Internet search engines were used to search for web-based materials. Further information was sought by manually searching the bibliographies of selected papers and through contacts with appropriate experts and agencies.

Reference Manager®, citation management software, was used in the pre-selection stage to manage the references obtained from PubMed and all DIALOG® databases. Separate databases were created to address each of the three project components: clinical, economic and program overview. Selected references were incorporated into one database for use during report-writing.

4.1.2 Selection criteria and method

a) Selection criteria

Study design

We included abstracts for the purpose of finding full study reports about comparative trials of diagnostic accuracy of LBC versus Pap smears and HPV testing versus Pap smears.

Population

The population in included trials consisted of women undergoing testing for primary screening and those being evaluated for previous cytologic abnormalities.

Types of intervention

The intervention group included women whose cervical smears were screened using LBC or HPV. The control group consisted of women being screened with the use of Pap smears.

The following two primary comparisons are made:

1) LBC versus Pap smears
2) HPV testing versus Pap smears.

Types of outcome measures
The primary outcomes are estimates of test sensitivity and specificity. Results are reported using the 2001 Bethesda system nomenclature (Appendix 1) at a cytology threshold of ASCUS and above (ASCUS+), LSIL and above (LSIL+), or HSIL and squamous cell carcinoma (HSIL+). For the comparison of LBC versus Pap smears, a secondary outcome is the proportion of unsatisfactory specimens reported.

b) Selection method

Two reviewers (HN and AB) independently reviewed citation titles and abstracts to determine which would be retrieved as full-text articles (Appendix 3). Disagreements about study inclusions were resolved by consensus between the two reviewers. The same reviewers also independently reviewed the full-text articles. Reference Manager® was used to record the study's objectives and reviewers' comments. New report formats allowed this information to be exchanged and consolidated electronically.

4.1.3 Data extraction-abstraction strategy

Once trials were included in the review, data were independently extracted by the same reviewers using a standard form for both clinical and economic reviews (Appendices 4, 5). The forms were developed while reviewing three reports that were identified through the feasibility assessment (one trial each on the two study comparisons[34,35] and one economic evaluation[36]).

4.1.4 Strategy for quality assessment

Quality assessment was done during data extraction (Appendix 4). Quality criteria are adapted from systematic reviews by McCrory (1999) for the Agency for Health Research and Quality in the US[22] and by Broadstock (2000) for New Zealand Health Technology Assessment.[23] Five criteria are used:

a) Recruitment

How was the study sample collected (random or not random)?

b) Verification

Was the decision to perform the reference standard independent of the test results (positives and negatives, positives and random fraction of negatives, positives and selected samples of negatives, positives only, none)? Trials were considered to be bias-controlled if verification was undertaken among all participants.[25] Trials that corrected for estimates, with verification in a random or select sample of test-negative women, were considered to be bias-adjusted.[25]

c) Reference standard

Was the test compared to a valid reference standard (histology-colposcopy or biopsy, independent review of test results by a panel of at least two cytologists)?

d) Blind verification

Was the test and reference standard measured independently (blind to each other) (yes, no, not reported)?

e) Industry support

What was the industry's role in the trial (none, not done or funded by industry; partial, some funding from industry to authors or to the project; total, done on behalf of industry)?

4.1.5 Data analysis methods

For data pooling, the outcomes from each trial were expressed as relative risks (RR) with 95% confidence intervals (95% CI). Results for each outcome were also reported as a range of values. In the presence of heterogeneity and depending on the number of trials identified, sensitivity analyses were undertaken using varying patient and intervention characteristics. Statistical analysis was performed using Review Manager version 4.1 software. Where data pooling was considered to be inappropriate (e.g., a few trials had sufficient data for computing the actual numbers of participants with positive or negative test results), a range of values were used to do a simple computation for each outcome.

4.2 Results

4.2.1 LBC versus Pap smears

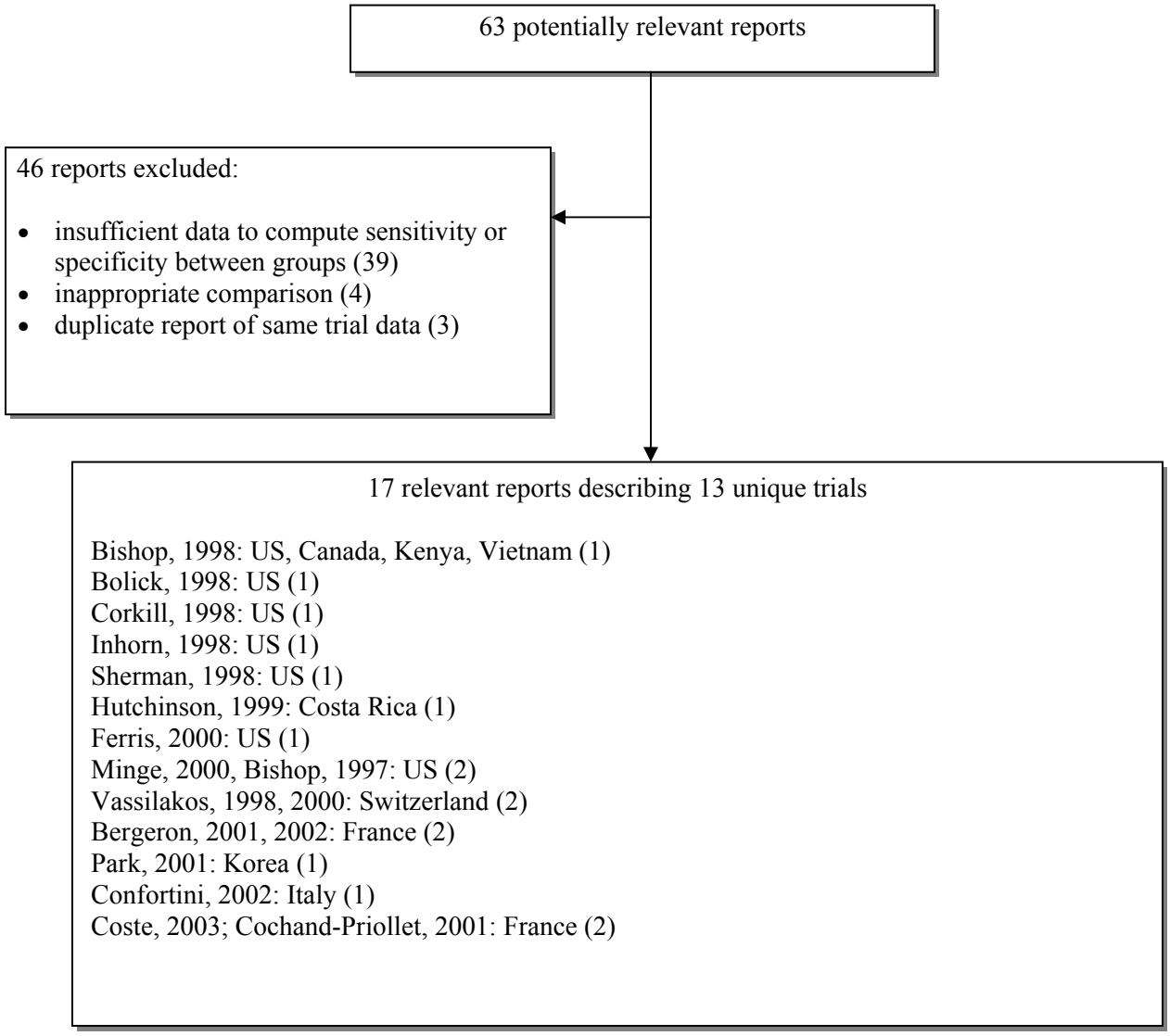
a) Quantity of research available

Of the 63 reports retrieved on the diagnostic accuracy of LBC versus Pap smears; 17 reports on 13 unique trials meet the selection criteria[34,37-52] and 46 do not (Appendix 6). The flow chart for selection is shown in Figure 1.

b) Trial characteristics

All 13 trials report on sensitivity rates and six report on specificity.[37,38,43,44,49,51] The 13 trials are conducted in nine countries: US (n=6), France (n=2), one trial each in Costa Rica, Italy, Korea and Switzerland. There is one multi-centre trial recruiting women in four countries (Canada, Kenya, US and Vietnam) (Figure 1). Four trials are reported in multiple publications: preliminary results[45,47] and follow-up results[44,46] using a larger group of women from the same in two trials were reported in two publications; similar results from one trial by Bergeron *et al.* of France were reported in an abstract[48] and in a full publication;[34] and the protocol (2001) and analysis (2003) of the trial by Coste *et al.* from France were reported in two publications.[51,52]

Figure 1: Flow chart of selected reports



The trial characteristics are summarized in Table 1. Details of the 13 trials are shown in Appendix 7. None of the trials randomize patients to either LBC or Pap smears. Instead, all trials use an observational design, with over 75% using a split-sample design. Seven trials report on participants' ages, which range from 10 to 87 years, with three reporting the median age between 25 to 44 years.[38,47,51]

Table 1: Summary of trial characteristics

Parameter		Number of trials (n=13)
LBC technique	ThinPrep AutoCyte	9 4
Study design	Split-sample Two-cohort	10 3
Spectrum of subjects	Ordinary risk populations High-risk populations Both types of populations	5 7 1
Verification	Positives and negatives Positives and random or selected negatives Positives only	4 2 7
Reference standard	Histology Panel review by two or more cytologists Histology and panel review	10 2 1
Positive threshold	LSIL+ Invasive cancer	12 1
Industry funding	Total support Partial support No support	4 4 5

Over two-thirds of trials report on ThinPrep (Table 1). Five trials report on routine-screen (ordinary risk) populations (38.5%) and seven on high risk populations (54%). The trial by Coste (2003) covers both types of populations.[51] The recruitment of participants is rarely described and is assumed to be non-random in all but two trials.[42,46] Seven trials include the histological verification of only those who test positive (Table 1).[37,38,40,42-44,46] Two trials on ordinary risk populations include verification by a panel review of all those who test positive and a random 5% of those who test negative.[39,41] The remaining four trials include a verification of disease status among all participants; three trials on high risk populations (referrals for colposcopy and[50] cone biopsy[34] or a population with a large proportion of patients with abnormal cervical abnormalities[49]) and the trial by Coste (2003) on both types of populations.[51]

Ten trials use histology as their reference standard and two trials use a panel review by two or more cytologists (Table 1).[39,41] The trial by Hutchinson (1999) uses a histology and a cytology review.[42] The primary outcome in most trials is a cytologic diagnosis of LSIL+; the outcome reported by Inhorn (1998) is biopsy-based invasive cervical cancer in 47 cases.[40] Total or partial industry support is present in eight trials (61.5%).[37,39-44,49] Ten trials (77%) report the blinding of outcome assessors.[34,37,39-42,44,49-51]

c) Data analyses and synthesis

Sensitivity

Eleven of 13 trials have enough data for a meta-analysis of sensitivity; collectively, these trials examined 4,406 samples of cervical cells.[34,37-43,46,49,50] These consist of nine trials that use histology as the reference standard. The trial by Hutchinson (1999), even though it uses a histology and a cytology review, is included in the analysis of trials using histology, as over 90% of cases had histological verification.[42] The sensitivity ranges for LBC and Pap smears are 53% to 96% and 34.5% to 94% respectively. The meta-analysis shows that LBC is associated with an 11% improvement in sensitivity over Pap smears (RR 1.11 95% CI 1.03; 1.20) (Figure 2). A random effects model is used for the pooled estimate of sensitivity, as there is heterogeneity among the trials according to the chi-square statistic derived in the fixed effects model ($p<0.00001$). The presence of funnel plot asymmetry for sensitivity across the 11 trials is evidence of publication bias (Figure 3).

Figure 2: Forest plot of pooled estimates for sensitivity of LBC versus Pap smears

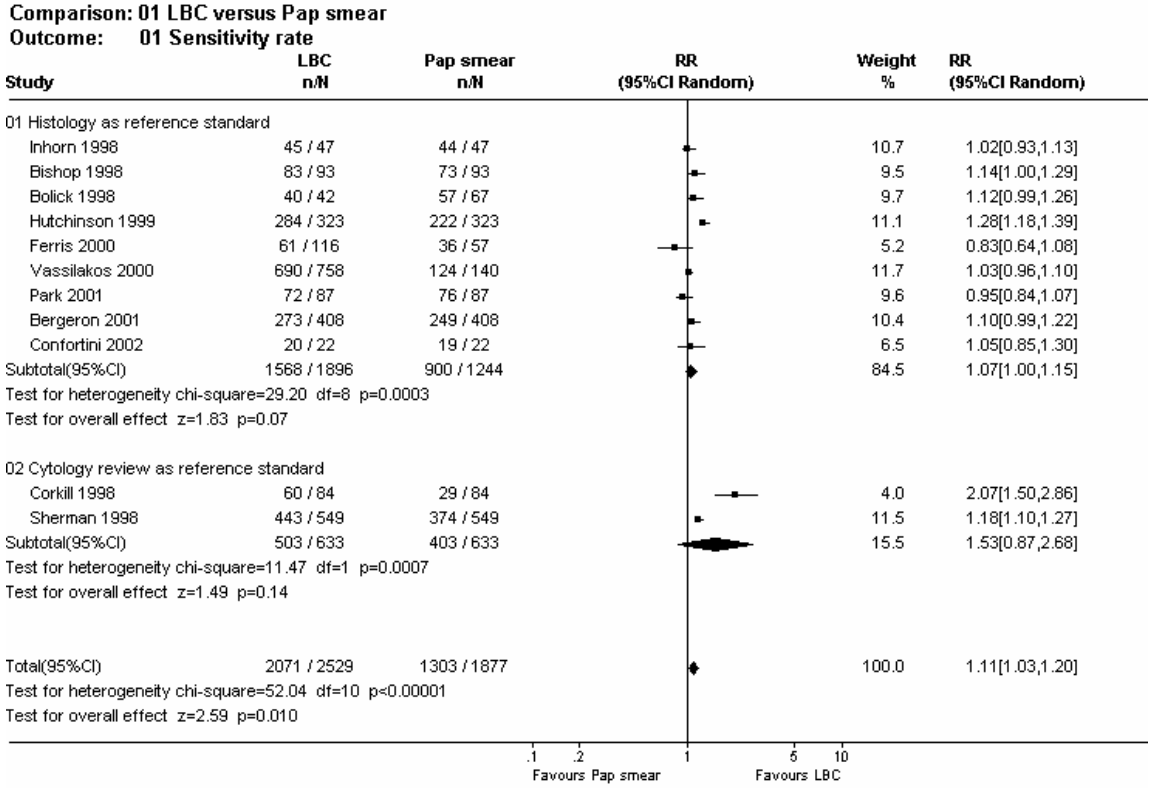
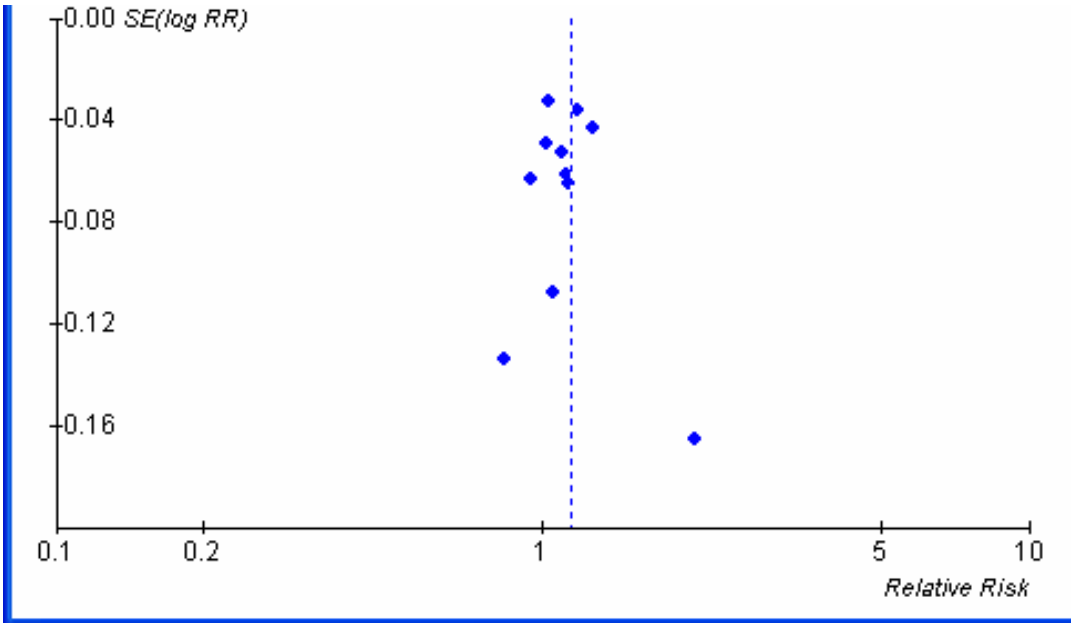


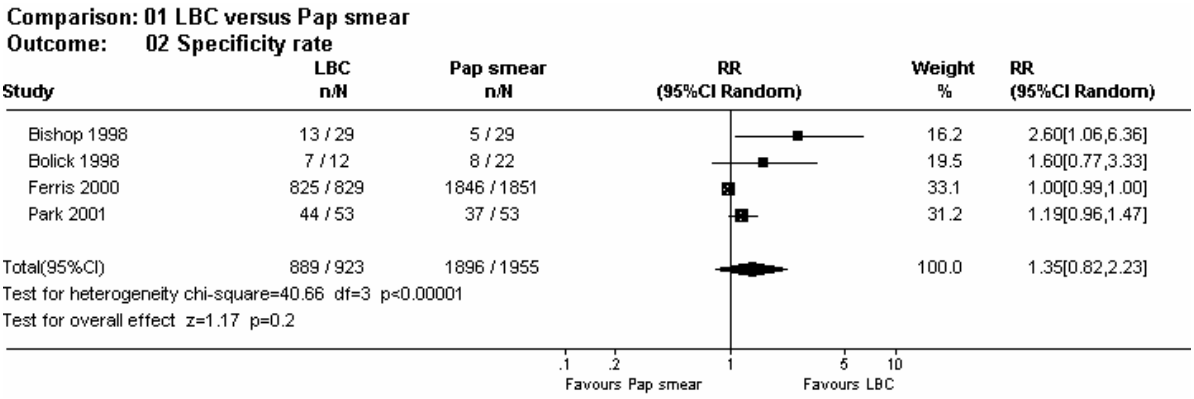
Figure 3: Funnel plot reporting on sensitivity for LBC versus Pap smears (n=11)



Specificity

Four of six trials have enough data for a meta-analysis of specificity; these trials examined 2,878 samples.[37,38,43,49] All trials use histology as a reference standard. The specificity ranges for LBC and Pap smears are 45% to 99.5% and 17% to 99.7% respectively. Pooled results indicate no significant difference in specificity between LBC and Pap smears (RR 1.35 95% CI 0.82; 2.23) (Figure 4). A random effects model is used for the pooled estimate for specificity, as there is heterogeneity among the trials according to the chi-square statistic derived in the fixed effects model ($p<0.00001$).

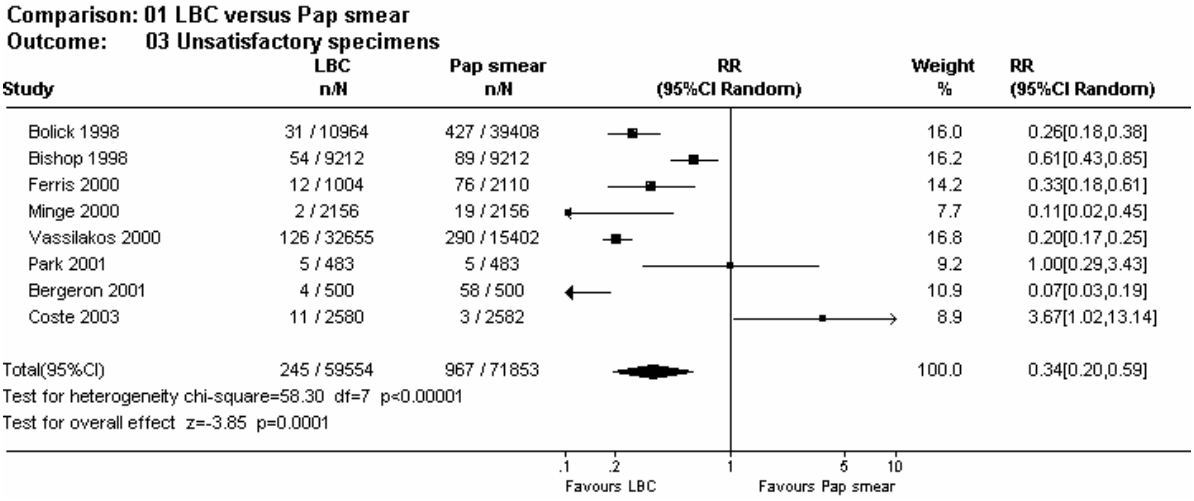
Figure 4: Forest plot of pooled estimates for specificity of LBC versus Pap smears



Unsatisfactory specimens

Eight trials report on the rate of unsatisfactory specimens for evaluation.[34,37,38,43,44,46,49,51] All eight have enough data for a meta-analysis of unsatisfactory specimens; these trials examined 131,407 samples. The rates of unsatisfactory specimens range from 0.1% to 1% for LBC and 0.1% to 12% for Pap smears. A lower rate of unsatisfactory specimens is observed with LBC compared to Pap smears (RR 0.34 95% CI 0.20; 0.59) (Figure 5). A random effects model is used as there is heterogeneity between trials, according to the chi-square statistic derived in the fixed effects model ($p<0.00001$).

Figure 5: Forest plot of pooled estimates for unsatisfactory specimens



Sensitivity analyses

Sensitivity analyses were used to test the influence of the population being screened (ordinary versus high risk), LBC technique (ThinPrep versus AutoCyte Prep), type of study design (split-sample versus two-cohort) and verification bias on the sensitivity and specificity rates of LBC and Pap smears. The impact of LBC technique and type of study design on the rate of inadequate specimens was also assessed.

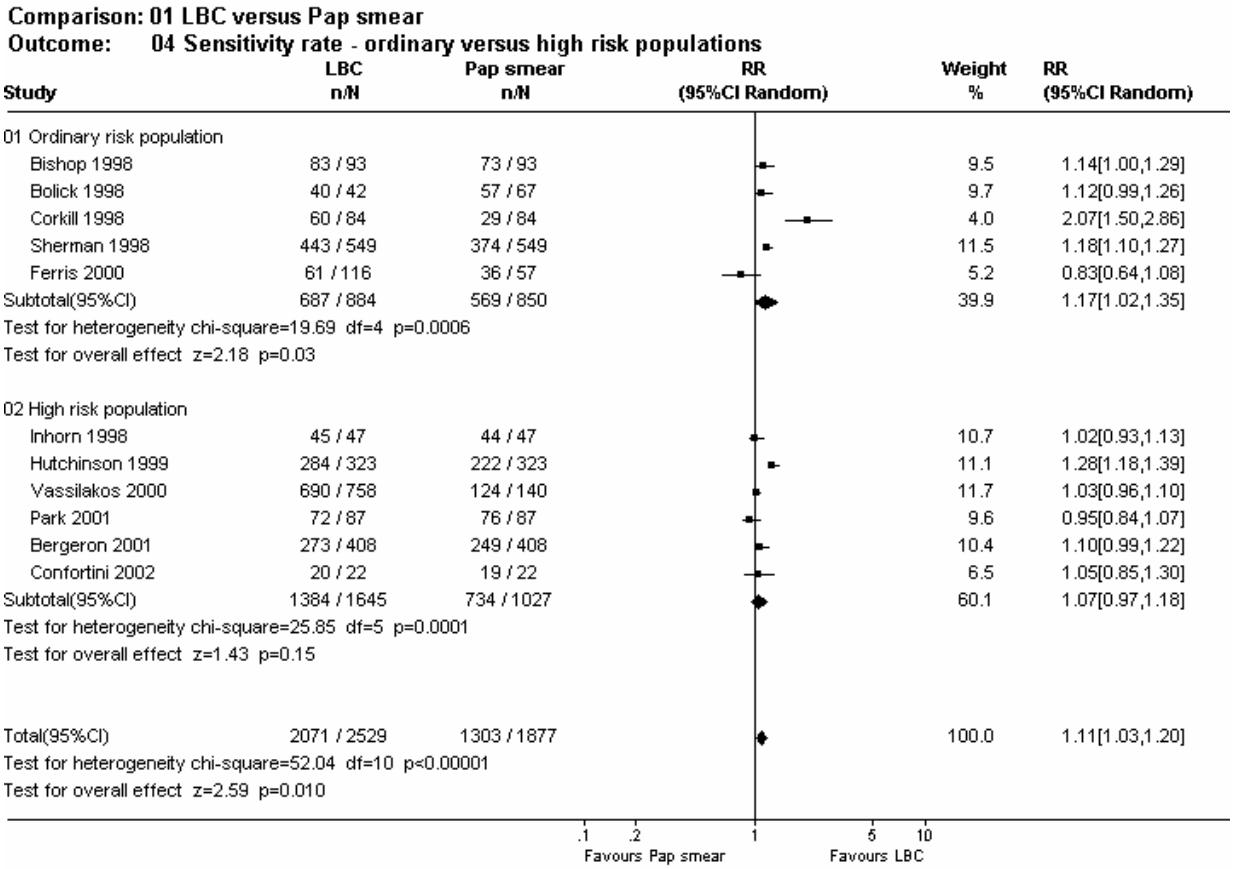
Sensitivity

Figure 6 differentiates the 11 trials that compare alternative screening strategies in ordinary populations and in high risk populations. The five trials based on screening ordinary populations show a statistically significant RR for sensitivity of 1.17 (95% CI 1.02; 1.35),[37-39,41,43] whilst the analysis of high risk populations in six trials shows an insignificant RR of 1.07 (95% CI 0.97; 1.18).[34,40,42,46,49,50] No differences are observed in sensitivity rates between groups based on LBC technique (eight trials on ThinPrep, RR 1.12 95% CI 1.00; 1.26,[38-43,49,50] and three trials on AutoCyte Prep, RR 1.07 95% CI 1.00; 1.14).[34,37,46]

The eight trials based on the split-sample study design show a statistically significant RR for sensitivity in favour of LBC over Pap smears of 1.15 (95% CI 1.04; 1.26).[34,37,39-42,49,50] The analysis in three trials using the two-cohort design reveals an insignificant RR of 1.03 (95% CI 0.91; 1.06).[38,43,46]

Three trials (27%) included in the meta-analysis of sensitivity have histological verification of positive and negative LBC and Pap smear test results.[34,49,50] These trials are based on screening for high risk populations and represent half of the trials in this category. The remaining three trials on high risk populations include verification for only those who test positive. There is no difference in sensitivity between LBC and Pap smear in this group of trials with verification of positives and negatives (RR 1.03 95% CI 0.93; 1.15) when compared to the overall analysis on high risk populations (Figure 6).

Figure 6: Forest plot for sensitivity in ordinary versus high risk populations



Specificity

No significant differences are observed in specificity rates across the four trials between LBC and Pap smears based on either type of population being screened (three trials on ordinary risk populations, RR 1.00 95% CI 0.98; 1.02,[37,38,43] and one trial by Park (2001)[49] on a high risk population, RR 1.19 95% CI 0.96; 1.47) or type of study design (two split-sample trials, RR 1.59 95% CI 0.69; 3.65[37,49] and two two-cohort trials, RR 1.00 95% CI 0.99; 1.01).[38,43]

The three trials based on the ThinPrep technique show no difference in specificity between LBC and Pap smears (RR 1.00 95% CI 0.98; 1.02).[38,43,49] The trial by Bishop (1998)[37] on AutoCyte Prep reports a significant difference between the two groups (RR 2.60 95% CI 1.06; 6.36). One

trial by Park (2001), which controlled for verification bias on high risk populations, reports estimates of specificity with no significant difference between LBC and Pap smears (RR 1.19 95% CI 0.96; 1.47).[49]

Unsatisfactory specimens

Figure 7 differentiates the eight trials that compare alternative screening strategies based on LBC technique. The four trials on ThinPrep show an insignificant RR of 0.62 for the rate of unsatisfactory specimens (95% CI 0.25; 1.57),[38,43,49,51] whilst analysis of the four trials on AutoCyte Prep shows a statistically significant RR of 0.20 (95% CI 0.09; 0.47).[34,37,44,46]

Figure 7: Forest plot of unsatisfactory specimens for ThinPrep versus AutoCyte Prep

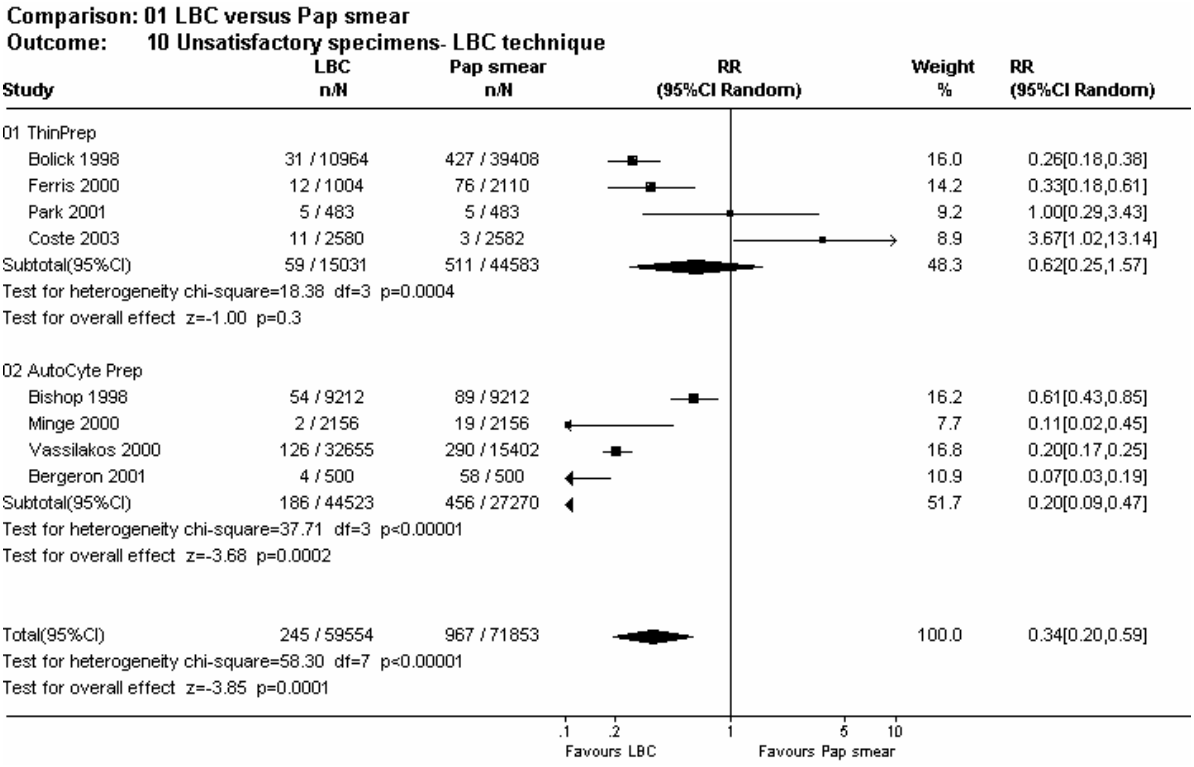
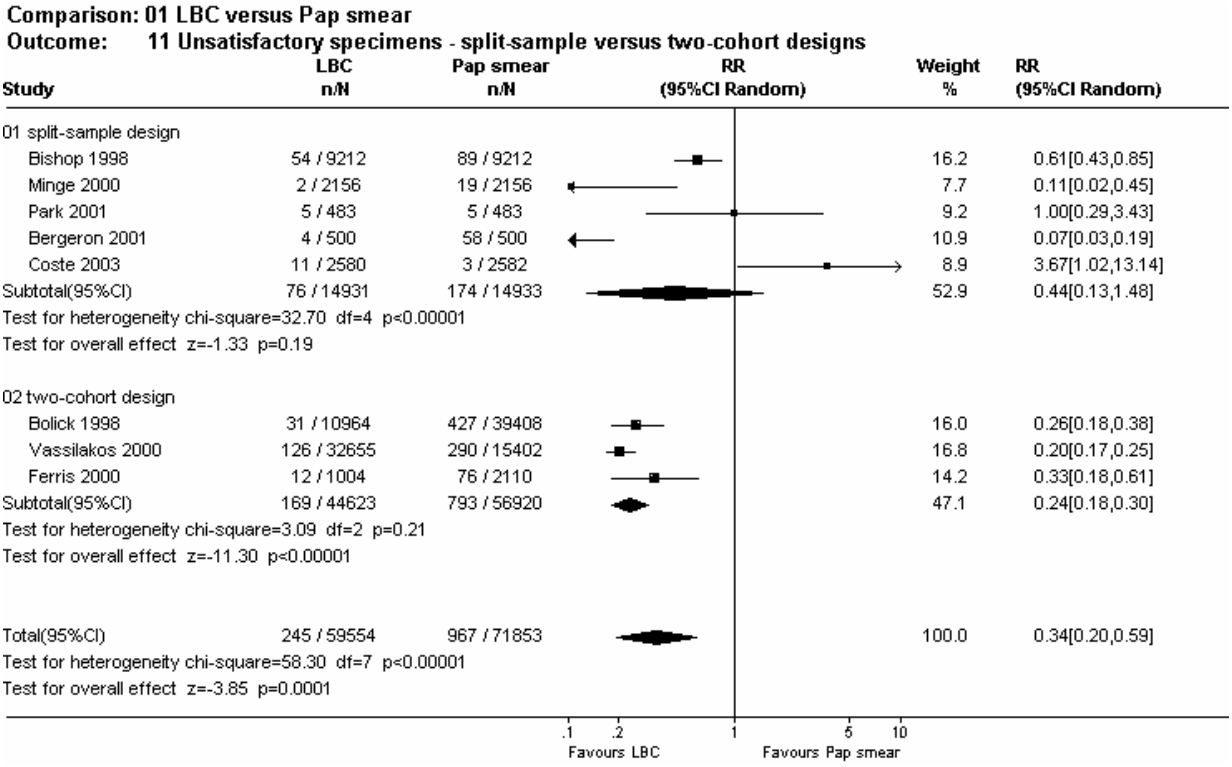


Figure 8 differentiates the eight trials based on study design. The five trials using the split-sample design show an insignificant RR of 0.44 for the rate of unsatisfactory specimens with variability across trials (95% CI 0.13; 1.48).[34,37,44,49,51] Analysis of the three trials using the two-cohort design shows a statistically significant RR of 0.24 (95% CI 0.18; 0.30).[38,43,46]

Figure 8: Forest plot of unsatisfactory specimens for split-sample versus two-cohort designs



d) Summary

Thirteen unique trials meet the selection criteria for the comparison of LBC versus Pap smears. These trials are undertaken in nine countries: six trials in the US; two in France; one trial each in Costa Rica, Italy, Korea and Switzerland; and one multi-centre trial recruiting women in Canada, Kenya, US and Vietnam. The age of participants ranges from 10 to 87 years. Of these 13 trials, 10 use a split-sample design (77%) and nine compare ThinPrep (69%) to Pap smears. Seven trials report on high risk populations, five on ordinary risk populations and one on both populations. Total or partial industry support is indicated for eight trials (61.5%).

Sensitivity

- Eleven trials (n=4,406 samples) are included in the meta-analysis of sensitivity for LSIL+ lesions. The aggregate RR (1.11, 95% CI 1.03; 1.20) shows an improvement in sensitivity of 11% for LBC in comparison to Pap smears. The sensitivity ranges are 53% to 96% and 34.5% to 94% respectively.
- In the analysis on screening ordinary populations, there is a statistically significant RR of 1.17 for sensitivity (95% CI 1.02; 1.35); in the analysis on high risk populations, there is an insignificant RR of 1.07 (95% CI 0.97; 1.18).
- Trials using the split-sample design (n=8) report a statistically significant benefit in sensitivity rates for LBC in comparison to Pap smears.

Specificity

- The meta-analysis of four trials on specificity shows no significant difference between LBC and Pap smears (RR 1.35 95% CI 0.82; 2.23), where the specificity ranges are 45% to 99.5% and 17% to 99.7% respectively.

Unsatisfactory specimens

- Eight trials (n=131,407 samples) report on the rate of unsatisfactory specimens used for evaluation. The aggregate RR is 0.34 (95% CI 0.20; 0.59), where the rates of unsatisfactory specimens for LBC and Pap smears range from 0.1% to 1% and 0.1% to 12% respectively.
- In the sensitivity analysis on ThinPrep trials, there is an insignificant RR of 0.62 for the rate of unsatisfactory specimens (95% CI 0.25; 1.57); in the analysis on AutoCyte Prep trials, there is a statistically significant RR of 0.20 (95% CI 0.09; 0.47).
- Trials using the two-cohort design (n=3 trials) report a significant reduction in unsatisfactory specimens for LBC in comparison to Pap smears (RR 0.24 95% CI 0.18; 0.30).

4.2.2 HPV testing versus Pap smears

a) Quantity of research available

We retrieved 83 reports on HPV testing versus cytology; 30 reports reporting on 22 unique trials met the selection criteria[35,51-79] and 53 did not (Appendix 6). The flow chart for selection is shown in Figure 9.

The ALTS (ASCUS/LSIL Triage Study), published to date in six reports, is an excluded trial that does not meet the selection criteria for this review (Appendix 6). Participants in the control-cytology triage arm had slides prepared by ThinPrep and not by Pap smear. Given the significance of the ALTS for cervical cancer screening, its key findings are summarized in Appendix 8.

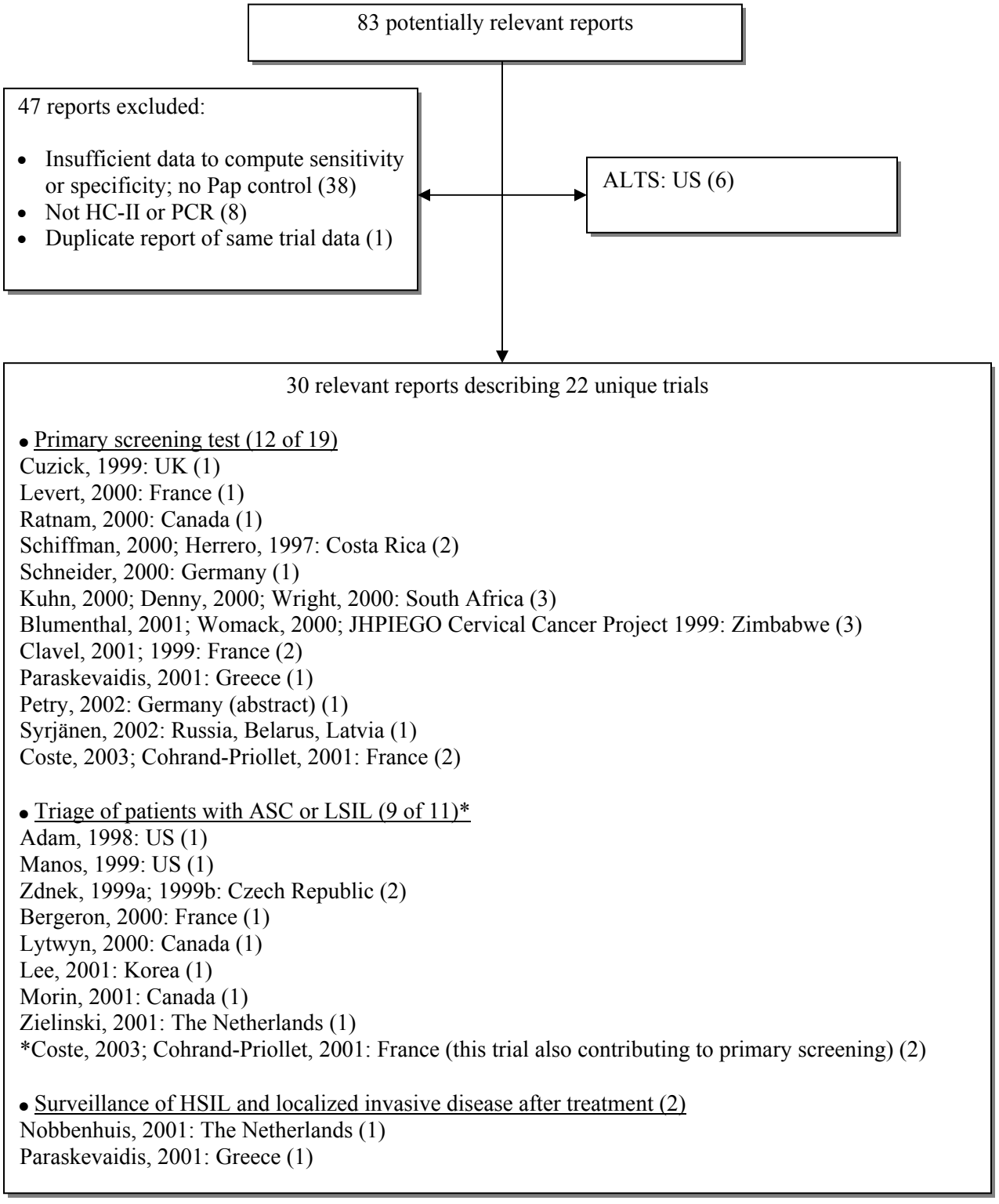
b) Trial characteristics

The 22 trials consist of 12 that use HPV testing for primary screening, nine for triage of patients with ASCUS+, and two for surveillance of CIN after treatment. The trial by Coste (2003) reports on data regarding HPV testing used for primary screening and triage.

HPV testing as a primary screening test

The 12 trials on primary screening are undertaken in 11 countries: three trials in France; two in Germany with one by Petry (2002) reported in abstract form; one trial each in Canada, Costa Rica, Greece, South Africa, the UK and Zimbabwe; and one multi-centre trial recruiting participants in Belarus, Latvia and Russia (Figure 9). Four trials are reported in multiple publications (The trial by Coste *et al.* from France is reported in two publications, as described in the comparison of LBC versus Pap smears.)

Figure 9: Flow chart of selected reports



- The trial by Clavel *et al.* from France (n=7,932) is reported in two publications: Clavel *et al.* report the preliminary results (n=1,518) in 1999[59] and the follow-up results from the same population in 2001.[35]

- The trial by Wright *et al.* from South Africa (n=2,944) is reported in three publications. Denny *et al.* (2000) report their analysis, which compares the Pap smear to HPV testing using HC I.[66] Kuhn *et al.* (2000) use both the first generation HC test (HC-I) and HC-II.[65] Wright *et al.* (2000) use HC-II alone on a subset (n=1,415) of the same population.[64]

- The trial by Schiffman *et al.* from Costa Rica (n=8,554) is reported in two publications. Herrero *et al.* (1997) report the trial design and methods.[63] Schiffman *et al.* (2000) report the analysis.[62]

- The trial by Blumenthal *et al.* from Zimbabwe (n=10,934) is reported in three publications. The first publication reports the test qualities of visual inspection with acetic acid for cervical cancer screening (n=2,203).[54] Womack *et al.* (2000) report on the qualities of HPV testing (n=2,140)[68] and Blumenthal *et al.* (2001) report on the diagnostic accuracy of these methods compared to Pap smears (n=2,073).[67]

Table 2: Summary of trial characteristics using HPV testing for primary screening

Parameter		**Number of trials (n=12)**
Comparison	HPV testing alone versus Pap smears HPV testing and Pap smears versus Pap smears	12 (4)
Spectrum of subjects	Ordinary risk populations High risk populations	12 0
HPV technique Other	HC-II PCR HC-I and HC-II	9 3* 1
Verification	Positives and negatives Positives and random/selected negatives Positives only Other	2 3 6 1
Reference standard	CIN 1 CIN 2/3	0 12
Positive threshold	ASCUS+ LSIL+ HSIL(+)	2 6 4
Industry funding	Total support Partial support No support Not reported	0 1 9 2

*The trial by Cuzick (1999)[57] includes separate analyses by HC-II and PCR for HPV testing.

The trial characteristics are summarized in Table 2 and the details for the 12 trials appear in Appendix 9. None of these trials randomize participants to have their cervical samples analyzed with HPV testing or Pap smears. All trials report on participant age, which ranges from 15 to 85 years, with a mean age across nine trials of 36 years.

All 12 trials compare HPV testing alone to Pap smears. Four of these (33%) compare combined HPV testing and Pap smears to Pap smears.[55,58,61,67] All trials involve comparisons in ordinary risk populations; the trial by Coste (2003) uses HPV testing in ordinary populations as a primary screening test and in high risk populations for the triage of participants with HSIL.[51] Ten trials use HC-II for HPV testing (Table 2): nine use HC-II alone[35,51,53,56-58,62,64,67] and the trial by Ratnam (2000) uses HC-I and HC-II during the trial period (November 1996 to August 1998) with the former method used to test participants until September 30, 1997.[61]

The recruitment of participants is rarely described, so it is assumed to be non-random in all but one trial by Schiffman (2000).[62] Six trials either controlled (two trials in which all of the women underwent colposcopy by design)[51,67] or adjusted (four trials in which the results from a random or selected fraction of women with negative screening tests were extrapolated to those without colposcopic verification) (Table 2) for verification bias.[56,60-62] The reference standard in all trials is a histologic outcome of CIN 2/3. The primary smear abnormality in six trials (50%) is a diagnosis of LSIL+.[55,57,60,61,64,67] Eight trials report on the blinding of outcome assessors.[51,55-57,60,62,64,67] Partial industry support is indicated in the trial by Schiffman (2000) (Table 2).[62]

HPV testing as a triage test

The nine trials on triage are undertaken in six countries: two trials each in Canada, France and the US and one trial each in the Czech Republic, Korea and the Netherlands (Figure 9). The trial by Zdenek *et al.* from the Czech Republic reports similar results in two publications [in Czechoslovakian (1999)[77] and in English (1999)[76]].

The trial characteristics are summarized in Table 3. Details for the nine trials appear in Appendix 9. Eight trials report on participant age which ranges from 15 to 85 years, with a mean age, across six trials of 36 years.[51,69,70,73,74,76]

All nine trials compare HPV testing alone to Pap smears. Four of these (44%) compare combined HPV testing and Pap smears to Pap smears alone.[69,71,72,76] All trials involve comparisons in high risk populations. Eight trials use HC-II: seven use HC-II alone[51,69,70,72-74,76] and one trial uses HC-II and PCR.[71] The recruitment of participants is described as random in one trial by Lytwyn (2000).[70] Verification bias is controlled or adjusted in all nine trials (Table 3). The reference standard in all trials is a histologic outcome of CIN 2 or higher. All trials use HPV testing for the triage of Pap smear results of ASCUS+. Four trials report on the blinding of outcome assessors.[51,69,70,72] Partial industry support is indicated in Manos (1999)[73] and Bergeron (2000) (Table 3).[69]

Table 3: Summary of trial characteristics using HPV testing for triage

Parameter		Number of trials (n=9)
Comparison	HPV testing alone versus Pap smears HPV testing and Pap smears versus Pap smears	9 (4)
Spectrum of subjects	Ordinary risk populations High risk populations	0 9
HPV technique Other	HC-II PCR HC-II and PCR	7 1 1
Verification	Positive and negatives Positives and random or selected negatives Positives	8 1 0
Reference standard	CIN1 CIN 2/3	0 9
Positive threshold	ASCUS+ LSIL+ HSIL(+)	4 2 3
Industry funding	Total support Partial support No support Not reported	0 2 6 1

HPV testing as a surveillance test

The two trials that were identified for this review examine the role of HPV testing alone versus that of repeat Pap smears for the surveillance of CIN after treatment. The trial by Nobbenhuis (2001) is a prospective analysis undertaken in the Netherlands[79] and that by Paraskevaidis (2001) in Greece is a retrospective analysis.[78] Both trials use PCR for HPV testing and both report the mean age of participants as 34 years. The recruitment of participants is non-random in both trials. In the trial by Nobbenhuis (2001), outcome assessors are blinded. Verification bias is controlled for in the trial by Paraskevaidis (2001). Details of the characteristics for the two trials appear in Appendix 9.

c) Data analyses and synthesis

A meta-analysis of sensitivity and specificity rates was impossible as few trials had enough data for computing the numbers of participants with positive or negative test results. Most trials reported sensitivity and specificity rates as percentages (Appendix 9).

HPV testing as a primary screening test
HPV testing alone versus Pap smears

Table 4: Primary screening trials using HC-II or PCR with histologic CIN 2/3 as an outcome

Positive Threshold	Sensitivity (% range); n=12 trials		Specificity (% range); n=11 trials	
	HPV testing	Pap smears	HPV testing	Pap smears
ASCUS+; n=2	88 to 98	42 to 78	89 to 96	94 to 98
LSIL+; n=6	68 to 95	20 to 89	61 to 97*	87 to 99*
HSIL(+); n=4	96 to 100	60 to 86	16 to 87	89 to 99

*From five trials.

All 12 trials report on sensitivity rates comparing HPV testing alone to Pap smears for primary screening with a histologic outcome of CIN 2/3. The overall sensitivity range of HPV testing across 12 trials is 68% to 100%. For Pap smears, it is 20% to 89% (Table 4). All trials using HC-II report a higher sensitivity of HPV testing in comparison to Pap smears. Two trials using PCR also report the higher[60] or similar[55] sensitivity rates of HPV testing in comparison to Pap smears. All 11 trials reporting on specificity show lower rates of HPV testing (16% to 97%) in comparison to Pap smears (87% to 99%) (Table 4). The ranges of sensitivity and specificity of HPV testing across six trials that controlled or adjusted for verification bias are 68% to 98% and 61% to 96% respectively. For Pap smears, the respective rates are 20% to 78% and 91% to 99%.

HPV testing and Pap smears versus Pap smears
The sensitivity range of combined HPV testing and Pap smears across four trials is 43% to 96% and that of Pap smears is 27% to 89%. The specificity range of combined testing across three trials is 17% to 91% and that of Pap smears is 89% to 96%.[58,61,67]

HPV testing as a triage test
HPV testing alone versus Pap smears

Table 5: Triage trials using HC-II or PCR with histologic CIN 2/3 as outcome

Positive Threshold	Sensitivity (% range); n=9 trials		Specificity (% range); n=8 trials	
	HPV testing	Pap smears	HPV testing	Pap smears
ASCUS+; n=4	67.5 to 88	56 to 93	35 to 67	31 to 62
LSIL+; n=2	89.5 to 96	56 to 74	59 to 60	63 to 76
HSIL(+); n=3	66 to 89	35 to 85	50 to 66	92*

*From two trials that report similar rates.

All nine trials report on sensitivity rates comparing HPV testing alone to Pap smears for triage with a histologic outcome of CIN 2/3. The overall sensitivity range of HPV testing across nine trials is 66% to 96% and that of Pap smears is 35% to 93% (Table 5). Eight trials report a higher sensitivity of HPV testing (six on HC-II and two on PCR) in comparison to Pap smear. The overall specificity range of HPV testing across eight trials is 35% to 67% and that of Pap smears is 31% to 92% (Table 5). Seven trials report a lower specificity of HPV testing (six trials on HC-II and one trial on PCR) in comparison to Pap smears.

HPV testing and Pap smears versus Pap smears

The sensitivity range of combined HPV testing (using HC-II) across four trials is 83% to 95% and that of Pap smears alone is 35% to 93%. The respective specificity rates are 29% to 73% and 31% to 92%. Three trials report higher sensitivity and lower specificity with combined testing in comparison to Pap smears alone. Lee (2001) reports a similar sensitivity between the two groups (93%)[72] and Morin (2001) reports a higher specificity with combined testing using HC-II and Pap smears (73%), but not with PCR and Pap smears (58%) in comparison to Pap smears alone (63%).[71]

HPV testing as a surveillance test

Paraskevaidis (2001), using a histologic outcome of CIN 1+, reports sensitivity and specificity rates of 93% and 84% for HPV testing and 49% and 87% for Pap smears, at four months post-treatment.[78] Nobbenhuis (2001), using a histologic outcome of CIN 2/3, also reports higher sensitivity rates of HPV testing in comparison to Pap smears for up to a year of follow-up. An equivalent sensitivity rate between groups, however, is reported at two years (93%).[79] An inverse trend is observed for specificity with respect to follow-up, i.e., in comparison to Pap smears, there are lower rates for HPV testing at three months (86% versus 91%) and higher rates at two years (99% versus 96%).[79]

d) Summary

Twenty-three unique trials meet the selection criteria for the comparison of HPV testing versus Pap smears. These consist of 12 trials using HPV testing as a primary screening test, nine trials as a triage of patients with ASCUS+ (with one trial also contributing to primary screening) and two trials as surveillance of CIN after treatment. For trials on primary screening and triage, the mean age of participants is 36 years (range 15 to 85 years) and the reference standard is a histologic outcome of CIN 2 or higher.

Primary screening

The 12 trials on primary screening are undertaken in 11 countries: three trials in France; two in Germany; one trial each in Canada, Costa Rica, Greece, South Africa, the UK and Zimbabwe; and one multi-centre trial recruiting participants in Belarus, Latvia and Russia. All trials compare HPV testing alone to Pap smears and four (33%) compare adjunctive testing with Pap smears. Ten trials use HC-II and two trials use PCR for HPV testing. Verification bias is controlled or corrected for in six trials (50%). The primary smear abnormality in two trials is a diagnosis of ASCUS+; in six trials, a diagnosis of LSIL+; and in four trials, HSIL+. Partial industry support is indicated in one trial.

- The overall sensitivity range of HPV testing across 12 trials is 68% to 100% and that of Pap smears is 20% to 89%. All trials using HC-II report a higher sensitivity of HPV testing in comparison to Pap smears. The respective ranges across six trials that controlled or adjusted for verification bias are 68% to 98% and 20% to 78%.

- All 11 trials reporting on specificity show lower rates of HPV testing (16% to 97%) in comparison to Pap smears (87% to 99%). The respective ranges across six trials that controlled or adjusted for verification bias are 61% to 96% and 91% to 99%.

- The sensitivity range of combined HPV testing and Pap smears across four trials is 43% to 96% and that of Pap smears is 27% to 89%. The specificity range of combined testing across three trials is 17% to 91% and that of Pap smears is 89% to 96%.

Triage

The nine trials on triage are undertaken in six countries: two trials each in Canada, France and the US; and one trial each in the Czech Republic, Korea and the Netherlands. All trials compare HPV testing alone to Pap smears for the triage of ASCUS+. Four of these trials (44%) compare adjunctive testing with Pap smears. Eight trials use HC-II. Verification bias is controlled or adjusted for in all trials. The primary smear abnormality in four trials is a diagnosis of ASCUS+; in two trials, a diagnosis of LSIL+; and in three trials, HSIL+. Partial industry support is indicated in two trials.

- The overall sensitivity range of HPV testing across nine trials is 66% to 96% and that of Pap smears, is 35% to 93%. Eight trials report a higher sensitivity of HPV testing (six on HC-II and two on PCR) in comparison to Pap smear.

- The overall specificity range of HPV testing across eight trials is 35% to 67% and that of Pap smears is 31% to 92%. Seven trials report a lower specificity of HPV testing (six trials on HC-II and one trial on PCR) in comparison to Pap smears.

- The sensitivity range of combined HPV testing (using HC-II) across four trials is 83% to 95% and that of Pap smears alone is 35% to 93%. The respective specificity rates are 29% to 73% and 31 to 92%. Three trials report a higher sensitivity and lower specificity with combined testing in comparison to Pap smears alone.

Surveillance

- There is insufficient evidence on the comparative sensitivity and specificity of HPV testing for surveillance.

5 REVIEW OF ECONOMIC STUDIES

5.1 Methods

A protocol was written *a priori* and followed throughout the review process.

5.1.1 Literature search strategy

The economic search strategy was patterned after the clinical search strategy (Appendix 2). Instead of a clinical trial and test quality filter, an economic filter was used. All sources consulted for the clinical search were also consulted for the economic search. In addition, the CD-ROM version of Health Economic Evaluations Database (HEED) was searched and updated as new issues arrived (Appendix 2).

5.1.2 Selection criteria

An economic study was eligible for inclusion if it met each of the criteria described below:

a) Study design

- a full economic evaluation (comparative analysis of the costs and consequences of alternative courses of action) that included cost benefit studies (consequences measured in dollars), cost-effectiveness studies (consequences measured in natural units), cost utility studies (consequences measured in derived units such as quality adjusted life years) and cost minimization studies (with proof that the intervention and comparator are equally effective)[80]

  or

- a comparative cost study examining costs at the micro level.

b) Population

- as in the clinical review.

c) Intervention/Comparator

- as in the clinical review.

d) Primary outcomes

- outcomes presented as an incremental measure of the implication of moving from the comparator to the intervention, i.e., an incremental cost effectiveness ratio or an incremental net benefit measure (as in cost per quality adjusted life year, cost per year of life saved, cost per lesion averted)

  or

- if a comparative cost study, costs expressed in dollars or in terms of resource.

5.1.3 Selection method

Once the results of the search process had been obtained, two reviewers (AB and HN) broadly applied the eligibility criteria to the title of each citation, abstract and key words (if available). Where disagreements or uncertainty occurred, the paper was retained for the next step in the process. The remaining papers were identified for retrieval as full text hard copies.

The same reviewers then applied the eligibility criteria to the papers obtained in full text. They used an inclusion-exclusion form (Appendix 3B). If a study received a "yes" for all questions, it was accepted for inclusion in the review. Disagreements between the reviewers were resolved by consensus.

5.1.4 Data extraction/abstraction strategy

Two reviewers used a data extraction form to independently extract and document relevant information (Appendix 5).

5.1.5 Strategy for quality assessment of the studies

Because of time limitations, no tool was used to assess the quality of the included studies. The source of funding for the studies, however, was noted.

5.1.6 Data analysis methods

As the tables in section 5.2 show, there was heterogeneity in the included studies in terms of design and other characteristics. Thus, no attempt was made to pool the results quantitatively. Instead, a qualitative analysis was done. Laupacis *et al.* have discussed cost-effectiveness ranges for consistent funding decisions.[81] Although the designation of an intervention as "cost-effective" is arbitrary, it can be a useful indicator.

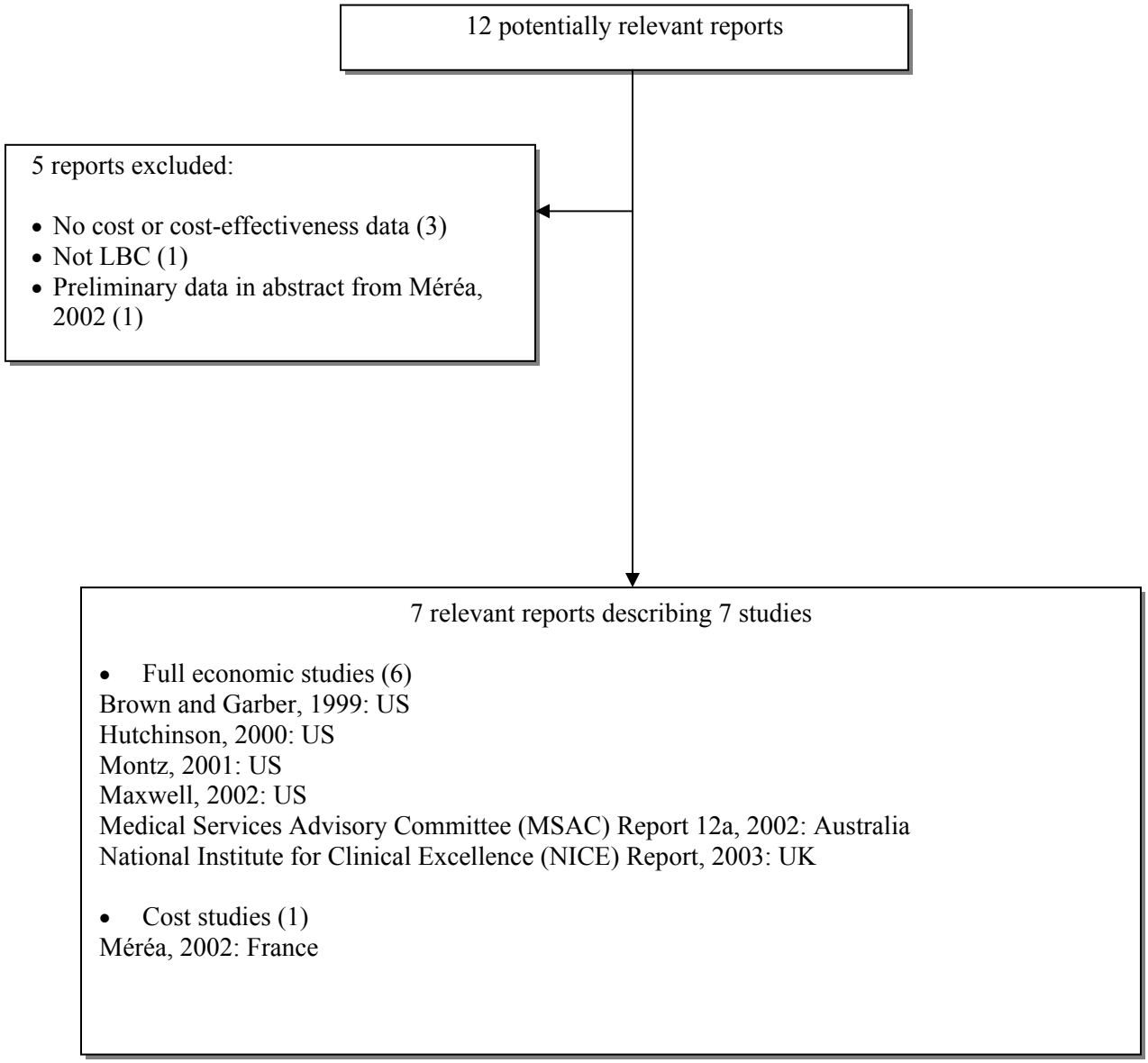
5.2 Results

5.2.1 Quantity of research available

a) LBC versus Pap smears

Twelve reports were retrieved on LBC versus Pap smears. Seven reports met the selection criteria[19,20,36,82-85] and five did not (Appendix 6). The flow chart for selection is shown in Figure 10.

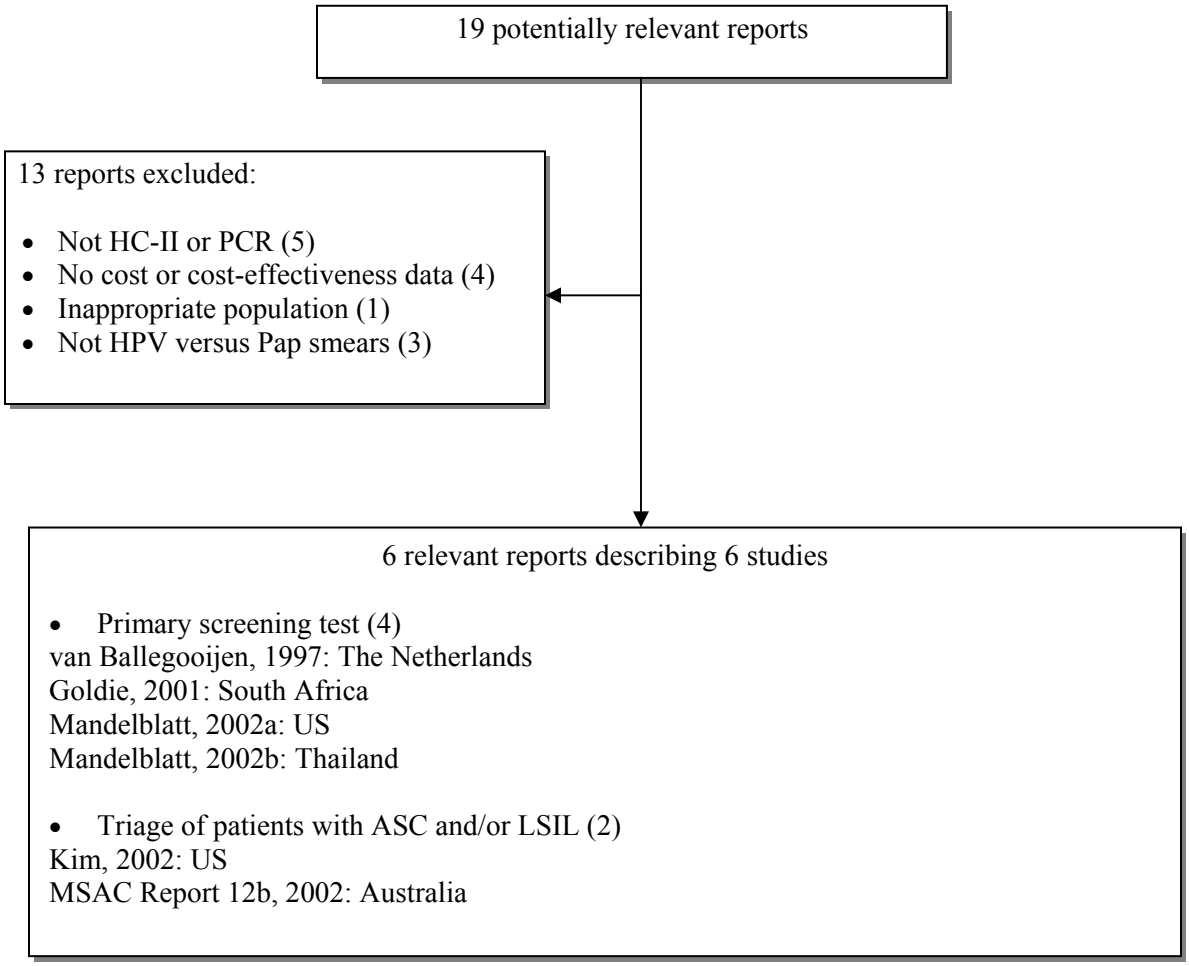
Figure 10: Flow chart of selected reports



b) HPV testing versus Pap smears

We retrieved 19 reports on HPV testing versus Pap smears. Six reports met the selection criteria[6,86-90] and 13 did not (Appendix 6). The flow chart for selection is shown in Figure 11.

Figure 11: Flow chart of selected reports



5.2.2 Study characteristics

a) LBC versus Pap smears

Author, Year (Setting)	Method	Target Population/ Frequency of Intervention	Sensitivity (%)	Specificity (%)
Brown and Garber, 1999 (US)[36]	Nine state time-varying transition state model Societal perspective 3% discount for costs and benefits	Cohort of women aged 20 to 65 representative of the population	LBC 93 Pap 82	LBC 96 Pap 96
Hutchinson, 2000 (US)[82]	A Markov model describes progression from screening pool to four test result states. Other states describe progression from cancer treatment and survival to further survival and death. Payer perspective 3% discount for costs and benefits	Cohort of 100,000 women aged 20 to 65	(LSIL to HSIL) LBC 75 to 82 Pap 50 to 55	NR (LBC=Pap)
Montz, 2001 (US)[83]	Model as in Hutchinson 2000 Payer perspective 3% discount for costs and benefits	Cohort of 100,000 women aged 20 to 80	LBC 73 Pap 51	NR (LBC=Pap)
Maxwell, 2002 (US)[84]	Markov simulation model of natural history of cervical cancer in military health care setting Payer perspective 3% discount for costs and benefits	Cohort of 100,000 beneficiaries aged 18 to 85 Screening every year, every 2 years or every 3 years	LBC 82 Pap 51	LBC 92 Pap 97
MSAC 12a, 2002 (Australia)[19]	Decision analytic model Payer perspective Discount rate not reported	Cohort of women representative of population who will participate in cervical cancer screening program (two years)	LBC 80 Pap 80	LBC 99.4 Pap 99.4
NICE, 2003 (UK)[20]	Macro-simulation model assesses impact of screening program and life-table for age-specific all cause mortality Payer perspective 6% discount for costs and 1.5% for benefits	Followed the life experience of cohort of women aged 18 to 95 years	LBC 67 Pap 60	LBC 97 Pap 97
Méréa, 2002 (France)[85]	Cost study using direct observation Payer perspective 5% discount for costs	100,000 examinations per year	NR	NR

b) HPV testing versus Pap smears

Author, Year (Setting)	Method	Target Population/ Frequency of Intervention	Sensitivity (%)	Specificity (%)
Primary screening				
van Ballegooijen, 1997 (The Netherlands)[90]	Two models developed: A. Long duration of HPV infection and high sensitivity of HPV testing B. Short duration of HPV infection and low sensitivity of HPV testing Payer perspective No discount rate PCR HPV method	Women between 30 to 60 years Screening every 3 years, every 5 years or every 10 years	HPV 50 to 100 Pap 80 to 87.5	HPV NR Pap NR
Goldie, 2001 (South Africa)[86]	Natural history and screening model in low-resource setting Societal perspective 3% discount for costs and benefits HC-II HPV method	Hypothetical cohort of previously unscreened 30-year-old women Single lifetime screen compared to no screening	HPV 84 Pap 60	HPV 88 Pap 95
Mandelblatt, 2002a (US)[88]	Simulation model of neoplasia natural history with 18 screening scenarios (two screening intervals and three strategies) Societal perspective Discount rate not reported HC-II and PCR HPV method	Women between 20 to 65 years, 75 years or death Screening every 2 years or every 3 years compared to no screening	HPV 55 to 89 Pap 67 to 80	HPV 86 Pap 87
Mandelblatt, 2002b (Thailand)[89]	Population-based simulation model for developing country (17 health states and seven screening strategies) Societal perspective 3% discount for costs and benefits HC-II and PCR HPV method	Cohort aged 20 to 70 years Screening every 5 years or every 10 years compared to no screening	HPV 56 to 79 Pap 20 to 46	HPV 79 Pap 94.5
Triage				
Kim, 2002 (US)[87]	Natural history model used to compare three strategies: immediate colposcopy, HPV triage or repeat Pap smear Societal perspective 3% discount for costs and benefits HC-II HPV method	Hypothetical cohort of adolescent girls entered into model at 13 years with a cytologic results of ASCUS Screening every two years	HPV 83 to 93 Pap 56 to 64	HPV 75 to 85 Pap 95
MSAC 12b, 2002 (Australia)[6]	Decision analytic model Two-year horizon with current National Health and Medical Research Council (NHMRC) guideline approach as comparator Perspective and discounting not reported HC-II HPV method	Cohort of women representative of population with cytologic prediction of low grade abnormality	HPV 92 Pap 80	HPV 54 Pap 99.4

5.2.3 Results

a) LBC versus Pap smears

Author, Currency (Currency year)	Strategy	Average Cost*	Life Days Saved†	Cost per Life Year Saved‡	Sensitivity Analysis
Brown and Garber, US$ (1996)[36]	Pap 4 yearly ThinPrep 4 yearly Thin Prep 3 yearly ThinPrep 2 yearly ThinPrep yearly	446 505 695 1,059 2,194	23.91 25.07 25.73 26.19 26.80	 18,565§ 36,958 93,560 363,498	Cancer incidence has largest effect among population parameters. ThinPrep is cost-effective if additional sensitivity is 50% higher than baseline assumption.
Hutchinson, US$ (1997)[82]	Pap 10 yearly ThinPrep 10 yearly ThinPrep 5 yearly ThinPrep 3 yearly ThinPrep 2 yearly ThinPrep yearly	556 569 647 729 836 1,191	3.5 5.1 6.9 7.7 8.2 8.8	 2,966 5,054 12,167 28,157 117,722	Data describing actual compliance rates show that ThinPrep is cost-effective (<US$50,000) in full population (9.5/100,000 cancers per year), but not in population comprising women who are screened at least every 3 years (3.4/100,000 cancers per year).
Montz, US$ (1997)[83]	Pap, self-reported compliance LBC, same compliance	NR NR	NR NR	 15,296	LBC is shown to be cost-effective over all compliance assumptions.
Maxwell, USA$ (2000)[84]	Pap 3 yearly LBC 3 yearly LBC 2 yearly LBC yearly LBC+HPV 3 yearly	484 601 792 1,441 597	27.7033** 27.7082 27.7137 27.7166 27.7113	 23,837 65,679 154,692 14,112	As Pap smear sensitivity increases, specificity decreases. At high levels of sensitivity (98% for LBC), one option, LBC+HPV testing every three years, costs less than US$50,000 per year of life saved.
MSAC 12a, Australian$ (2001)[19]	Pap 2 yearly LBC 2 yearly	89 101	NR NR	(no difference between groups in proportion of women with high grade lesions)	Minimum sensitivity at which LBC produces a cost-effectiveness ratio of AUS$40,000 or less per life year saved is 90% compared to 80% for Pap smear, assuming specificity remains at 99.4%.
NICE, UK£ (2003)[20]	Pap 5 yearly LBC 5 yearly LBC 3 yearly LBC 2 yearly	52.26 52.97 80.26 113.90	57 58.5 57.5 57.2	 174 677 2140	Several analyses indicate that with LBC, 2-year interval may be cost-effective.
Méréa, US$ (1999)[85]	Pap every year ThinPrep every year	11.5 14	NR NR	NR NR	For both techniques, mean cost is higher for laboratories in private sector compared with public sector.

* Average cost of LBC test
† Estimated life days saved per patient by application of LBC test
‡ Incremental cost per additional life year saved (LBC relative to Pap smear)
§ Compared to Pap screening at same frequency interval
** Mean life expectancy in years

b) HPV testing versus Pap smears

Author, Currency (Currency year)	Strategy	Average Cost*	Life Days Saved†	Cost per Life Year Saved‡	Sensitivity Analysis
Primary screening					
van Ballegooijen, Dutch Dfl (1997)[90]	Pap 3 yearly HPV 3 yearly (B) HPV 10 yearly (A) Pap+HPV 10 yearly (A)	740 1,250 230 460	23.72 22.65 24.09 24.82	11,400 20,100 3,500 6,800	Changes in frequency of follow-up and costs of HPV testing did not alter relative c-e of baseline model.
Goldie, US$ (1999)[86]	Pap smear followed by treatment of screen positive women at second visit HPV (same follow-up as Pap smear)	44 43	19.15§ 19.17	HPV weakly dominant	Rank ordering of screening strategies did not change in one-way analysis.
Mandelblatt (a), US$ (2000)[88]	Pap 3 yearly to 100 years HPV 3 yearly HPV 2 yearly Pap+HPV 3 yearly Pap+HPV 2 yearly	6,851 6,964 7,489 7,422 7980	27.0204** 27.0213 27.0356 27.0352 27.045	 12,556†† 1,810,000 38,581 70,737	HPV testing would be more effective and less costly than Pap smear at a cost threshold of US$5 for HPV test.
Mandelblatt (b), US$ (2000)[89]	Pap 5 yearly HPV 5 yearly HPV 10 yearly Pap+HPV 10 yearly Pap+HPV 5 yearly	55 182 102 125 224	27.0408‡‡ 27.0523 27.0498 27.0504 27.0618	 11,043 4,863 6,118 8,048	Baseline results were sensitive to several variables including costs and test characteristics.
Triage					
Kim, US$ (2000)[87]	Repeat Pap 2 yearly HPV 2 yearly	1,520 1,461	28.78807 §§ 28.78987	HPV weakly dominant	Repeat cytology no longer dominated when cost of HPV testing exceeded US$190.
MSAC 12b, Australian$ (2002)[6]	NHMRC guidelines HPV	455.09 528.11	9.2%*** 8.8%	NHMRC approach dominates HPV testing for management of low grade abnormality	Conclusion is particularly sensitive to estimated prevalence of high grade lesions in women with cytologic prediction of low-grade abnormality.

* Average cost of HPV test
† Estimated life days saved per patient by application of HPV test
‡ Incremental cost (HPV relative to Pap smear) per additional life year saved (HPV relative to Pap smear)
§ Mean life expectancy in years
** Quality-adjusted life years (QALY) saved
†† Compared to Pap screening at same frequency interval (cost per QALY)
‡‡ Life years and cost-effectiveness compared to Pap screening at same frequency interval)
§§ Mean life expectancy in years
*** Women with high grade lesions detected

5.2.4 Funding and support

Brown and Garber, 1999	Supported by Technology Evaluation Center of Blue Cross-Blue Shield.
Hutchinson, 2000	Funded by Cytyc Corporation.
Montz, 2001	Supported in part by unrestricted grant from Cytyc Corporation. Dr. Montz received honorarium for participation in a conference sponsored by Cytyc Corporation.
Maxwell, 2002	One co-author (Myers) previously received unrestricted grant from Digene Inc. for evaluation of economic issues surrounding HPV testing. Another co-author (Carlson) wrote decision brief that led to implementation of liquid-based cytology and reflex HPV testing using ThinPrep and HC-II, all US army medical facilities worldwide.
MSAC Report 12a, 2002	No industry funding reported.
NICE Report, 2003	No industry funding reported.
Méréa, 2002	Grant sponsors were French Ministry of Social Affairs and Cancer research Association.
Van Ballegooijen, 1997	Funded by Dutch Health Insurance Council.
Goldie, 2001	Co-author Wright is on speakers' bureau of Cytyc Corp and has received grant support from Digene Corp and 3M Pharmaceuticals.
Mandelblatt, 2002a	Co-author Barter is on speakers' bureau for Digene and Cytyc Corp; and owns stock in Digene.
Mandelblatt, 2002b	Prepared under contract for Johns Hopkins Program for International Education in Gynecology and Obstetrics Corp. Supported in part by National Institute on Aging, US Department of the Army and Bill and Melinda Gates Foundation.
Kim, 2002	Co-author Wright was principal investigator for clinical trials investigating HPV DNA testing and LBC funded by Digene Corp and Cytyc Corporation.
MSAC Report 12b, 2002	No industry funding reported.

5.3 Summary

Thirteen studies (from Australia, France, the Netherlands, the UK, the US; and from two less developed countries, South Africa and Thailand) meet the selection criteria. Seven studies are on LBC (six economic evaluations and one cost study) and six are on HPV testing (all economic evaluations: four for primary screening and two for triage). Determination of the incremental cost-effectiveness of LBC and HPV testing can be problematic given the uncertainty about key parameters such as their comparative sensitivity and specificity relative to current programs based on Pap smear screening.

a) LBC versus Pap smears

In terms of reported sensitivity and specificity, clinical and economic reviews give similar results with a few exceptions. For LBC, the trials of Hutchinson,[82] Montz[83] and Maxwell[84] have higher sensitivity versus the clinical review. The MSAC[19] study has lower sensitivity than the clinical review, but most studies have equal specificity. Six of the seven included studies are done from a payer perspective and one is societal. There is a lack of reporting on specificity by Hutchinson[82] and Montz[83] and on cost and outcomes by Montz[83] and Merea.[85]

The LBC results suggest that testing with a frequency of three years or longer may be cost-effective, while screening annually or every two years may not. This is consistent with the UK guidance document[24] (based on NICE's report[20]). It is concluded that the LBC is likely to be cost-effective compared to the Pap smear, despite its higher associated cost; and after considering the potential for increased sensitivity, reduction of inadequate smears and probable improvements in laboratory efficiency.

b) HPV testing versus Pap smears

For HPV testing, the trials of Van Ballegooijen[90] and Mandelblatt[88] have overall lower sensitivity compared to the clinical review. Economic studies in general have high specificity rates for HPV testing compared with the clinical review. Four of the six HPV studies are societal and one is not reported. There is a lack of reporting by MSAC[6] on perspective and discounting. HPV results are less clear-cut in comparison to LBC. US-based models suggest that HPV testing for primary screening at a frequency of three years or longer is cost-effective relative to Pap smears. Evidence from an Australian-based triage model suggest that HPV testing of women with low-grade cytologic abnormalities is more expensive and less effective than the current management plan.

6 DISCUSSION

6.1 Summary of Results

6.1.1 Clinical review

a) LBC versus Pap smears

The use of LBC decreases false-negative results when compared with Pap smears. An increase in sensitivity with LBC compared with Pap smears is reported in other systematic reviews.[19,20,91,92] This result must be considered tentative because of issues with the representativeness and completeness of the samples in the trials. As in previous systematic reviews, over 50% of trials in this review assess sensitivity and specificity on a select subset of women who test positive with LBC or Pap smears and who further undergo examination, this being histology in most trials. This is usually a small subset, which is often incomplete because not all participants are recruited into definitive studies, thereby only permitting the calculation of relative estimates of sensitivity and specificity. Many trials also fail to determine an upper limit to the period over which the histological outcome is determined.

Participants in these trials come from ordinary risk and high risk populations. This has a significant effect on the diagnosis made on the basis of the relative incidence of disease. When stratified by spectrum of disease, there is no statistical difference in sensitivity rates between LBC and Pap smears for high risk populations. There is, however, statistical difference for ordinary risk populations between the two methods. This result is consistent with the findings from a recent meta-analysis commissioned by the NICE in the UK.[20] In August 2003, based on the findings of the commissioned report, the UK National Health Service recommended that LBC be used as the primary means of processing samples in the cervical screening program in England and Wales.[24] It is also recommended that further evaluation of the LBC techniques be done, as there is insufficient evidence to show one method is better than another.[24]

Much of the evidence in support of LBC is based on results from split-sample trials. The cervical specimen is split into separate samples: one used for a conventional Pap smear and one for LBC. This may be an unfair assessment of both techniques because less of the specimen is available for either.[20,92] The influence of study design on sensitivity rates is difficult to assess given the small number of trials used in this analysis.

Efforts to increase test sensitivity are commonly associated with decreases in specificity and therefore increased false-positive diagnoses. There is little evidence relating to the specificity of LBC.[19,20] False-positive diagnoses have received little research attention to date. The adverse impact on a woman's quality of life caused by unnecessary repeat smears and possible investigations would reduce the cost-effectiveness of screening technologies that reduce specificity.

A decrease in the proportion of unsatisfactory specimens for evaluation with LBC is observed, although the trials identified for this review reveal an overlapping range in this proportion with LBC and Pap smears. Sensitivity analysis reveals that differences in the evaluation of specimen adequacy may be due to several factors, including variation in LBC technique and use of study design.

Laboratories may choose to introduce LBC for reasons other than diagnostic accuracy, including an increase in market share, the ability to conduct additional tests (HPV testing, automated screening methods) or more uniformity across laboratories.[19,20] Nearly two-thirds of the trials in this review are funded partially or completely by manufacturers of LBC technologies.

b) HPV versus Pap smears

HPV testing seems to be more sensitive but less specific than Pap smears as a primary screening test and as a method of triage for women with cytologic abnormalities. There is insufficient evidence on the comparative sensitivity and specificity of HPV testing for surveillance. Trials evaluating the use of the HC-II or PCR test in triage reveal that positive thresholds (i.e., if results lie above these levels, then further investigation is warranted) vary across trials, making it inappropriate to calculate an overall study statistic. As with LBC, the failure of some trials to meet several validity criteria, combined with the limitation of not having all women receive the reference standard of colposcopy, makes interpretation difficult. The increased sensitivity achieved with adjunctive HPV testing and Pap smears may allow the interval between screening procedures to be safely extended from one to two years, which is recommended with cytologic testing, to three or more years, with the used of combined tests.

The use of HPV is age-dependent. HPV testing may be unsuitable for screening in younger women because of a high positive rate due to transient infections with oncogenic strains of HPV.[4] As Wright and Schiffman note: "At present in the United States, most young women become infected with HPV within a few years after they become sexually active. Multiple concurrent and sequential infections with different oncogenic types of HPV are common. These tens of millions of infections are usually transient and clinically non-significant, although they frequently produce temporary cytologic changes. Fortunately, few HPV-infected women actually become persistently infected (for example, approximately 10% remain infected at five years); it is this smaller group that has a substantial risk (higher than 50%) of development of a high-grade precancerous lesion or cervical cancer if screening is not performed. Thus, the possibility of overuse of HPV DNA testing is particularly problematic for women in their teens and 20s who are likely to have new, transient HPV infections but are unlikely to have cervical cancer because of the long period of latency–years or even decades–between the onset of HPV infection and the development of cancer."[93] The trials in the current review recruited women of varying ages, but most report a mean age of 36 years across the HPV and Pap smear groups.

The most appropriate role for HPV testing (as primary screening or in the triage of women with borderline or low-grade cytologic abnormalities) depends on the existing screening infrastructure.[94] For clinical settings in which an effective, well organized, Pap-smear based program is in place, the issue is whether HPV testing adds to the existing program, as questions arise about cost-effectiveness, quality control and added value to current practice. In contrast,

for settings commonly found in developing countries, where screening is non-existent or ineffective because of low quality cytology, the basic issues of sensitivity, specificity and cost of testing become paramount. Trials in this review are representative of both these settings.

The ALTS is excluded from the current analysis of triage[95-97] as the slides from participants in the control arm are prepared by ThinPrep and not by Pap smear. The ALTS is a multi-centre, randomized controlled trial conducted by the US National Cancer Institute, to compare strategies for managing the two to three million women with ASCUS and the 1.25 million women with LSIL cytology results in the US each year. The ALTS has published its clinical findings to date in six reports. The key findings from this trial are summarized in Appendix 8. The ALTS shows that the cytologic interpretations of LSIL are so highly associated with HPV that an HPV triage test is not useful. With an ASCUS interpretation, however, approximately 40% to 50% of women are HPV positive. The ALTS data suggest that HPV triage is the most effective strategy for the management of women with ASCUS. The cost-effectiveness analyses of these data are being undertaken and will be published.

6.1.2 Economic review

Estimates of test sensitivity and specificity are the primary sources of uncertainty in the economic models that are used to investigate the cost-effectiveness of LBC and HPV testing. There are increased costs (mainly laboratory costs) associated with these techniques. The magnitude of any savings (such as in a lower number of repeat tests or with reduced treatment of invasive disease) is difficult to quantify using the results of the economic studies in this review. In the economic analyses of these tests, minimal or no attempt is made to quantify the financial impacts on patients. As none of the included studies were done in Canada, there are implications for the generalizability of the findings. Also, some of the included studies were done in less developed countries.

This review does not consider the use of computer-assisted methods in cervical cancer screening. These methods are used with LBC in many cytopathology laboratories, so this factor should be considered when assessing the economic impact of LBC. Some of the methodological issues associated with HPV testing will be addressed in the ongoing ALTS cost-effectiveness analysis and in other trials.

6.2 Study Limitations

The most important limitation of the LBC and HPC trials is that the true sensitivity and specificity of the screening tests, both Pap smears and new technologies, are unobservable without subjecting women to unnecessary and invasive investigations. Less than half the trials in this review control or adjust for verification bias. These failures of not having all women receive the reference test hamper interpretation of the findings. Another limitation is that data from international trials must be interpreted in the Canadian context.

6.3 Health Services Impact

This review provides information to provincial and territorial policy-makers and program providers about LBC and HPV testing in cervical cancer screening. Although the evidence allows for more rational consideration of these issues, it is impossible to state whether investment in such technologies will reduce the burden of cervical cancer among women in Canada when compared with other public health strategies designed to increase the recruitment of women into existing screening programs. As there are limited resources, the relative allocation of resources to these areas will be reflected in the policy developed at the jurisdictional level. In the context of the Canadian health care system, it is important to ensure that investment in new technologies brings benefits to the population rather than to a limited group of individuals. Likewise, the health of any individual should not be compromised by an investment in the population.

A key issue when considering HPV testing as a screening tool is having to abandon a public domain technology (Pap smear) in favour of one that would make the health services budget dependent on a commercial monopoly (at present Digene Diagnostics). Nearly 75% of the HPV trials in this review use the HC test. This situation will likely change if HPV testing becomes accepted and other biotechnology companies take the opportunity to make inroads on the market. Local government or international regulation may become imperative after the existing HPV test producer loses its patent protection. Furthermore, change to using HPV testing rather than conventional cytology must be considered. This includes a focus on cervical cancer as a sexually transmitted disease and on the existing health practice on many women who seek regular Pap smears.

6.4 Knowledge Gaps

The aim of screening tests is to reduce the morbidity and mortality from invasive cervical cancer. Ideally, this is achieved through randomized controlled trials (RCTs). RCTs using cancer incidence or mortality as outcome measures, however, are difficult to undertake in this context, partially because of the prolonged natural history of the disease, the low prevalence of invasive cancer and research consent issues. There is a need for high quality outcome trials with independent sources of funding to generate valid estimates of test sensitivity and specificity. There are a few large RCTs ongoing in Canada and elsewhere. Of note are the Canadian Cervical Cancer Screening Trial (CCCaST)[98] and the UK trials of HPV testing in primary cervical cancer screening (ARTISTIC)[99] and of management of borderline and low-grade abnormal smears (TOMBOLA).[100]

The CCCaST will enrol 12,000 women between 30 and 69 years of age from multiple centres in Quebec and Newfoundland.[25,98] Women will have an HPV test and a Pap smear, but will be randomly assigned as to the order in which the tests will be done. All women with an ASCUS Pap smear or a positive HPV test will undergo colposcopy and biopsy, as will a random sample of women with negative test results.[25] An economic evaluation of Pap testing compared with HPV testing is also planned with the CCCaST.[101] The definitive results from these trials will likely be available in two to five years.

7 CONCLUSIONS

The evidence shows that the LBC technique reduces the number of false-negative results as compared with the Pap smear for ordinary populations of women, although not for high risk populations. LBC also reduces the proportion of unsatisfactory specimens compared with Pap smears.

The evidence shows that HPV testing, alone or with cytology, is more sensitive but less specific than Pap smears for primary screening and triage.

The failure of some trials to meet several validity criteria, including the limitation of not having all women receive the reference test, hampers the interpretation of the results. Results from high quality trials that control for verification bias are needed to form a valid and reliable judgment about the diagnostic accuracy of LBC and HPV.

The economic evidence suggests that LBC screening every three years or longer may be cost-effective relative to Pap smear screening. Economic modelling based on the use of LBC in a Canadian context is needed before cost-effectiveness conclusions can be reached about the use of HPV testing.

8 REFERENCES

1. National Cancer Institute of Canada. *Canadian cancer statistics 2003*. Toronto: The Society; 2003. Available: http://www.cancer.ca/vgn/images/portal/cit_776/61/38/56158640niw_stats_en.pdf (accessed 2003 Apr 28).

2. Liu S, Semenciw R, Probert A, Mao Y. Cervical cancer in Canada: changing patterns in incidence and mortality. *Int J Gynecol Cancer* 2001;11(1):24-31.

3. Muñoz N, Bosch FX, de Sanjosé S, Herrero R, Castellsagué X, Shah KV, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med* 2003;348(6):518-27.

4. Cuzick J, Sasieni P, Davies P, Adams J, Normand C, Frater A, et al. A systematic review of the role of human papillomavirus testing within a cervical screening programme. *Health Technol Assess* 1999;3(14):i-196.

5. Cuzick J, Sasieni P, Davies P, Adams J, Normand C, Frater A, et al. A systematic review of the role of human papilloma virus (HPV) testing within a cervical screening programme: summary and conclusions. *Br J Cancer* 2000;83(5):561-5.

6. *Human papillomavirus testing in women with cytological prediction of low-grade abnormality*. Canberra: Medical Services Advisory Committee; 2002. MSAC reference 12b. Available: http://www.msac.gov.au/pdfs/msacref12b.pdf (accessed 2003 Apr 3).

7. *Cervical cancer screening in Canada: 1998 surveillance report*. Ottawa: Health Canada; 2002. Cat no H39-616/1998E. Available: http://www.hc-sc.gc.ca/pphb-dgspsp/publicat/ccsic-dccuac/pdf/cervical-e3.pdf.

8. Cervical cancer screening programs. *CMAJ* 1976;114(11):1003-33.

9. Cervical cancer screening programs: summary of the 1982 Canadian Task Force report. *CMAJ* 1982;127(7):581-9.

10. Miller AB, Anderson G, Brisson J, Laidlaw J, Le Pitre N, Malcolmson P, et al. Report of a National Workshop on Screening for Cancer of the Cervix. *CMAJ* 1991;145(10):1301-25.

11. Carmichael JA, Jeffrey JF, Steele HD, Ohlke ID. The cytologic history of 245 patients developing invasive cervical carcinoma. *Am J Obstet Gynecol* 1984;148(5):685-90.

12. Benoit AG, Krepart GV, Lotocki RJ. Results of prior cytologic screening in patients with a diagnosis of Stage I carcinoma of the cervix. *Am J Obstet Gynecol* 1984;148(5):690-4.

13. Sweet L, Tesch M, Dryer D, McAleer C. A review of the cervical cytology screening history of PEI women diagnosed with carcinoma of the cervix: 1981-1986. *Chronic Dis Can* 1991;12:1-3.

14. Stuart GC, McGregor SE, Duggan MA, Nation JG. Review of the screening history of Alberta women with invasive cervical cancer. *CMAJ* 1997;157(5):513-9. Available: http://www.cmaj.ca/cgi/reprint/157/5/513.pdf (accessed 2003 Sep 29).

15. Anderson GH, Benedet JL, Le Riche JC, Matisic JP, Thompson JE. Invasive cancer of the cervix in British Columbia: a review of the demography and screening histories of 437 cases seen from 1985-1988. *Obstet Gynecol* 1992;80(1):1-4.

16. *Interchange '95: a Canadian forum to collaborate on cervical cancer screening: program implementation strategies, February 27, 28 and March 1, 1995, Ottawa, Ontario, Canada*. Ottawa: Health Canada; 1995. Cat no H39-357/1995E.

17. Society of Canadian Colposcopists, College of Family Physicians of Canada, Canadian Society of Cytology, Society of Gynecologic Oncologists of Canada, Society of Obstetricians and Gynaecologists of Canada. *Programmatic guidelines for screening for cancer of the cervix in Canada*. Ottawa: Society of Gynecologic Oncologists of Canada; 1998. Cat no H39-436/1998E. Available: http://www.hc-sc.gc.ca/hppb/ahi/cervicalcancer/pubs/screening.pdf.

18. Noorani HZ. *Assessment of techniques for cervical cancer screening*. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 1997. CCOHTA report 1997: 2E. Available: http://www.ccohta.ca/entry_e.html.

19. *Liquid based cytology for cervical screening*. Canberra: Medical Services Advisory Committee; 2002. MSAC reference 12a. Available: http://www.msac.gov.au/pdfs/msacref12a.pdf (accessed 2003 Apr 3).

20. Karnon J, Peters J, Platt J, Chilcott J, McGoogan E. *Liquid-based cytology in cervical screening: an updated rapid and systematic review*. Sheffield (UK): School of Health and Related Research, University of Sheffield; 2003.

21. Nanda K, McCrory DC, Myers ER, Bastian LA, Hasselblad V, Hickey JD, et al. Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. *Ann Intern Med* 2000;132(10):810-9.

22. McCrory DC, Matchar DB, Bastian L, Datta S, Hasselblad V, Hickey J, et al. *Evaluation of cervical cytology* [Evidence report/technology assessment no 5]. Rockville (MD): Agency for Health Care Policy and Research; 1999. AHCPR Publ no 99-E010. Available: http://hstat.nlm.nih.gov/hq/Hquest/db/9/screen/DocTitle/odas/1/s/54797.

23. Broadstock M. *Effectiveness and cost effectiveness of automated and semi-automated cervical screening devices: a systematic review of the literature* [NZHTA report vol 3, no 1]. Christchurch (NZ): New Zealand Health Technology Assessment; 2000. Available: http://nzhta.chmeds.ac.nz/nzhtainfo/csv3n1.PDF.

24. *Guidance on the use of liquid-based cytology screening for cervical cancer: review of existing guidance number 5* [Final appraisal determination]. London: The Institute; 2003. Available: http://www.nice.org.uk/pdf/FAD_LBC.pdf (accessed 2003 Aug 27).

25. Franco EL. Chapter 13: primary screening of cervical cancer with human papillomavirus tests. *J Natl Cancer Inst Monogr* 2003;(31):89-96.

26. Khan KS, ter Rief G, Glanville J, Sowden AJ, Kleijnen J, editors. *Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews*. 2nd ed. York (UK): NHS Centre for Reviews and Dissemination, University of York; 2001. CRD report no 4. Available: http://www.york.ac.uk/inst/crd/report4.htm.

27. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. *Clin Chem* 2003;49(1):7-18.

28. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *BMJ* 2003;326(7379):41-4.

29. Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. *JAMA* 2002;287(16):2114-9.

30. Wright TC, Cox JT, Massad LS, Twiggs LB, Wilkinson EJ. 2001 Consensus Guidelines for the management of women with cervical cytological abnormalities. *JAMA* 2002;287(16):2120-9.

31. Wacholder S. Chapter 18: statistical issues in the design and analysis of studies of human papillomavirus and cervical neoplasia. *J Natl Cancer Inst Monogr* 2003;(31):125-30.

32. Saslow D, Runowicz CD, Solomon D, Moscicki AB, Smith RA, Eyre HJ, et al. American Cancer Society guideline for the early detection of cervical neoplasia and cancer. *CA Cancer J Clin* 2002;52(6):342-62. Available: http://caonline.amcancersoc.org/cgi/reprint/52/6/342.pdf (accessed 2003 Sep 30).

33. Solomon D. Chapter 14: role of triage testing in cervical cancer screening. *J Natl Cancer Inst Monogr* 2003;(31):97-101.

34. Bergeron C, Bishop J, Lemarie A, Cas F, Ayivi J, Huynh B, et al. Accuracy of thin-layer cytology in patients undergoing cervical cone biopsy. *Acta Cytol* 2001;45(4):519-24.

35. Clavel C, Masure M, Bory JP, Putaud I, Mangeonjean C, Lorenzato M, et al. Human papillomavirus testing in primary screening for the detection of high-grade cervical lesions: a study of 7932 women. *Br J Cancer* 2001;84(12):1616-23.

36. Brown AD, Garber AM. Cost-effectiveness of 3 methods to enhance the sensitivity of Papanicolaou testing. *JAMA* 1999;281(4):347-53. Available: http://jama.ama-assn.org/issues/v281n4/rpdf/joc81634.pdf.

37. Bishop JW, Bigner SH, Colgan TJ, Husain M, Pleotis Howell L, McIntosh KM, et al. Multicenter masked evaluation of AutoCyte PREP thin layers with matched conventional smears. Including initial biopsy results. *Acta Cytol* 1998;42(1):189-97.

38. Bolick DR, Hellman DJ. Laboratory implementation and efficacy assessment of the ThinPrep cervical cancer screening system. *Acta Cytol* 1998;42(1):209-13.

39. Corkill M, Knapp D, Hutchinson ML. Improved accuracy for cervical cytology with the ThinPrep method and the endocervical brush-spatula collection procedure. *J Lower Genital Tract Dis* 1998;2(1):12-6.

40. Inhorn S, Wilbur D, Zahniser D, Linder J. Validation of the ThinPrep Papanicolaou test for cervical cancer diagnosis. *J Lower Genital Tract Dis* 1998;2(4):208-12.

41. Sherman ME, Mendoza M, Lee KR, Ashfaq R, Birdsong GG, Corkill ME, et al. Performance of liquid-based, thin-layer cervical cytology: correlation with reference diagnoses and human papillomavirus testing. *Mod Pathol* 1998;11(9):837-43.

42. Hutchinson ML, Zahniser DJ, Sherman ME, Herrero R, Alfaro M, Bratti MC, et al. Utility of liquid-based cytology for cervical carcinoma screening: results of a population-based study conducted in a region of Costa Rica with a high incidence of cervical carcinoma. *Cancer* 1999;87(2):48-55.

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

44. Minge L, Fleming M, VanGeem T, Bishop JW. AutoCyte Prep® system vs. conventional cervical cytology. Comparison based on 2,156 cases. *J Reprod Med* 2000;45(3):179-84.

45. Bishop JW. Comparison of the CytoRich system with conventional cervical cytology. Preliminary data on 2,032 cases from a clinical trial site. *Acta Cytol* 1997;41(1):15-23.

46. Vassilakos P, Schwartz D, de Marval F, Yousfi L, Broquet G, Mathez-Loic F, et al. Biopsy-based comparison of liquid-based, thin-layer preparations to conventional Pap smears. *J Reprod Med* 2000;45(1):11-6.

47. Vassilakos P, Griffin S, Megevand E, Campana A. CytoRich liquid-based cervical cytologic test. Screening results in a routine cytopathology service. *Acta Cytol* 1998;42(1):198-202.

48. Bergeron C, Bishop J, Lemarie A, Cas F, Ayivi J, Huynh B, et al. Accuracy of thin layer cytology in patients presenting for cone biopsy [abstract]. *Acta Cytol* 2002;46(1 Suppl):93.

49. Park IA, Lee SN, Chae SW, Park KH, Kim JW, Lee HP. Comparing the accuracy of ThinPrep Pap tests and conventional Papanicolaou smears on the basis of the histologic diagnosis: a clinical study of women with cervical abnormalities. *Acta Cytol* 2001;45(4):525-31.

50. Confortini M, Bulgaresi P, Cariaggi MP, Carozzi FM, Cecchini S, Cipparrone I, et al. Conventional pap smear and liquid-based cervical cytology smear: comparison from the same patient. *Tumori* 2002;88(4):288-90.

51. Coste J, Cochand-Priollet B, de Cremoux P, Le Galès C, Cartier I, Molinié V, et al. Cross sectional study of conventional cervical smear, monolayer cytology, and human papillomavirus DNA testing for cervical cancer screening. *BMJ* 2003;326(7392):733-7.

52. Cochand-Priollet B, Le Galès C, de Cremoux P, Molinié V, Sastre-Garau X, Vacher-Lavenu MC, et al. Cost-effectiveness of monolayers and human papillomavirus testing compared to that of conventional Papanicolaou smears for cervical cancer screening: protocol of the study of the French Society of Clinical Cytology. *Diagn Cytopathol* 2001;24(6):412-20.

53. Levert M, Clavel C, Graesslin O, Masure M, Birembaut P, Quereux C, et al. Typage des Papillomavirus humains dans les frottis cervicaux de routine. Résultats sur une série de 3 778 patientes. *Gynecol Obstet Fertil* 2000;28(10):722-8.

54. University of Zimbabwe/JHPIEGO Cervical Cancer Project. Visual inspection with acetic acid for cervical-cancer screening: test qualities in a primary-care setting. *Lancet* 1999;353(9156):869-73. Available: http://pdf.thelancet.com/pdfdownload?uid=llan.353.9156.original_research.4630.1&x=x.pdf.

55. Paraskevaidis E, Malamou-Mitsi V, Koliopoulos G, Pappa L, Lolis E, Georgiou I, et al. Expanded cytological referral criteria for colposcopy in cervical screening: comparison with human papillomavirus testing. *Gynecol Oncol* 2001;82(2):355-9.

56. Petry KU, Menton M, Böhmer G, Iftner T. Human papillomavirus DNA-testing for primary cervical cancer screening in Germany [abstract]. *Anticancer Res* 2002;22(1B):482.

57. Cuzick J, Beverley E, Ho L, Terry G, Sapper H, Mielzynska I, et al. HPV testing in primary screening of older women. *Br J Cancer* 1999;81(3):554-8.

58. Syrjänen S, Shabalova IP, Petrovichev N, Kozachenko VP, Zakharova T, Pajanidi J, et al. Human papillomavirus testing and conventional pap smear cytology as optional screening tools of women at different risks for cervical cancer in the countries of the former Soviet Union. *J Lower Genital Tract Dis* 2002;6(2):97-110.

59. Clavel C, Masure M, Bory JP, Putaud I, Mangeonjean C, Lorenzato M, et al. Hybrid Capture II-based human papillomavirus detection, a sensitive test to detect in routine high-grade cervical lesions: a preliminary study on 1518 women. *Br J Cancer* 1999;80(9):1306-11.

60. Schneider A, Hoyer H, Lotz B, Leistritza S, Kühne-Heid R, Nindl I, et al. Screening for high-grade cervical intra-epithelial neoplasia and cancer by testing for high-risk HPV, routine cytology or colposcopy. *Int J Cancer* 2000;89(6):529-34.

61. Ratnam S, Franco EL, Ferenczy A. Human papillomavirus testing for primary screening of cervical cancer precursors. *Cancer Epidemiol Biomarkers Prev* 2000;9(9):945-51.

62. Schiffman M, Herrero R, Hildesheim A, Sherman ME, Bratti M, Wacholder S, et al. HPV DNA testing in cervical cancer screening: results from women in a high-risk province of Costa Rica. *JAMA* 2000;283(1):87-93.

63. Herrero R, Schiffman MH, Bratti C, Hildesheim A, Balmaceda I, Sherman ME, et al. Design and methods of a population-based natural history study of cervical neoplasia in a rural province of Costa Rica: the Guanacaste Project. *Rev Panam Salud Publica* 1997;1(5):362-75.

64. Wright TC, Denny L, Kuhn L, Pollack A, Lorincz A. HPV DNA testing of self-collected vaginal samples compared with cytologic screening to detect cervical cancer. *JAMA* 2000;283(1):81-6.

65. Kuhn L, Denny L, Pollack A, Lorincz A, Richart RM, Wright TC. Human papillomavirus DNA testing for cervical cancer screening in low-resource settings. *J Natl Cancer Inst* 2000;92(10):818-25.

66. Denny L, Kuhn L, Pollack A, Wainwright H, Wright TC. Evaluation of alternative methods of cervical cancer screening for resource-poor settings. *Cancer* 2000;89(4):826-33.

67. Blumenthal PD, Gaffikin L, Chirenje ZM, McGrath J, Womack S, Shah K. Adjunctive testing for cervical cancer in low resource settings with visual inspection, HPV, and the Pap smear. *Int J Gynaecol Obstet* 2001;72(1):47-53.

68. Womack SD, Chirenje ZM, Blumenthal PD, Gaffikin L, McGrath JA, Chipato T, et al. Evaluation of a human papillomavirus assay in cervical screening in Zimbabwe. *BJOG* 2000;107(1):33-8.

69. Bergeron C, Jeannel D, Poveda JD, Cassonnet P, Orth G. Human papillomavirus testing in women with mild cytologic atypia. *Obstet Gynecol* 2000;95(6 Pt 1):821-7.

70. Lytwyn A, Sellors JW, Mahony JB, Daya D, Chapman W, Ellis N, et al. Comparison of human papillomavirus DNA testing and repeat Papanicolaou test in women with low-grade cervical cytologic abnormalities: a randomized trial. *CMAJ* 2000;163(6):701-7. Available: http://www.cmaj.ca/cgi/reprint/163/6/701.pdf.

71. Morin C, Bairati I, Bouchard C, Fortier M, Roy M, Moore L, et al. Managing atypical squamous cells of undetermined significance in Papanicolaou smears. *J Reprod Med* 2001;46(9):799-805.

72. Lee NW, Kim D, Park JT, Kim A. Is the human papillomavirus test in combination with the Papanicolaou test useful for management of patients with diagnoses of atypical squamous cells of undetermined significance/low-grade squamous intraepithelial lesions? *Arch Pathol Lab Med* 2001;125(11):1453-7.

73. Manos MM, Kinney WK, Hurley LB, Sherman ME, Shieh-Ngai J, Kurman RJ, et al. Identifying women with cervical neoplasia: using human papillomavirus DNA testing for equivocal Papanicolaou results. *JAMA* 1999;281(17):1605-10.

74. Zielinski GD, Snijders PJF, Rozendaal L, Voorhorst FJ, Runsink AP, de Schipper FA, et al. High-risk HPV testing in women with borderline and mild dyskaryosis: long-term follow-up data and clinical relevance. *J Pathol* 2001;195(3):300-6.

75. Adam E, Kaufman RH, Berkova Z, Icenogle J, Reeves WC. Is human papillomavirus testing an effective triage method for detection of high-grade (grade 2 or 3) cervical intraepithelial neoplasia? *Am J Obstet Gynecol* 1998;178(6):1235-44.

76. Zdenek H, Lukac J, Jabor A, Chvalova M, Voracek J, Brozkova MH. Human papillomavirus deoxyribonucleic acid testing in screening of high grade cervical intraepithelial neoplasia. *Saudi Med J* 1999;20(11):861-4.

77. Holub Z, Lukác J, Chválová M, Brozková H, Nováková M, Poustková M. [Evaluation of the role of the HPV test in common clinical practice: prospective study]. *Cesk Gynekol* 1999;64(4):238-41.

78. Paraskevaidis E, Koliopoulos G, Alamanos Y, Malamou-Mitsi V, Lolis ED, Kitchener HC. Human papillomavirus testing and the outcome of treatment for cervical intraepithelial neoplasia. *Obstet Gynecol* 2001;98(5 Pt 1):833-6.

79. Nobbenhuis MA, Meijer CJ, van den Brule AJ, Rozendaal L, Voorhorst FJ, Risse EK, et al. Addition of high-risk HPV testing improves the current guidelines on follow-up after treatment for cervical intraepithelial neoplasia. *Br J Cancer* 2001;84(6):796-801.

80. Drummond MF, O'Brien BJ, Stoddart GL, Torrance GW. *Methods for the economic evaluation of health care programmes*. 2nd ed. Toronto: Oxford University Press; 1997.

81. Laupacis A. Inclusion of drugs in provincial drug benefit programs: who is making these decisions, and are they the right ones? *CMAJ* 2002;166(1):44-7. Available: http://www.cmaj.ca/cgi/content/full/166/1/44.

82. Hutchinson ML, Berger BM, Farber FL. Clinical and cost implications of new technologies for cervical cancer screening: the impact of test sensitivity. *Am J Manag Care* 2000;6(7):766-80.

83. Montz FJ, Farber FL, Bristow RE, Cornelison T. Impact of increasing Papanicolaou test sensitivity and compliance: a modeled cost and outcomes analysis. *Obstet Gynecol* 2001;97(5 Pt 1):781-8.

84. Maxwell GL, Carlson JW, Ochoa M, Krivak T, Rose GS, Myers ER. Costs and effectiveness of alternative strategies for cervical cancer screening in military beneficiaries. *Obstet Gynecol* 2002;100(4):740-8.

85. Méréa E, Le Galès C, Cochand-Priollet B, Cartier I, de Crémoux P, Vacher-Lavenu MC, et al. Cost of screening for cancerous and precancerous lesions of the cervix. *Diagn Cytopathol* 2002;27(4):251-7.

86. Goldie SJ, Kuhn L, Denny L, Pollack A, Wright TC. Policy analysis of cervical cancer screening strategies in low-resource settings: clinical benefits and cost-effectiveness. *JAMA* 2001;285(24):3107-15. Available: http://jama.ama-assn.org/issues/v285n24/rpdf/joc10234.pdf.

87. Kim JJ, Wright TC, Goldie SJ. Cost-effectiveness of alternative triage strategies for atypical squamous cells of undetermined significance. *JAMA* 2002;287(18):2382-90. Available: http://jama.ama-assn.org/issues/v287n18/rpdf/joc11842.pdf.

88. Mandelblatt JS, Lawrence WF, Womack SM, Jacobson D, Yi B, Hwang YT, et al. Benefits and costs of using HPV testing to screen for cervical cancer. *JAMA* 2002;287(18):2372-81. Available: http://jama.ama-assn.org/issues/v287n18/rpdf/joc11104.pdf.

89. Mandelblatt JS, Lawrence WF, Gaffikin L, Limpahayom KK, Lumbiganon P, Warakamin S, et al. Costs and benefits of different strategies to screen for cervical cancer in less-developed countries. *J Natl Cancer Inst* 2002;94(19):1469-83.

90. van Ballegooijen M, van den Akker-van Marle ME, Warmerdam PG, Meijer CJ, Walboomers JM, Habbema JD. Present evidence on the value of HPV testing for cervical cancer screening: a model-based exploration of the (cost-)effectiveness. *Br J Cancer* 1997;76(5):651-7.

91. Sulik SM, Kroeger K, Schultz JK, Brown JL, Becker LA, Grant WD. Are fluid-based cytologies superior to the conventional Papanicolaou test? A systematic review. *J Fam Pract* 2001;50(12):1040-6.

92. Bernstein SJ, Sanchez-Ramos L, Ndubisi B. Liquid-based cervical cytologic smear study and conventional Papanicolaou smears: a metaanalysis of prospective studies comparing cytologic diagnosis and sample adequacy. *Am J Obstet Gynecol* 2001;185(2):308-17.

93. Wright TC, Schiffman M. Adding a test for human papillomavirus DNA to cervical-cancer screening. *N Engl J Med* 2003;348(6):489-90.

94. Cuzick J. Time to consider HPV testing in cervical screening. *Ann Oncol* 2001;12(11):1511-4.

95. Sherman ME, Solomon D, Schiffman M, ALTS Group. Qualification of ASCUS. A comparison of equivocal LSIL and equivocal HSIL cervical cytology in the ASCUS LSIL Triage Study. *Am J Clin Pathol* 2001;116(3):386-94.

96. Sherman ME, Schiffman M, Cox JT. Effects of age and human papilloma viral load on colposcopy triage: data from the randomized Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesion Triage Study (ALTS). *J Natl Cancer Inst* 2002;94(2):102-7.

97. Sherman ME, Wang SS, Tarone R, Rich L, Schiffman M. Histopathologic extent of cervical intraepithelial neoplasia 3 lesions in the Atypical Squamous Cells of Undetermined Significance Low-grade Squamous Intraepithelial Lesion Triage Study: implications for subject safety and lead-time bias. *Cancer Epidemiol Biomarkers Prev* 2003;12(4):372-9.

98. *CCCaST: Canadian Cervical Cancer Screening Trial* [web site]. Montreal: CCast Study, Dept. of Oncology, McGill University; 2003. Available: http://www.mcgill.ca/ccast/ (accessed 2003 Sep 29).

99. A randomised trial of human papillomavirus testing in primary cervical screening. In: *metaRegister of Controlled Trials (mRCT)* [database online]. London: Current Controlled Trials, Ltd.; 2003. Available: http://www.controlled-trials.com/mrct/ (accessed 2003 Oct 2).

100. Trial of management of borderline and other low-grade abnormal smears (TOMBOLA). In: *metaRegister of Controlled Trials (mRCT)* [database online]. London: Current Controlled Trials, Ltd.; 2003. Available: http://www.controlled-trials.com/mrct/ (accessed 2003 Oct 2).

101. *NCIC's database of funded research* [database online]. Toronto: National Cancer Institute of Canada; 2003. Available: http://66.59.133.168/grsearch/demncic_en.html (accessed 2003 Sep 29).

102. Schiffman M, Adrianza ME. ASCUS-LSIL Triage Study. Design, methods and characteristics of trial participants. *Acta Cytol* 2000;44(5):726-42.

103. Solomon D, Schiffman M, Tarone R. Comparison of three management strategies for patients with atypical squamous cells of undetermined significance: baseline results from a randomized trial. *J Natl Cancer Inst* 2001;93(4):293-9.

104. Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesions Triage Study (ALTS) Group. Human papillomavirus testing for triage of women with cytologic evidence of low-grade squamous intraepithelial lesions: baseline data from a randomized trial. *J Natl Cancer Inst* 2000;92(5):397-402.

Appendix 1: Cervical Screening Terminology

Canadian institutions mainly use the Bethesda cytology classification system[29] which was modified in 2001. The abridged version shown here specifies the cytologic categories used in this review. Cervical cytology is primarily a screening test for squamous epithelial lesions and squamous cancer.[29] Based on the Bethesda system nomenclature, a woman with a cervical cytology result interpreted as ASC has a 5% to 17% chance of having CIN 2/3 confirmed by biopsy. The risk of invasive cervical cancer in a woman with an ASC lesion is low (approximately 0.1% to 0.2%).[30] Approximately 15% to 30% of women with LSIL on cervical cytology will have CIN 2/3 identified on a subsequent cervical biopsy.[30] Women with a cytologic diagnosis of HSIL have approximately a 70% to 75% chance of having biopsy-confirmed CIN 2/3 and a 1% to 2% chance of having invasive cervical cancer.[30]

Specimen adequacy
- Satisfactory for evaluation
- Unsatisfactory for evaluation (specify reason)
  - Specimen rejected or not processed
  - Specimen processed or examined, but unsatisfactory because of… (specify reason)

General categorization
- Negative for intraepithelial lesion or malignancy
- Epithelial cell abnormality: see interpretation and result
- Other: endometrial cells in women ≥40 years of age

Automated review and ancillary testing
- Specify if case examined by an automated device, type and result; describe test methods and report result

Interpretation and result
- Negative for intraepithelial lesion or malignancy
- Epithelial cell abnormalities
  - Squamous cell
    - Atypical squamous cells (ASC) of undetermined significance (ASC-US)
    - Atypical squamous cells, cannot exclude HSIL (ASC-H)
    - Low grade squamous intraepithelial lesion (LSIL)
      - Encompassing HPV, mild dysplasia, cervical intraepithelial neoplasia (CIN) 1
    - High grade squamous intraepithelial lesion (HSIL)
      - Encompassing moderate and severe dysplasia, carcinoma in situ, CIN 2, CIN 3
    - Squamous cell carcinoma
  - Glandular cell: Atypical glandular cells, endocervical adenocarcinoma in situ, adenocarcinoma

---

Appendix 2: Cervical Cancer Screening - Search Strategy

?	Truncation symbol, one character only
*	Truncation symbol, any number of characters
n	Near/next (i.e., terms are near/next to one another, any order)
" "	Phrase
l	Link (i.e., to subheading)
ti	Title
ab	Abstract
au	Author
de	Descriptor
dt	Publication type
tn	Trade name
mn	Manufacturer name
nd	Device name
md	Device manufacturer
rn	Registry number (i.e., CAS)
tw	Text word

DATABASES	**LIMITS**	**KEYWORDS/DESCRIPTORS**
DIALOG®		Clinical Search:
BIOSIS Previews® CANCERLIT® EMBASE® MEDLINE® PASCAL	1997- Human *(BIOSIS, CANCERLIT EMBASE, MEDLINE only)*	MEDLINE/CANCERLIT: cervical intraepithelial neoplasia(l)di/de *OR* cervical intraepithelial neoplasia(l)pa/de *OR* cervical intraepithelial neoplasia(l)pc/de *OR* cervical intraepithelial neoplasia(l)vi/de *OR* cervix neoplasms(l)/di/de *OR* cervix neoplasms(l)pa/de *OR* cervix neoplasms(l)pc/de *OR* cervix neoplasms(l)vi/de *OR* cervix dysplasia(l)di/de *OR* cervix dysplasia(l)pa/de *OR* cervix dysplasia(l)pc/de *OR* cervix dysplasia(l)vi/de EMBASE: uterine cervix cancer!/de *OR* uterine cervix dysplasia/de BIOSIS: cervical cancer/de *OR* cervical carcinoma/de *OR* cervical dysplasia/de *OR* cervical intraepithelial neoplasia/de *OR* cervical neoplasia/de *OR* cervical squamous cell carcinoma/de All databases: "cancer(2n)cervix" *OR* "cervical cancer" *OR* "cervical neoplasm*" *OR* "cervix neoplasm*" *OR* "cervix cancer" *OR* "neoplas* cervical" *OR* "neoplas* cervix" *OR* "neoplas* cervical intraepithelial" *OR* "cervical intraepithelial neoplas*" *OR* "intraepithelial neoplas* cervical" *OR* "cervix dysplasia" *OR* "cervical dysplasia" *OR* "cervical carcinoma" *OR* "cervix carcinoma" *OR* MEDLINE/CANCERLIT: [(papillomavirus infections!(l)di/de *OR* papillomavirus infections!(l)pa/de *OR* papillomavirus infections!(l)pc/de *OR* papillomavirus infections!(l)vi/de

		AND MEDLINE/CANCERLIT: papillomavirus, human/de) *OR* EMBASE: papilloma virus!/de BIOSIS: human papillomavirus infection/de All databases: "papillomavirus* infection*"/ti,ab *OR* "papilloma virus* infection*"/ti,ab *OR* "human papillomavirus*"/ti,ab *OR* "human papilloma virus*"/ti,ab *OR* "papilloma virus* human"/ti,ab *OR* "infectious human wart virus*"/ti,ab *OR* "human wart virus* infectious"/ti,ab *OR* HPV/ti,ab] *AND* MEDLINE/CANCERLIT: mass screening!(l)is/de *OR* mass screening!(l)/mt/de *OR* mass screening!(l)st/de *OR* mass screening!(l)td//de *OR* vaginal smears(l)is/de *OR* vaginal smears(l)mt/de *OR* vaginal smears(l)st/de *OR* vaginal smears(l)td/de *OR* cytological techniques!(l)is/de *OR* cytological techniques!(l)mt/de *OR* cytological techniques!(l)st/de OR cytological techniques!(l)td/de EMBASE: cancer screening/de *OR* vagina smear/de *OR* cancer cytodiagnosis/de BIOSIS: cervical cancer screening/de *OR* cervical smear/de *OR* pap smear/de All databases: "cervical screening"/ti,ab *OR* "cervix screening"/ti,ab *OR* "cervical cancer screening"/ti,ab *OR* "cervix cancer screening"/ti,ab *OR* "pap smear*"/ti,ab *OR* "pap test*"/ti,ab *OR* "Papanicolaou smear*"/ti,ab *OR* "Papanicolaou test*"/ti,ab *OR* "cervical smear*"/ti,ab *OR* "cervical test*"/ti,ab *OR* "vagina* smear*"/ti,ab *OR* "vagina* test*"/ti,ab *OR* "cervical cytolog* screening*"/ti,ab *OR* "cervical cytolog* test*"/ti,ab *OR* "HPV test*"/ti,ab OR "HPV screening*"/ti,ab *OR* papilloma*(3n)screen*/ti,ab *OR* papilloma*(3n)test*/ti,ab *AND* MEDLINE/CANCERLIT: DNA Probes, HPV/de EMBASE: DNA Probe/de BIOSIS:

		DNA probes/de All databases: thinprep/ti,ab,tn *OR* autocyte/ti,ab,tn *OR* cytorich/ti,ab,tn *OR* cytosavant/ti,ab,tn alts/ti,ab *OR* "thin-layer cytolog*"/ti,ab *OR* "thin layer cytolog*"/ti,ab *OR* "thin-layer preparation*"/ti,ab *OR* "thin layer preparation*"/ti,ab *OR* "fluid-based cytolog*"/ti,ab *OR* "fluid based cytolog*"/ti,ab *OR* "fluid-based preparation*"/ti,ab *OR* "fluid based preparation*"/ti,ab *OR* "fluid-based techn*"/ti,ab *OR* "fluid based techn*"/ti,ab *OR* "fluid-based smear*"/ti,ab *OR* "fluid based smear*"/ti,ab *OR* "fluid-based test*"/ti,ab *OR* "fluid based test*"/ti,ab *OR* "liquid-based cytolog*"/ti,ab *OR* "liquid based cytolog*"/ti,ab *OR* "liquid-based preparation*"/ti,ab *OR* "liquid based preparation*"/ti,ab *OR* "liquid-based techn*"/ti,ab *OR* "liquid based techn*"/ti,ab *OR* "liquid-based smear*"/ti,ab *OR* "liquid based smear*"/ti,ab *OR* "liquid-based test*"/ti,ab *OR* "liquid based test*"/ti,ab *OR* "HPV test*"/ti,ab *OR* "HPV screen*"/ti,ab *OR* "HPV techn*"/ti,ab *OR* "HPV probe*"/ti,ab *OR* "HPV DNA"/ti,ab *OR* "human papillomavirus DNA"/ti,ab *OR* "DNA assay*"/ti,ab *OR* "DNA probe*"/ti,ab *OR* "DNA test*"/ti,ab *OR* "DNA screen*"/ti,ab *OR* papilloma*(3n)screen*/ti,ab *OR* papilloma*(3n)test*/ti,ab *AND* MEDLINE/CANCERLIT: Evaluation Studies/dt *OR* Meta-Analysis/dt *OR* Review/dt Case-Control Studies/de *OR* Diagnostic Errors!/de *OR* Evaluation Studies!/de *OR* Evidence-Based Medicine/de *OR* Program Evaluation/de *OR* Quality Control/de *OR* Quality Assurance, Health Care!/de *OR* Reproducibility of Results/de *OR* Sensitivity and Specificity/de *OR* Outcome Assessment (Health Care)!/de *OR* Quality Control/de EMBASE: comparative study/de *OR* diagnostic error/de *OR* evaluation and follow up/de *OR* evidence based medicine/de *OR* practice guideline/de *OR* quality control!/de *OR* reproducibility/de *OR* sensitivity and specificity/de *OR* review/de *OR* short survey/de BIOSIS: literature review/dt *OR* product review/dt clinical evaluation/de *OR* clinical practice guidelines/de *OR* comparative study/de *OR* diagnostic accuracy/de *OR* evaluation/de *OR* evidence-based medicine/de *OR* meta-analysis/de *OR* practice guidelines/de *OR* quality assurance/de *OR* quality control/de *OR* reproducibility/de *OR* sensitivity/de *OR* specificity/de *OR* validity/de All databases: accura*/ti,ab *OR* comparison*/ti,ab *OR* "comparative (study or studies or trial or trials)"/ti,ab *OR* diagnos*(2n)error*/ti,ab *OR* effective*/ti,ab *OR* efficac*/ti,ab *OR* evaluation*/ti,ab *OR* evidence-based/ti,ab *OR* "evidence based"/ti,ab *OR* false-negative/ti,ab *OR* "false negative"/ti,ab *OR* false-positive/ti,ab *OR* "false positive"/ti,ab *OR* matched-pair*/ti,ab *OR* "matched pair*"/ti,ab *OR* "paired comparison*"/ti,ab *OR* meta-analys*/ti,ab *OR* "meta analys*"/ti,ab *OR* metaanalys*/ti,ab *OR*

		"observer variation*"/ti,ab *OR* "interobserver variation*"/ti,ab *OR* "practice guideline*"/ti,ab *OR* cpg/ti,ab *OR* cpgs/ti,ab *OR* "predictive value*"/ti,ab *OR* "quality control*"/ti,ab *OR* "quality assurance*"/ti,ab *OR* "receiver operat* characteristic*"/ti,ab *OR* reliability/ti,ab *OR* reproducibility/ti,ab *OR* "ROC analys*"/ti,ab *OR* "ROC curve?"/ti,ab *OR* sensitivity/ti,ab *OR* specificity/ti,ab *OR* validity/ti,ab *OR* "systematic* (review* OR overview*)"/ti,ab *OR* random*/ti,ab *OR* "single (blind* *OR* dumm* *OR* mask*)/ti,ab" *OR* "double (blind* *OR* dumm* *OR* mask*)"/ti,ab *OR* "triple (blind* *OR* dumm* *OR* mask*)"/ti,ab *OR* "treble (blind* *OR* dumm* *OR* mask*)"/ti,ab *OR* placebo*/ti,ab *OR* "meta analy*" /ti,ab *OR* metaanaly*/ti,ab *OR* "quantitative* (review* *OR* overview*)"/ti,ab *OR* "methodologic* (review* *OR* overview*)"/ti,ab *OR* "control* (study *OR* studies *OR* trial*)"/ti,ab *OR* RCT?/ti,ab *Performed 29 Nov 2002* *559 unique records* BIOSIS – 40 records CANCERLIT – 1 record EMBASE - 100 hits MEDLINE - 395 records PASCAL - 23 hits
National Library of Medicine PubMed	1997- Human, Female	Clinical search: *Same descriptors and keywords as per MEDLINE search, adjusting syntax where necessary. All keywords limited to title and abstract fields.* *Performed 29 Nov 2002* *616 records*
The Cochrane Collaboration & Update Software Ltd. The Cochrane Library, 2003, Issue 1		Clinical Search: cervical intraepithelial neoplasia/de *OR* cervix neoplasms/de *OR* cervix dysplasia/de *OR* (papillomavirus infections!/de *AND* papillomavirus, human/de) *AND* mass screening!/de *OR* vaginal smears/de *OR* cytological techniques!/de *AND* DNA Probes, HPV/de *Same keywords as per DIALOG® MEDLINE search, excluding filter for test quality and adjusting syntax where necessary* The Cochrane Database of Systematic Reviews = 1 complete review; The Database of Abstracts of Reviews of Effectiveness = 4 records; CENTRAL = 32 references; Abstracts by INAHTA and other healthcare technology agencies = 5 records; The NHS Economic Evaluation Database = 5 records

DIALOG® *Alerts:* BIOSIS Previews® CANCERLIT® EMBASE® MEDLINE® PASCAL	Human *(BIOSIS, CANCERLIT EMBASE, MEDLINE only)*	Clinical Search: *Same descriptors and keywords as per MEDLINE, etc.*
DIALOG® BIOSIS Previews® CANCERLIT® EMBASE® MEDLINE® PASCAL	1997- Human *(BIOSIS, CANCERLIT EMBASE, MEDLINE only)*	Economic Search: *Same descriptors and keywords as per clinical search, excluding filter for test quality* *AND* MEDLINE/CANCERLIT: economics!/de *OR* quality-adjusted life years/de *OR* models, economic/de *OR* value of life/de EMBASE: economics/de *OR* economic aspect/de *OR* economic evaluation/de *OR* cost effectiveness analysis/de *OR* cost benefit analysis/de *OR* cost utility analysis/de *OR* health care cost/de *OR* quality adjusted life year/de BIOSIS: economics/de *OR* economic factors/de *OR* economic impact/de *OR* pharmacoeconomics/de *OR* cost/de *OR* costs/de *OR* cost-benefit analysis/de *OR* cost analysis/de *OR* cost effectiveness/de *OR* cost savings/de *OR* health care cost/de *OR* quality of life/de *OR* quality-of-life/de All databases: economic*/ti,ab *OR* cost/ti,ab *OR* costs/ti,ab *OR* cost-benefit/ti,ab *OR* price*/ti,ab *OR* pricing/ti,ab *OR* expenditure*/ti,ab *OR* budget*/ti,ab *OR* "quality adjusted life year*"/ti,ab *OR* "quality-adjusted life year*"/ti,ab *OR* qaly*/ti,ab *OR* "willingness to pay"/ti,ab *OR* "value of life"/ti,ab *OR* "life value*"/ti,ab *OR* econometric*/ti,ab *Performed 29 Nov 2002* *128 unique records* BIOSIS – 11 records CANCERLIT – 0 records EMBASE - 40 records MEDLINE - 71 records PASCAL - 6 records
National Library of Medicine PubMed	1997- Human, Female	Economic Search: *Same descriptors and keywords as per MEDLINE search, adjusting syntax where necessary. All keywords limited to title and abstract fields.* *Performed 29 Nov 2003* *93 records*

The Cochrane Collaboration & Update Software Ltd. The Cochrane Library, 2003, Issue 1		Economic Search: cervical intraepithelial neoplasia/de *OR* cervix neoplasms/de *OR* cervix dysplasia/de *OR* (papillomavirus infections!/de *AND* papillomavirus, human/de) *AND* mass screening!/de *OR* vaginal smears/de *OR* cytological techniques!/de *AND* DNA Probes, HPV/de *Same keywords as per DIALOG® MEDLINE search, adjusting syntax where necessary* The Cochrane Database of Systematic Reviews = 1 complete review; The Database of Abstracts of Reviews of Effectiveness = 2 records; CENTRAL = 1 references; Abstracts by INAHTA and other healthcare technology agencies = 3 records; The NHS Economic Evaluation Database = 4 records
OHE-IFPMA Database Ltd. HEED: health economic evaluations database Mar 2003 issue	1997-	Economic Search: (cervical *OR* cervix *OR* papilloma)/tw *AND* (cancer *OR* cancers *OR* neoplasm *OR* neoplasms *OR* carcinoma *OR* dysplasia *OR* virus)/tw *AND* (screening *OR* smear *OR* smears *OR* pap *OR* papanicolaou *OR* cytology)/tw *80 records*
DIALOG® *Alerts:* BIOSIS Previews® CANCERLIT® EMBASE® MEDLINE® PASCAL	Human *(BIOSIS, CANCERLIT EMBASE, MEDLINE only)*	Economic Search: *Same descriptors and keywords as per MEDLINE, etc.*

DIALOG® BIOSIS Previews® CANCERLIT® EMBASE® MEDLINE® PASCAL	 1997- Human *(BIOSIS, CANCERLIT EMBASE, MEDLINE only)*	Program Overview: *Same descriptors and keywords as per clinical search, excluding filters for new technologies and test quality* *AND* MEDLINE/CANCERLIT: National Health Programs/de *OR* Government programs/de *OR* Outcome Assessment (Health Care)!/de *OR* Program Evaluation!/de *OR* Community Health Services!/de *OR* Utilization Review!/de EMBASE: national health service/de *OR* outcomes research/de *OR* community care!/de *OR* utilization review/de BIOSIS: outcome measures/de All databases: "screening program*"/ti,ab *OR* "screenig polic*"/ti,ab *OR* "screening strateg*"/ti,ab *OR* community-based(2n)program*/ti,ab *OR* "community based"(2n)program*/ti,ab *OR* community(2n) program*/ti,ab *OR* program*(2n)appropriateness/ti,ab *OR* program*(2n)effectiveness/ti,ab *OR* program*(2n)sustainability/ti,ab *OR* "outcome* study"/ti,ab *OR* "outcome* studies"/ti,ab *OR* "outcome* assessment*"/ti,ab *OR* "outcome* measure*"/ti,ab *OR* "outcome* research"/ti,ab *OR* "government-sponsored program*"/ti,ab *OR* "government sponsored program*"/ti,ab *OR* "state medicine"/ti,ab *OR* "national health insurance"/ti,ab *OR* "national health service*"/ti,ab *OR* "utili?ation review*"/ti,ab *AND* MEDLINE/CANCERLIT/EMBASE: Canada!/de BIOSIS: Canada/de *OR* British Columbia/de *OR* Alberta/de *OR* Saskatchewan/de *OR* Manitoba/de *OR* Ontario/de *OR* Quebec/de *OR* Nova Scotia/de *OR* New Brunswick/de *OR* Prince Edward Island/de *OR* Newfoundland/de *OR* Yukon/de *OR* Northwest Territories/de *OR* Nunavut/de All databases: Canada/ti,ab *OR* "British Columbia"/ti,ab *OR* Alberta/ti,ab *OR* Saskatchewan/ti,ab *OR* Manitoba/ti,ab *OR* Ontario/ti,ab *OR* Quebec/ti,ab *OR* "Nova Scotia"/ti,ab *OR* "New Brunswick"/ti,ab *OR* "Prince Edward Island"/ti,ab *OR* Newfoundland/ti,ab *OR* Yukon/ti,ab *OR* "Northwest Territories"/ti,ab *OR* Nunavut/ti,ab *Performed 29 Nov 2002* *36 unique records* BIOSIS – 0 records CANCERLIT – 0 records EMBASE - 5 records

		MEDLINE - 31 records PASCAL - 0 records
National Library of Medicine PubMed	1997- Human, Female	Program Overview: *Same descriptors and keywords as per MEDLINE search, adjusting syntax where necessary. All keywords limited to title and abstract fields.* *Performed 29 Nov 2003* *32 records*
DIALOG® *Alerts:* BIOSIS Previews® CANCERLIT® EMBASE® MEDLINE® PASCAL	Human *(BIOSIS, CANCERLIT EMBASE, MEDLINE only)*	Program Overview: *Same descriptors and keywords as per MEDLINE, etc.*
National Health Service (UK) Cervical Cancer Screening Literature Database		"Trials, Epidemiology & Evaluation" and "Automation/New Technology" categories
Websites of health technology assessment (HTA) and related agencies; clinical trial registries; other databases		e.g. NZHTA; AHRQ; National Research Register; University of York NHS Centre for Reviews and Dissemination – CRD databases; LILACS

Appendix 3: Study Inclusion - Exclusion Form

A. Clinical Review

Study ID Citation Year Reviewer

1.	Comparative study	Yes____	No____	Can't tell___
2.	Women at risk for cervical cancer	Yes____	No____	Can't tell___
3.	Study objectives (answer part a or part b)			
a.	LBC versus Pap smears	Yes____	No____	Can't tell___
b.	HPV testing versus Pap smears (answer i, ii or iii)			
i)	Primary screening	Yes____	No____	Can't tell___
ii)	Triage	Yes____	No____	Can't tell___
iii)	Surveillance	Yes____	No____	Can't tell___
4.	Assesses epithelial cell abnormalities or cervical specimen adequacy	Yes____	No____	Can't tell____

SCORING

Highlight one of the following: if 1 to 4 all "yes," include study; if any of 1 to 4 "can't tell" and the rest "yes" or if all 1 to 4 are "can't tell," order full paper; if any of 1 to 4 "no," exclude study.

B. Economic Review

Study ID Citation Year Reviewer

1.	Type of study (answer part a or part b)			
	Full economic evaluation*	Yes____	No____	Can't tell___
	Cost study	Yes____	No____	Can't tell___
2.	Women at risk for cervical cancer	Yes____	No____	Can't tell___
3.	Study objectives (answer part a or part b)			
a.	LBC versus Pap smears	Yes____	No____	Can't tell___
b.	HPV testing versus Pap smears	Yes____	No____	Can't tell___
4.	Assesses costs, cost-effectiveness of LBC or HPV testing	Yes____	No____	Can't tell____

SCORING

Highlight one of the following: if 1 to 4 all "yes," include study; if any of 1 to 4 "can't tell" and the rest "yes" or if all 1 to 4 are "can't tell," order full paper; if any of 1 to 4 "no," exclude study.

* Defined as comparative analysis of two or more treatment alternatives in terms of costs and consequences. Includes cost minimization (needs evidence that consequences of treatment alternatives are identical); cost-effectiveness, cost utility and cost benefit analysis.

Appendix 4: Data Extraction and Quality Assessment Form for Clinical Review

Reviewer
Date
Study ID
Full citation*
Country (or countries) where study undertaken
Language of publication
Conflict of interest
Other reports of this trial† (give full citation)

1. Data Source

☐ Published only ☐ Unpublished only ☐ Mixed

2. Trial dates

☐ Start of recruitment ☐ End of recruitment

3. Study design

☐ Split-sample ☐ Cohort ☐ Other (please specify):

4. Study inclusion and exclusion criteria

a. Inclusion criteria

b. Exclusion criteria

c. Numbers of samples and women excluded‡

* If multiple studies by single group of investigators, cite the most comprehensive (with latest follow-up) report
† As cited in the reference list of the report
‡ If reported, give breakdown of overall number of exclusions by category

5. Description of study population

a. Intervention I

Number _____ Age (mean years and SD) _____

b. Intervention II

Number _____ Age (mean years and SD) _____

c. Pap smears

Number _____ Age (mean years and SD) _____

6. Description of intervention and comparison provided

a. Intervention I

b. Intervention II

c. Pap smears

d. Setting

☐ Multi-centre ☐ Single centre

7. Outcomes collected. Tick all available.

☐ Carcinoma* ☐ HSIL ☐ LSIL ☐ ASC

☐ Other cervical lesions (please state)

☐ Specimens classified as inadequate or unsatisfactory

* The terminology for clinical outcome measures is based on the 2001 Bethesda System for reporting results of cervical cytology.[29] These cervical lesions will be confirmed by colposcopy-directed biopsies.

8. Results

a. ☐ ≥LSIL ☐ ≥HSIL ☐ Other (please specify)

b. Sensitivity and Specificity

Intervention I			Intervention II			Pap smear		
Inadequate (n/N)	Sens (n/N)	Spec (n/N)	Inadequate (n/N)	Sens (n/N)	Spec (n/N)	Inadequate (n/N)	Sens (n/N)	Spec (n/N)

9. Other Notes and Observations

10. Quality Assessment

Provide a qualitative description for each of the four questions below.

1. Was the test compared with a valid reference standard?

☐ Histology (colposcopy or biopsy)

☐ Panel review (cytologic review by independent panel of at least two reviewers cytotechnologists or pathologists)

2. What was the industry's relationship to the project?

☐ No support
☐ Partial support (some funding from industry to authors or to project)
☐ Total support
☐ Not reported

3. Was the screening method allocation masked at the outcome assessment (blind review of test results)?

☐ Yes ☐ No ☐ Not reported

4. How was the study sample collected?

☐ Random ☐ Not random

Appendix 5: Data Extraction Form for Economic Review

Author
Title
Publication date
Geographic setting
Method
Study design
Study perspective
Discounting
Target population and frequency of intervention
Sensitivity
Specificity
Source of funding
Currency
Currency year
Strategy applied
Average cost
Life days saved (or other outcome measure)
Cost per life year saved (or other cost-effectiveness measure)
Sensitivity analysis

Appendix 6: Excluded Reports

Clinical Review

(1) LBC versus Pap smears (46 reports)

1. Corkill M, Knapp D, Martin J, Hutchinson ML. Specimen adequacy of ThinPrep sample preparations in a direct-to-vial study. *Acta Cytol* 1997;41(1):39-44.

2. Laverty CR, Farnsworth A, Thurloe JK, Grieves A, Bowditch R. Evaluation of the CytoRich slide preparation process. *Anal Quant Cytol Histol* 1997;19(3):239-45.

3. Lee KR, Ashfaq R, Birdsong GG, Corkill ME, McIntosh KM, Inhorn SL. Comparison of conventional Papanicolaou smears and a fluid-based, thin-layer system for cervical cancer screening. *Obstet Gynecol* 1997;90(2):278-84.

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

5. Takahashi M, Naito M. Application of the CytoRich monolayer preparation system for cervical cytology. A prelude to automated primary screening. *Acta Cytol* 1997;41(6):1785-9.

6. Weintraub J. The coming revolution in cervical cytology: a pathologist's guide for the clinician. *Ref Gynecol Obstet* 1997;5(2):169-75.

7. Wilbur DC, Facik MS, Rutkowski MA, Mulford DK, Atkison KM. Clinical trials of the CytoRich specimen-preparation device for cervical cytology. Preliminary results. *Acta Cytol* 1997;41(1):24-9.

8. Bednov YM, Brosky KR, Sidawy MK. Comparison of the efficacy of the ThinPrep method with the conventional cervical smear [abstract]. *Lab Invest* 1998;78(1):36A.

9. Dupree WB, Suprun HZ, Beckwith DG, Shane JJ, Lucente V. The promise and risk of a new technology: the Lehigh Valley Hospital's experience with liquid-based cervical cytology. *Cancer* 1998;84(4):202-7.

10. Howell LP, Davis RL, Belk TI, Agdigos R, Lowe J. The AutoCyte preparation system for gynecologic cytology. *Acta Cytol* 1998;42(1):171-7.

11. Kunz J, Rondez R, Yoshizaki C, Fivian M, Held G, Lind B. Vergleich konventioneller PAP-Abstriche mit Dünnschicht-Präparaten (Liquid-Based PAP-Test) und Korrelation der zytopathologischen Befunde mit dem HPV-Status nach Hybrid Capture System [Comparison of conventional PAP-smears with thin layer specimen (liquid-based PAP-test) and correlation of cytopathological findings with HPV-status detected by Hybrid Capture System]. *Schweiz Rundsch Med Prax* 1998;87(43):1434-40.

12. Papillo JL, Zarka MA, St.John TL. Evaluation of the ThinPrep Pap test in clinical practice. A seven-month, 16,314-case experience in northern Vermont. *Acta Cytol* 1998;42(1):203-8.

13. Stevens MW, Nespolon WW, Milne AJ, Rowland R. Evaluation of the CytoRich® technique for cervical smears. *Diagn Cytopathol* 1998;18(3):236-42.

14. Carpenter AB, Davey DD. ThinPrep® Pap Test: performance and biopsy follow-up in a university hospital. *Cancer* 1999;87(3):105-12.

15. Diaz-Rosario LA, Kabawat SE. Performance of a fluid-based, thin-layer Papanicolaou smear method in the clinical setting of an independent laboratory and an outpatient screening population in New England. *Arch Pathol Lab Med* 1999;123(9):817-21.

16. Guidos BJ, Selvaggi SM. Use of the Thin Prep® Pap Test™ in clinical practice. *Diagn Cytopathol* 1999;20(2):70-3.

17. Saurel J, Rabreau M, Landi M, Bondu C, Montoya G, Morancé C, et al. Dépistage cytologique du cancer du col utérin par prélèvements en milieu liquide (CytoRich®). Étude préliminaire d'une série de 111 292 patientes. *Contracept Fertil Sex* 1999;27(12):853-7.

18. Shield PW, Nolan GR, Phillips GE, Cummings MC. Improving cervical cytology screening in a remote, high risk population. *Med J Aust* 1999;170(6):255-8.

19. Vassilakos P, Saurel J, Rondez R. Direct-to-vial use of the AutoCyte PREP liquid-based preparation for cervical-vaginal specimens in three European laboratories. *Acta Cytol* 1999;43(1):65-8.

20. Wang TY, Chen HS, Yang YC, Tsou MC. Comparison of fluid-based, thin-layer processing and conventional Papanicolaou methods for uterine cervical cytology. *J Formos Med Assoc* 1999;98(7):500-5.

21. Yeoh GP, Chan KW. Cell block preparation on residual ThinPrep® sample. *Diagn Cytopathol* 1999;21(6):427-31.

22. Yeoh GPS, Chan KW, Lauder I, Lam MB. Evaluation of the ThinPrep Papanicolaou test in clinical practice: 6-month study of 16 541 cases with histological correlation in 220 cases. *Hong Kong Med J* 1999;5(3):233-9.

23. Benoit JL, Ezzat WM, Murray RB. Evaluation of the ThinPrep Pap test in a Canadian screening population [abstract]. *Pathol Int* 2000;50 Suppl:A53.

24. Bishop JW, Cheuvront DA, Sims KL. Evaluation of the AutoCyte SCREEN system in a clinical cytopathology laboratory. *Acta Cytol* 2000;44(2):128-36.

25. Ishag MT, Keyhani-Rofagha S. Cervical cytohistologic correlation: a comparison between ThinPrep and conventional Pap smear methods [abstract]. *Acta Cytol* 2000;44(5):860.

26. Shumate A, Lang E, Rubenchik I. ThinPrep pap test - evaluation of diagnostic accuracy through biopsy comparison [abstract]. *Lab Invest* 2000;80(3):53A.

27. Tench W. Preliminary assessment of the AutoCyte PREP. Direct-to-vial performance. *J Reprod Med* 2000;45(11):912-6.

28. Weintraub J, Morabia A. Efficacy of a liquid-based thin layer method for cervical cancer screening in a population with a low incidence of cervical cancer. *Diagn Cytopathol* 2000;22(1):52-9.

29. Anton RC, Ramzy I, Schwartz MR, Younes P, Chakraborty S, Mody DR. Should the cytologic diagnosis of "atypical squamous cells of undetermined significance" be qualified? An assessment including comparison between conventional and liquid-based technologies. *Cancer* 2001;93(2):93-9.

30. Gupta PK, Baloch ZW, Cobbs C, Bibbo M. Processing liquid-based gynecologic specimens: comparison of the available techniques. *Acta Cytol* 2001;45(6):995-8.

31. Healey SM, Aronson KJ, Mao Y, Schlecht NF, Mery LS, Ferenczy A, et al. Oncogenic human papillomavirus infection and cervical lesions in aboriginal women of Nunavut, Canada. *Sex Transm Dis* 2001;28(12):694-700.

32. Hessling JJ, Raso DS, Schiffer B, Callicott J, Husain M, Taylor D. Effectiveness of thin-layer preparations vs. conventional Pap smears in a blinded, split-sample study. Extended cytologic evaluation. *J Reprod Med* 2001;46(10):880-6.

33. Marino JF, Fremont-Smith M. Direct-to-vial experience with AutoCyte PREP in a small New England regional cytology practice. *J Reprod Med* 2001;46(4):353-8.

34. Monsonego J, Autillo-Touati A, Bergeron C, Dachez R, Liaras J, Saurel J, et al. Liquid-based cytology for primary cervical cancer screening: a multi-centre study. *Br J Cancer* 2001;84(3):360-6.

35. Monsonégo J, Autillo-Touati A, Bergeron C, Dachez R, Liaras J, Saurel J, et al. Cytologie en phase liquide dans le cadre du dépistage primaire du cancer du col utérin : une étude multicentrique. *Gynecol Obstet Fertil* 2001;29(11):799-807.

36. Obwegeser JH, Brack S. Does liquid-based technology really improve detection of cervical neoplasia? A prospective, randomized trial comparing the ThinPrep Pap test with the conventional Pap test, including follow-up of HSIL cases. *Acta Cytol* 2001;45(5):709-14.

37. Baker JJ. Conventional and liquid-based cervicovaginal cytology: a comparison study with clinical and histologic follow-up. *Diagn Cytopathol* 2002;27(3):185-8.

38. Biscotti CV, O'Brien DL, Gero MA, Gramlich TL, Kennedy AW, Easley KA. Thin-layer Pap test vs. conventional Pap smear. Analysis of 400 split samples. *J Reprod Med* 2002;47(1):9-13.

39. Chhieng DC, Talley LI, Roberson J, Gatscha RM, Jhala NC, Elgert PA. Interobserver variability: comparison between liquid-based and conventional preparations in gynecologic cytology. *Cancer* 2002;96(2):67-73.

40. Day SJ, Deszo EL, Freund GG. Dual sampling of the endocervix and its impact on AutoCyte Prep endocervical adequacy. *Am J Clin Pathol* 2002;118(1):41-6.

41. Luthra UK, Chishti M, Dey P, Jolly SV, Abdulla M, Das DK, et al. Performance of monolayered cervical smears in a gynecology outpatient setting in Kuwait. *Acta Cytol* 2002;46(2):303-10.

42. Ring M, Bolger N, O'Donnell M, Malkin A, Bermingham N, Akpan E, et al. Evaluation of liquid-based cytology in cervical screening of high-risk populations: a split study of colposcopy and genito-urinary medicine populations. *Cytopathology* 2002;13(3):152-9.

43. Robyr R, Nazeer S, Vassilakos P, Matute JC, Sando Z, Halle G, et al. Feasibility of cytology-based cervical cancer screening in rural Cameroon. *Acta Cytol* 2002;46(6):1110-6.

44. Vassilakos P, Petignat P, Boulvain M, Campana A. Primary screening for cervical cancer precursors by the combined use of liquid-based cytology, computer-assisted cytology and HPV DNA testing. *Br J Cancer* 2002;86(3):382-8.

45. Veneti S, Katsaneva C, Nassioutziki M, Zervoudis S. The Pap-test of the 21st century: a comparative study of Autocyte Prep liquid-based cytology and the conventional smear [abstract]. *Acta Cytol* 2002;46(1 Suppl):249.

46. Wang N, Emancipator SN, Rose P, Rodriguez M, Abdul-Karim FW. Histologic follow-up of atypical endocervical cells. Liquid-based, thin-layer preparation vs. conventional Pap smear. *Acta Cytol* 2002;46(3):453-7.

(2) HPV testing versus Pap smears (53 reports)

(a) 47 reports

1. Ferris DG, Kriegel D, Cote L, Litaker M, Woodward L. Women's triage and management preferences for cervical cytologic reports demonstrating atypical squamous cells of undetermined significance and low-grade squamous intraepithelial lesions. *Arch Fam Med* 1997;6(4):348-53.

2. McLachlin CM, Alanen K, Raymond L, Elit L, Kerkvliet N, Smith E. Evaluation of hybrid capture HPV testing in the management of patients with ASCUS/LSIL pap smears [abstract]. *Clin Invest Med* 1997;20(4 Suppl):S70.

3. Raymond L, Elit L, Kerkvliet N, McLachlin CM. Evaluation of hybrid capture HPV testing as an aid to the management of colposcopy patients [abstract]. *Lab Invest* 1997;76(1):38A.

4. Sherman ME, Schiffman MH, Lorincz AT, Herrero R, Hutchinson ML, Bratti C, et al. Cervical specimens collected in liquid buffer are suitable for both cytologic screening and ancillary human papillomavirus testing. *Cancer* 1997;81(2):89-97.

5. Sigurdsson K, Árnadóttir T, Snorradottir M, Benediktsóttir K, Saemundsson H. Human papillomavirus (HPV) in an Icelandic population: the role of HPV DNA testing based on hybrid capture and PCR assays among women with screen-detected abnormal Pap smears. *Int J Cancer* 1997;72(3):446-52.

6. Clavel C, Bory JP, Rihet S, Masure M, Duval-Binninger I, Putaud I, et al. Comparative analysis of human papillomavirus detection by hybrid capture assay and routine cytologic screening to detect high-grade cervical lesions. *Int J Cancer* 1998;75(4):525-8.

7. Ferris DG, Wright TC, Litaker MS, Richart RM, Lorincz AT, Sun XW, et al. Triage of women with ASCUS and LSIL on Pap smear reports: management by repeat Pap smear, HPV DNA testing, or colposcopy? *J Fam Pract* 1998;46(2):125-34.

8. Ferris DG, Wright TC, Litaker MS, Richart RM, Lorincz AT, Sun XW, et al. Comparison of two tests for detecting carcinogenic HPV in women with Papanicolaou smear reports of ASCUS and LSIL. *J Fam Pract* 1998;46(2):136-41.

9. Nyirjesy I, Billingsley FS, Forman MR. Evaluation of atypical and low-grade cervical cytology in private practice. *Obstet Gynecol* 1998;92(4 Pt 1):601-7.

10. Recio FO, Sahai Srivastava BI, Wong C, Hempling RE, Eltabbakh GH, Piver MS. The clinical value of digene hybrid capture HPV DNA testing in a referral-based population with abnormal pap smears. *Eur J Gynaecol Oncol* 1998;19(3):203-8.

11. Vassilakos P, de Marval F, Muñoz M, Broquet G, Campana A. Human papillomavirus (HPV) DNA assay as an adjunct to liquid-based Pap test in the diagnostic triage of women with an abnormal Pap smear. *Int J Gynaecol Obstet* 1998;61(1):45-50.

12. Wright TC, Lorincz A, Ferris DG, Richart RM, Ferenczy A, Mielzynska I, et al. Reflex human papillomavirus deoxyribonucleic acid testing in women with abnormal Papanicolaou smears. *Am J Obstet Gynecol* 1998;178(5):962-6.

13. Cruickshank ME, Buchan S, Melvin WT, Kitchener HC. Human papillomavirus type 16 and 18 detection in the management of mild dyskaryosis. *Br J Obstet Gynaecol* 1999;106(9):969-76.

14. Riethmuller D, Gay C, Bertrand X, Bettinger D, Schaal JP, Carbillet JP, et al. Genital human papillomavirus infection among women recruited for routine cervical cancer screening or for colposcopy determined by Hybrid Capture II and polymerase chain reaction. *Diagn Mol Pathol* 1999;8(3):157-64.

15. Tonon SA, Picconi MA, Zinovich JB, Liotta DJ, Bos PD, Galuppo JA, et al. Human papillomavirus cervical infection and associated risk factors in a region of Argentina with a high incidence of cervical carcinoma. *Infect Dis Obstet Gynecol* 1999;7(5):237-43.

16. Tranovich V, Balliett C, Keyhani-Rofagha S. HPV testing improves the sensitivity of detecting HGSIL [abstract]. *Mod Pathol* 1999;12(1):52A.

17. Birner P, Schindl M, Stani J, Oberhuber G, Czerwenka K, Vutuc C, et al. Hybrid capture based human papillomavirus typing in cervical screening compared to cytology and histology. *Wien Klin Wochenschr* 2000;112(17):761-6.

18. Carozzi F, Ronco G, Confortini M, Noferini D, Maddau C, Ciatto S, et al. Prediction of high-grade cervical intraepithelial neoplasia in cytologically normal women by human papillomavirus testing. *Br J Cancer* 2000;83(11):1462-7.

19. Costa S, Sideri M, Syrjänen K, Terzano P, De Nuzzo M, De Simone P, et al. Combined Pap smear, cervicography and HPV DNA testing in the detection of cervical intraepithelial neoplasia and cancer. *Acta Cytol* 2000;44(3):310-8.

20. Fait G, Kupferminc MJ, Daniel Y, Geva E, Ron IG, Lessing JB, et al. Contribution of human papillomavirus testing by hybrid capture in the triage of women with repeated abnormal pap smears before colposcopy referral. *Gynecol Oncol* 2000;79(2):177-80.

21. Kuperman L, Krumholz BA. The triage of women with ASCUS cytology using human papillomavirus DNA testing. *J Lower Genital Tract Dis* 2000;4(1):1-6.

22. Simsir A, Sun CC, Ioffe O, Khanna N. Is HPV testing useful in qualifying the ASCUS pap smear (PS)? [abstract]. *Lab Invest* 2000;80(3):54A.

23. Lin CT, Tseng CJ, Lai CH, Hsueh S, Huang HJ, Law KS. High-risk HPV DNA detection by Hybrid Capture II. An adjunctive test for mildly abnormal cytologic smears in women > or = 50 years of age. *J Reprod Med* 2000;45(4):345-50.

24. Shlay JC, Dunn T, Byers T, Baron AE, Douglas JM. Prediction of cervical intraepithelial neoplasia grade 2-3 using risk assessment and human papillomavirus testing in women with atypia on Papanicolaou smears. *Obstet Gynecol* 2000;96(3):410-6.

25. Zuna RE, Dunn ST. Utility of HPV testing as a quality assurance monitor for cervical cytology [abstract]. *Lab Invest* 2000;80(3):219A.

26. Belinson J, Qiao YL, Pretorius R, Zhang WH, Elson P, Li L, et al. Shanxi Province Cervical Cancer Screening Study: a cross-sectional comparative trial of multiple techniques to detect cervical neoplasia. *Gynecol Oncol* 2001;83(2):439-44.

27. Lanham S, Herbert A, Watt P. HPV detection and measurement of HPV-16, telomerase, and survivin transcripts in colposcopy clinic patients. *J Clin Pathol* 2001;54(4):304-8.

28. Lee CN, Cavanagh HM, Lo ST, Ng CS. Human papillomavirus infection in non-neoplastic uterine cervical disease in Hong Kong. *Br J Biomed Sci* 2001;58(2):85-91.

29. Oh YL, Shin KJ, Han J, Kim DS. Significance of high-risk human papillomavirus detection by polymerase chain reaction in primary cervical cancer screening. *Cytopathology* 2001;12(2):75-83.

30. Rebello G, Hallam N, Smart G, Farquharson D, McCafferty J. Human papillomavirus testing and the management of women with mildly abnormal cervical smears: an observational study. *BMJ* 2001;322(7291):893-4.

31. Schneede P, Hillemanns P, Ziller F, Hofstetter A, Stockfleth E, Arndt R, et al. Evaluation of HPV testing by Hybrid Capture II for routine gynecologic screening. *Acta Obstet Gynecol Scand* 2001;80(8):750-2.

32. Tanaka H, Karube A, Tanaka T, Nakagomi O. Much higher risk of premalignant and malignant cervical diseases in younger women positive for HPV16 than in older women positive for HPV16. *Microbiol Immunol* 2001;45(4):323-6.

33. Terry G, Ho L, Londesborough P, Cuzick J, Mielzynska-Lohnas I, Lorincz A. Detection of high-risk HPV types by the Hybrid Capture 2 test. *J Med Virol* 2001;65(1):155-62.

34. Zielinski GD, Snijders PJ, Rozendaal L, Voorhorst FJ, van der Linden HC, Runsink AP, et al. HPV presence precedes abnormal cytology in women developing cervical cancer and signals false negative smears. *Br J Cancer* 2001;85(3):398-404.

35. Bourgain CM, De Sutter PN, Willocx FJ, Arbyn MA. Combined HPV testing and liquid based cervical cytology: experience in primary and triage screening. *Acta Cytol* 2002;46(1 Suppl):99.

36. Castle PE, Wacholder S, Sherman ME, Lorincz AT, Glass AG, Scott DR, et al. Absolute risk of a subsequent abnormal Pap among oncogenic human papillomavirus DNA -positive, cytologically negative women. *Cancer* 2002;95(10):2145-51.

37. Dzuba IG, Díaz EY, Allen B, Leonard YF, Lazcano Ponce EC, Shah KV, et al. The acceptability of self-collected samples for HPV testing vs. the Pap test as alternatives in cervical cancer screening. *J Womens Health Gend Based Med* 2002;11(3):265-75.

38. Hong IS, Marshalleck J, Williams RH, Gaiter TE, Mielzynska-Lohnas I, Kim K. Comparative analysis of a liquid-based Pap test and concurrent HPV DNA assay of residual samples. A study of 608 cases. *Acta Cytol* 2002;46(5):828-34.

39. Hughes SA, Sun D, Gibson C, Bellerose B, Rushing L, Chen H, et al. Managing atypical squamous cells of undetermined significance (ASCUS): human papillomavirus testing, ASCUS subtyping,or follow-up cytology? *Am J Obstet Gynecol* 2002;186(3):396-403.

40. Kulasingam SL, Hughes JP, Kiviat NB, Mao C, Weiss NS, Kuypers JM, et al. Evaluation of human papillomavirus testing in primary screening for cervical abnormalities: comparison of sensitivity, specificity, and frequency of referral. *JAMA* 2002;288(14):1749-57.

41. Neumann HH, Kleijer G. Correlation between cytologic results and Hybrid Capture II: comparison between conventional Pap smears and AutoCyte PREP™ slides [abstract]. *Acta Cytol* 2002;46(1 Suppl):194.

42. Nobbenhuis MA, Helmerhorst TJ, van den Brule AJ, Rozendaal L, Jaspars LH, Voorhorst FJ, et al. Primary screening for high risk HPV by home obtained cervicovaginal lavage is an alternative screening tool for unscreened women. *J Clin Pathol* 2002;55(6):435-9.

43. Keyhani-Rofagha S, Tranovich V, Balliett C. HPV testing improves the sensitivity of detecting HSIL [abstract]. *Acta Cytol* 2002;46(1 Suppl):152.

44. Levi AW, Ronnett BM, Kelly DP, Rosenthal DL. The triage of ASCUS: correlation of AutoCyte PREP cytology with results of reflex HPV testing by Hybrid Capture II® (HC 2) and clinical follow-up [abstract]. *Lab Invest* 2002;82(1):78A.

45. Nene BM, Sankaranarayanan R, Dinshaw KA, Jayant K, Keskar VR, Rajeshwarkar R, et al. Comparative efficacy of visual inspection with acetic acid, HPV testing and conventional cytology in cervical cancer screening: a randomised intervention trial in Maharashtra State, India [abstract]. *Int J Cancer Suppl* 2002;(13):98.

46. Scott DR, Hagmar B, Maddox P, Hjerpe A, Dillner J, Cuzick J, et al. Use of human papillomavirus DNA testing to compare equivocal cervical cytologic interpretations in the United States, Scandinavia, and the United Kingdom. *Cancer* 2002;96(1):14-20.

47. Volkov VG, Koroleva LN. A comparative study of cervical cytology and human papillomavirus testing in females in Russia [abstract]. *Int J Cancer Suppl* 2002;(13):169.

(b) ALTS (6 reports)

1. Schiffman M, Adrianza ME. ASCUS-LSIL Triage Study. Design, methods and characteristics of trial participants. *Acta Cytol* 2000;44(5):726-42.

2. Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesions Triage Study (ALTS) Group. Human papillomavirus testing for triage of women with cytologic evidence of low-grade squamous intraepithelial lesions: baseline data from a randomized trial. *J Natl Cancer Inst* 2000;92(5):397-402.

3. Solomon D, Schiffman M, Tarone R. Comparison of three management strategies for patients with atypical squamous cells of undetermined significance: baseline results from a randomized trial. *J Natl Cancer Inst* 2001;93(4):293-9.

4. Sherman ME, Solomon D, Schiffman M, ALTS Group. Qualification of ASCUS. A comparison of equivocal LSIL and equivocal HSIL cervical cytology in the ASCUS LSIL Triage Study. *Am J Clin Pathol* 2001;116(3):386-94.

5. Sherman ME, Schiffman M, Cox JT. Effects of age and human papilloma viral load on colposcopy triage: data from the randomized Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesion Triage Study (ALTS). *J Natl Cancer Inst* 2002;94(2):102-7.

6. Sherman ME, Wang SS, Tarone R, Rich L, Schiffman M. Histopathologic extent of cervical intraepithelial neoplasia 3 lesions in the Atypical Squamous Cells of Undetermined Significance Low-grade Squamous Intraepithelial Lesion Triage Study: implications for subject safety and lead-time bias. *Cancer Epidemiol Biomarkers Prev* 2003;12(4):372-9.

Review of Economic Studies

(1) LBC versus Pap smears (5 reports)

1. Candel A, Davis B, Bakhos R, Selvaggi S. The ThinPrep Pap test: a cost savings perspective [abstract]. *Lab Invest* 1998;78(1):36A.

2. Raab SS, Zaleski MS, Silverman JF. The cost-effectiveness of the cytology laboratory and new cytology technologies in cervical cancer prevention. *Am J Clin Pathol* 1999;111(2):259-66.

3. Johnson T, Maksem JA, Belsheim BL, Roose EB, Klock LA, Eatwell L. Liquid-based cervical-cell collection with brushes and wooden spatulas: a comparison of 100 conventional smears from high-risk women to liquid-fixed cytocentrifuge slides, demonstrating a cost-effective, alternative monolayer slide preparation method. *Diagn Cytopathol* 2000;22(2):86-91.

4. Le Galès C, Méréa E, Cartier I, Coste J, Vacher-Lavenu MC, Vielh P, et al. Cost and effectiveness of human papillomavirus testing compared to that of conventional Pap smears for cervical cancer screening: protocol of the study of the French Society of Clinical Cytology [abstract]. *Acta Cytol* 2002;46(1 Suppl):167.

5. Maxwell GL, Carlson JW, Ochoa M, Krivak T, Rose GS, Myers ER. Costs and effectiveness of alternative strategies for cervical cancer screening in military beneficiaries. *Obstet Gynecol* 2002;100(4):740-8.

(2) HPV testing versus Pap smears (13 reports)

1. Shlay JC, Dunn T, Byers T, Baron AE, Douglas JM. Prediction of cervical intraepithelial neoplasia grade 2-3 using risk assessment and human papillomavirus testing in women with atypia on Papanicolaou smears. *Obstet Gynecol* 2000;96(3):410-6.

2. Philips Z, Whynes DK. Early withdrawal from cervical cancer screening: the question of cost-effectiveness. *Eur J Cancer* 2001;37(14):1775-80.

3. Taylor LA, Sorensen SV, Ray NF, Halpern MT, Harper DM. Cost-effectiveness of the conventional Papanicolaou test with a new adjunct to cytological screening for squamous cell carcinoma of the uterine cervix and its precursors. *Arch Fam Med* 2000;9(8):713-21. Available: http://archfami.ama-assn.org/issues/v9n8/fpdf/foc9048.pdf.

4. Gamzu R, Almog B, Levin I, Fainaru O, Niv J, Lessing JB, et al. Clinical and economic implications of adding HPV tests to the routine cytology follow-up and management of patients with histologically defined cervical intraepithelial neoplasia grade 1. *Gynecol Oncol* 2002;86(2):129-33.

5. McLachlin CM, Alanen KW, Elit LM, Smith EA, Kerkvliet NA. Hybrid Capture human papillomavirus testing as an adjunct to the follow-up of patients with ASCUS and LGSIL Pap smears: a study of a screening population. *J Lower Genital Tract Dis* 2000;4(1):12-7.

6. Kaufman RH, Adam E, Icenogle J, Reeves WC. Human papillomavirus testing as triage for atypical squamous cells of undetermined significance and low-grade squamous intraepithelial lesions: sensitivity, specificity, and cost-effectiveness. *Am J Obstet Gynecol* 1997;177(4):930-6.

7. Cardosi RJ, Arango HA, Phillips R, Towsley GA, Hoffman MS. Atypical squamous cells of undetermined significance: do we need colposcopy? *J Gynecol Surg* 1999;15(1):13-7.

8. Costa S, Sideri M, Bucchi L, Schettino F, Maini I, Spinaci L, et al. Cervicography and HPV DNA testing as triage criteria for patients with abnormal pap smear. *Gynecol Oncol* 1998;71(3):404-9.

9. Amestoy GM, Crimi G, Polverini G, Monge F, Abalo ER. Evaluación del rol de los DNA -- tests en el diagnóstico de la patología del cuello uterino [Evaluation of the role of DNA testing in the diagnosis of uterine cervical cancer]. *Prensa Med Argent* 1999;86(7):653-6.

10. Duttagupta C, Sengupta S, Roy M, Sengupta D, Chakraborty S, Bhattacharya P, et al. Oncogenic human papillomavirus (HPV) infection and uterine cervical cancer: a screening strategy in the perspective of rural India. *Eur J Cancer Prev* 2002;11(5):447-56.

11. Sherlaw-Johnson C, Gallivan S, Jenkins D. Evaluating cervical cancer screening programmes for developing countries. *Int J Cancer* 1997;72(2):210-6.

12. Myers ER, McCrory DC, Nanda K, Bastian L, Matchar DB. Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. *Am J Epidemiol* 2000;151(12):1158-71.

13. Goldie SJ, Freedberg KA, Weinstein MC, Wright TC, Kuntz KM. Cost effectiveness of human papillomavirus testing to augment cervical cancer screening in women infected with the human immunodeficiency virus. *Am J Med* 2001;111(2):140-9.

Appendix 7: Diagnostic Accuracy Trials on LBC Versus Pap Smears

Author, Year (Setting)	Design	Participant Characteristics			LBC				Pap smear			Quality
		Sample (number)	Age (years)	Lesion	Technique	Unsatis (%)	Sens (%)	Spec (%)	Unsatis (%)	Sens (%)	Spec (%)	
Bishop, 1998 (US, Canada, Kenya, Vietnam)[37]	Split-sample	Routine screening from eight centres (n=9,835)	16 to 87	LSIL+	AutoCyte Prep	54/ 9,212 (0.6)	83/93 (89)	13/29 (45)	89/9,212 (1)	73/93 (78.5)	5/29 (17)	Recruitment, not random; verification, positives only; Ref Stand, histology; blind verification, yes; industry, total.
Bolick, 1998 (US)[38]	Two-cohort	Routine screening from variety of clinical practices (n=10,694 for LBC, n=39,408 for Pap smear)	≥15 (median 30 to 39)	LSIL+	ThinPrep-2000	31/ 10,964 (0.3)	40/42 (95)	7/12 (58)	427/ 39,408 (1)	57/67 (85)	8/22 (36)	Recruitment, not random; verification, positives only; Ref Stand, histology; blind verification, no; industry, none.
Corkill, 1998 (US)[39]	Split-sample	Routine screening at regional planned parenthood clinics (n=1,583)	18 to 66	LSIL+	ThinPrep-2000	NR	60/84 (71)	NR	NR	29/84 (34.5)	NR	Recruitment, not random; verification, positives with 5% random negatives; Ref Stand, independent review; blind verification, yes; industry: total.
Inhorn, 1998 (US)[40]	Two FDA split-sample trials and two validation trials	Participants with cervical cancer (n=47)	NR	Invasive cancer	ThinPrep-Beta/2000	NR	45/47 (96)	NR	NR	44/47 (94)	NR	Recruitment, not random; verification, positives only; Ref Stand, histology; blind verification, yes in ThinPrep 2000 arm; industry, total.

Author, Year (Setting)	Design	Participant Characteristics			LBC				Pap smear			Quality
		Sample (number)	Age (years)	Lesion	Technique	Unsatis (%)	Sens (%)	Spec (%)	Unsatis (%)	Sens (%)	Spec (%)	
Sherman, 1998 (US)[41]	Split-sample	Routine screening from larger group participating in trial, from three screening centres and three hospital centres (1,780)	NR	LSIL+	ThinPrep-2000	NR	443/549 (81)	NR	NR	374/ 549 (68)	NR	Recruitment, not random; verification, positives with 5% random negatives; Ref Stand, independent review; blind verification, yes; industry, total.
Hutchinson, 1999 (Costa Rica)[42]	Split-sample	Voluntary participants with cancer incidence of 30/100,000 per year, (in US National Cancer Institute trial) (n=10,049)	NR	LSIL+	ThinPrep-Beta	NR	284/323 (88)	NR	NR	222/ 323 (69)	NR	Recruitment, random; verification, positives only; Ref Stand, histology or cytology; blind verification, yes; industry, partial.
Ferris, 2000 (US)[43]	Two-cohort	Routine screening from three centres; 80% from general screening cohort and 20% from colposcopy cohort (LBC, 1,004; Pap smear, 2,110)	≥18	LSIL+	ThinPrep-2000	12/ 1,004 (1)	61/116 (53)	825/ 829 (99.5)	76/ 2,110 (4)	36/57 (63)	1,846/ 1,851 (99.7)	Recruitment, not random; verification, positives only; Ref Stand, histology; blind verification, no; industry, partial.

Author, Year (Setting)	Design	Participant Characteristics			LBC				Pap smear			Quality
		Sample (number)	Age (years)	Lesion	Technique	Unsatis (%)	Sens (%)	Spec (%)	Unsatis (%)	Sens (%)	Spec (%)	
Minge, 2000 (US)[44]	Split-sample	Population with SIL prevalence of 6.5% from three obstetric-gynecologic practices (n=2,156)	15 to 57	LSIL+	AutoCyte Prep	2/2,156 (0.1)	NR (53)	NR (79)	19/ 2,156 (0.9)	NR (62)	NR (89)	Recruitment, not random; verification, positives only; Ref Stand, histology; blind verification, yes; industry, partial.
Vassilakos, 2000 (Switzerland)[46]	Two-cohort	High risk population (≥ASC) from one geographic area, with participation of 97 physicians (n=101,043)	≥10 (median 25 to 44)	LSIL+	AutoCyte Prep	126/ 32,655 (0.4)	690/ 758 (91)	NR	290/ 15,402 (2)	124/ 140 (89)	NR	Recruitment, random; verification, positives only; Ref Stand, histology; blind verification, no; industry none.
Bergeron, 2001 (France)[34]	Split-sample	Patients with previous abnormal cytology referred for management (n=500)	NR	LSIL+	AutoCyte Prep	4/500 (0.8)	273/ 408 (82)	NR	58/500 (12)	249/ 408 (61)	NR	Recruitment, not random; verification, positives and negatives; Ref Stand, histology; blind verification, yes; industry, none.
Park, 2001 (Korea)[49]	Split-sample	Patients with known or suspected cervical abnormalities (n=483)	NR	LSIL+	ThinPrep-2000	5/483 (1)	72/87 (83)	44/53 (83)	5/483 (1)	76/87 (87)	37/53 (70)	Recruitment, not random; verification, positives and negatives; Ref Stand, histology; blind verification, yes; industry, partial.

Author, Year (Setting)	Design	Participant Characteristics			LBC				Pap smear			Quality
		Sample (number)	Age (years)	Lesion	Technique	Unsatis (%)	Sens (%)	Spec (%)	Unsatis (%)	Sens (%)	Spec (%)	
Confortini, 2002 (Italy)[50]	Split-sample	Participants undergoing colposcopy in screening program of one district (n=99)	NR	LSIL+	ThinPrep-2000	NR	20/22 (91)	NR	NR	19/22 (86)	NR	Recruitment, not random; verification, positives and negatives; Ref Stand, histology; blind verification, yes; industry, none.
Coste, 2003 (France)[51]	Split-sample	Participants referred for colposcopy (n=828)	Mean (SD) 38 (12)	LSIL+	ThinPrep-2000	11/ 2,580 (0.4)	NR (83)	NR (85)	3/2,582 (0.1)	NR (86)	NR (89)	Recruitment, not random; verification, positives and negatives; Ref Stand, histology; blind verification, yes; industry, none.
		routine screening (n=1,757)	33 (11)				NR (61)	NR (95)		NR (57)	NR (96)	

NR = not reported
Sens = sensitivity
Spec = specificity
Ref Stand = reference standard
Unsatis = unsatisfactory specimens for evaluation

Appendix 8: The ALTS (ASCUS/LSIL Triage Study)

The ALTS, sponsored by the US National Cancer Institute, is a multi-centre randomized clinical trial comparing the sensitivity and specificity of three strategies to detect CIN 3: immediate colposcopy (considered to be the reference standard), triage to colposcopy based on HPV results from HC-II and ThinPrep results or triage based on cytology results. Our inspection of the published report on the design and methods of the ALTS,[102] showed that the slides from participants in the cytology triage arm were prepared using ThinPrep and not Pap smear. Throughout follow-up, only the ThinPrep cytology results were used for referral to colposcopy. The rationale for using ThinPrep was based on preliminary data gathered by the trial investigators. These unpublished data demonstrated an equivalent sensitivity of the ThinPrep and Pap smear for the detection of HSIL.[102] Also, diagnostic characteristics presented in the ALTS are not truly representative of women randomized to the HPV triage arm as test performance is "….based on the combined HPV triage and immediate colposcopy arms…."[103]

The ALTS published its clinical findings[95-97,102-104] and cost-effectiveness data will be published as separate reports. The key findings from this trial are listed here.

- The HPV triage arm for women referred with a cytologic diagnosis of LSIL (n=642) was closed early, because an interim analysis showed that 83% of these women would undergo triage to colposcopy based on a positive HPV test. This high frequency was confirmed by PCR assays in a subset of 210 paired specimens tested by HC-II and PCR (81% were positive according to both methods).[104]

- The HPV triage arm for women referred with a cytologic diagnosis of ASCUS (n=3,488) showed that 56% of women would undergo triage to colposcopy based on a positive HPV test (96% overall sensitivity to detect CIN 3 or above).[103] The sensitivity rate varied minimally with age (range 94% to 98%), but HPV testing at this threshold would refer 31% of women aged 29 years or older to colposcopy, compared with more than 65% of younger women.[96] Among women aged 29 years or older with ASCUS, referral for repeat cytopathology (using ThinPrep) had a sensitivity of 91% and would refer 50% of women to colposcopy.[96]

- According to the authors, "for women with ASCUS, HPV testing was highly sensitive for detecting CIN 3 and cancer with dramatically fewer referrals of older women. Neither a single HPV test nor repeat cytopathology provides useful triage for women with LSIL."[96]

Appendix 9: Diagnostic Accuracy Trials on HPV Testing Versus Pap Smears

Author, Year (Setting)	Participant Characteristics		HPV				Pap smear			Quality
	Sample (number)	Age (years)	Method	Reference standard	Sens (%)	Spec (%)	Lesion	Sens (%)	Spec (%)	
Primary Screening										
Cuzick, 1999 (UK)[57]	Routine screening in 40 general practices (n=2,988)	46 (34 to 70)	HC-II*	CIN 2+	20/21 (95)	(95)	LSIL+	(79)	(99)	Recruitment, not random; verification, positives only; Ref Stand, histology; blind verification, yes; industry, none.
			PCR		(74)	(97)				
Levert, 2000 (France)[53]	Participants undergoing routine screening (n=3,778)	36 (15 to 85)	HC-II	CIN 2+	85/85 (100)	3,187/ 3,693 (86)	HSIL	73/85 (86)	3,472/ 3,693 (94)	Recruitment, not random; verification, positives only; Ref Stand, histology; blind verification, not reported; industry: none.
Ratnam, 2000 (Canada)[61]	Routine screening in 10 clinics representing different regions in Newfoundland (n=2,098)	30 (18 to 69)	HC-I or II	CIN 2+	(68)	(91)	LSIL+	(27)	(96)	Recruitment, not random; verification, positives with random 10% negatives; Ref Stand, histology; blind verification, no; industry, none.
					HPV+ Pap (76)	HPV+ Pap (89)				
Schiffman, 2000 (Costa Rica)[62]	Subset of a larger population-based trial; participants with no history of hysterectomy (n=8,554)	37 (18 to 90)	HC-II†	CIN 2+	(88)	(89)	ASCUS+	(78)	(94)	Recruitment, random; verification, positives and random 2% negatives; Ref Stand, histology; blind verification, yes; industry, partial.

* Stratified sample of 1,703
† Stratified sample of 1,119

Author, Year (Setting)	Participant Characteristics		HPV				Pap smear			Quality
	Sample (number)	Age (years)	Method	Reference standard	Sens (%)	Spec (%)	Lesion	Sens (%)	Spec (%)	
Primary Screening										
Schneider, 2000 (Germany)[60]	Participants who visited eight offices of 10 private gynecologists (n=4,761)	35 (18 to 70)	PCR	CIN 2+	(89)	(94)	LSIL+	(20)	(99)	Recruitment, not random; verification, the true prevalence of CIN 2+ estimated by projection from histologically verified subgroups (Begg-corrected estimates); Ref Stand, histology; blind verification, yes; industry, none.
Wright, 2000 (South Africa)[64]	Routine screening using clinican-obtained cervical sample at primary care clinical site in one pre-urban settlement (n=1,415)	35 to 65	HC-II	CIN 2+	47/56 (84)	1,072/ 1,269 (84.5)	LSIL+	34/56 (61)	1,102/ 1,269 (87)	Recruitment, not random; verification, positives only; Ref Stand, histology; blind verification, yes; industry, none.
Blumenthal, 2001 (Zimbabwe)[67]	Participants attending 15 primary care in two peri-urban areas (n=2,073)	25 to 55	HC-II	CIN 2+	(80) HPV+ Pap (43)	(61) HPV+ Pap (91)	LSIL+	(44)	(91)	Recruitment, not random; verification, positives and negatives; Ref Stand, histology; blind verification, yes; industry, none.

Author, Year (Setting)	Participant Characteristics		HPV				Pap smear			Quality
	Sample (number)	Age (years)	Method	Reference standard	Sens (%)	Spec (%)	Lesion	Sens (%)	Spec (%)	
Primary Screening										
Clavel, 2001 (France)[35]	Participants undergoing biennial or triennial routine screening in department of obstetrics and gynecology (n=7,932)	34 (15 to 76)	HC-II	CIN 2+	47/47 (100)	1,950/ 2,234 (87)	HSIL	32/47 (68)	2,130/ 2,234 (95)	Recruitment, not random; verification, positives only; Ref Stand, histology; blind verification, no; industry: none.
Paraskevaidis, 2001 (Greece)[55]	Participants at outpatient clinics of department of obstetrics and gynecology of university hospital (n=1,000)	38 (17 to 79)	PCR	CIN 2+	25/28 (89) HPV+ Pap (96)	NR	LSIL+	25/28 (89)	NR	Recruitment, not random; verification, positives only; Ref Stand, histology; blind verification, yes; industry, not reported.
Petry, 2002 (Germany)[56]	Attending gynecologists in two regions for routine screening (n=8,468)	30 to 55	HC-II	CIN 2+	(98)	(96)	ASCUS+	(42)	(98)	Recruitment, not random; verification, positives and 5% of negatives; Ref Stand, histology; blind verification, yes; industry, not reported.
Syrjänen, 2002 (Russia, Belarus, Latvia)[58]	Participants from six clinics (screening, gynecological, or STD patients) (n=3,175)	33 (15 to 85)	HC-II	CIN 3+	(97) HPV+ Pap (93.5)	(16) HPV+ Pap (17)	HSIL	(64)	(89)	Recruitment, not random; verification, positives only; Ref Stand, histology; blind verification, no; industry, none.
Coste, 2003 (France)[51]	Routine screening (n=1,757)	33 (11)	HC-II	CIN 2+	96	85	HSIL+	60	99	Recruitment, not random; verification, positives and negatives; Ref Stand, histology; blind verification, yes; industry, none.

Author, Year (Setting)	Participant Characteristics		HPV				Pap smear			Quality
	Sample (number)	Age (years)	Method	Reference standard	Sens (%)	Spec (%)	Lesion	Sens (%)	Spec (%)	
Triage										
Adam, 1998 (US)[75]	Participants referred after two Pap smears reported as ASCUS or LSIL (n=454); 553 referred after one smear reported as HSIL	NR	PCR	CIN 2+	(67.5)*	(35)	ASCUS+	(62)	(62)	Recruitment, not random; verification, positives and negatives; Ref Stand, histology; blind verification, not reported; industry, none.
Manos, 1999 (US)[73]	995 participants with ASCUS Pap smear results; from cohort (n=46,009) who had routine screening in large HMO	37 (15 to 78)	HC-II	CIN 2+	(89)†	(64)	HSIL+	(76)	NR	Recruitment, not random; verification, positives and negatives; Ref Stand, histology; blind verification, not reported; industry, partial.
Zdenek, 1999 (Czech Republic)[76]	Referred (ASCUS+) with abnormal cytology and colposcopy or both, from 102 outpatient clinics (n=1,158)	35 (16 to 73)	HC-II	CIN 2+	160/ 245 (66) HPV+ Pap (83)	603/913 (66) HPV+ Pap (69)	HSIL	84/245 (35)	840/913 (92)	Recruitment, not random; verification, positives and negatives; Ref Stand, histology; blind verification, no; industry, none.
Bergeron, 2000 (France)[69]	Participants with ASCUS (n=111) or LSIL (n=267) assessed in private laboratory	35 (15 to 75)	HC-II	CIN 2+	(88)‡ HPV+ Pap (94)	(53) HPV+ Pap (57)	ASCUS+	(83)	(58)	Recruitment, not random; verification, positives and negatives; Ref Stand, histology; blind verification, yes; industry, partial.

* Sensitivity of HPV testing is 71% for ASCUS or LSIL and 64% for HSIL; specificity is 23.5% and 46%.
† Test conducted on specimen taken using LBC.
‡ Sensitivity of HPV testing is 83% for ASCUS and 93% for LSIL; specificity is 62% and 44%. For Pap smear, the respective values are 66% and 100% for sensitivity and 71% and 45% for specificity.

Author, Year (Setting)	Participant Characteristics		HPV				Pap smear			Quality
	Sample (number)	Age (years)	Method	Reference standard	Sens (%)	Spec (%)	Lesion	Sens (%)	Spec (%)	
Triage										
Lytwyn, 2000 (Canada)[70]	Participants with ASCUS or LSIL on Pap smear; recruited from 52 community-based family practices and one university student health clinic in Ontario (n=212)	30 (16 to 50)	HC-II	CIN 2+	7/8 (87.5)	40/79 (51)	ASCUS+	5/9 (56)	35/63 (56)	Recruitment, random; verification, positives and negatives; Ref Stand, histology; blind verification, yes; industry, none.
Lee, 2001 (Korea)[72]	Participants who had diagnoses of ASCUS, LSIL or HSIL (n=457)	19 to 85	HC-II	CIN 2+	(88) HPV+ Pap (93)	(67) HPV+ Pap (29)	ASCUS+	(93)	(31)	Recruitment, not random; verification, positives and select fraction of negatives; Ref Stand, histology; blind verification, yes; industry, none.
Morin, 2001 (Canada)[71]	Participants diagnosed with ASCUS (n=360)	18 to 50	HC-II/ PCR	CIN 2+	(89.5)/ (89.5) HC-II+ Pap (95) PCR+ Pap (95)	(74)/ (59) HC-II+ Pap (73) PCR+ Pap (58)	LSIL+	(74)	(63)	Recruitment, not random; verification, positives and negatives; Ref Stand, histology; blind verification, NR; industry, none.
Zielinski, 2001 (The Netherlands)[74]	Participants with single Pap smear (n=172) or two sequential smears (n=106) taken within six months, read as borderline or mild dyskaryosis	40 (20 to 76); 41 (24 to 67)	HC-II	CIN 2+	(96)	(60)	LSIL+	(56)	(76)	Recruitment: not random; verification, positives and negatives; Ref Stand, histology; blind verification, NR; industry, NR.
Coste, 2003 (France)[51]	Participants with ASCUS+ referred for colposcopy (n=828)	38 (12)	HC-II	CIN 2+	(81)	(50)	HSIL	(85)	(92)	Recruitment, not random; verification, positives and negatives; Ref Stand: histology; blind verification, yes; industry, none.

Author, Year (Setting)	Participant Characteristics		HPV				Pap smear			Quality
	Sample (number)	Age (years)	Method	Reference standard	Sens (%)	Spec (%)	Lesion	Sens (%)	Spec (%)	
Surveillance										
Paraskevaidis, 2001 (Greece)[78]	41 participants who developed CIN after treatment and 82 without CIN for five years after treatment (retrospective analysis)	34 (31.5 to 40)	PCR	CIN 1+	At 4 months (93)	(84)	LSIL+	At 4 months (49)	(87)	Recruitment, not random; verification, positives and negatives; Ref Stand, histology; blind verification, NR; industry, none.
Nobbenhuis, 2001 (The Netherlands)[79]	Participants treated for CIN 2/3 (n=184), post-treatment comparison between HPV testing and Pap smear	34 (21 to 70)	PCR	CIN 2/3	3 months (93)	(86)	LSIL+	3 months (58)	(91)	Recruitment, not random; verification, positives only; Ref Stand, histology; blind verification, yes; industry, none.
					12 months (90)	(96)		12 months (72)	(95)	
					24 months (93)	(99)		24 months (93)	(96)	

NR = not reported
Sens = sensitivity
Spec = specificity
Ref Stand = reference standard