ASSESSMENT OF TECHNIQUES FOR CERVICAL CANCER SCREENING
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ASSESSMENT OF TECHNIQUES FOR CERVICAL CANCER SCREENING

PROJECT DIRECTOR:
Hussein Z. Noorani

PROJECT TEAM:
Cheryl Arratoon
Annie Hall

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110-955 Green Valley Crescent
Ottawa, Ontario, Canada K2C 3V4
Telephone (613) 226-2553
Facsimile (613) 226-5392
Internet http://www.ccohta.ca
Email ccohta@ccohta.ca
This report was reviewed by external reviewers and by members of a subcommittee of CCOHTA’s Scientific Advisory Panel. These individuals kindly provided comments on drafts of this report. This final document incorporates most of the Reviewers comments, however, the authors take sole responsibility for its form and content.

**External Reviewers**

Dr. William Geddie  
Director, Cytopathology Laboratory  
Credit Valley Hospital  
Mississauga, Ontario

Dr. Jean Parboosingh  
Senior Medical Consultant  
Adult Health Division  
Health Promotion and Programs Branch  
Health Canada

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Dr. Murray Krahn  
Staff Physician  
Division of General Internal Medicine & Clinical Epidemiology  
The Toronto Hospital  
Toronto, Ontario
EXECUTIVE SUMMARY

Cervical cancer is one of the few readily preventable forms of cancer. Although the Papanicolaou (Pap) smear has had an enormous impact on the incidence and mortality rates of cervical cancer over the past four decades, concerns over false-negative rates and their adverse effects on patients have driven the search for strategies to improve the Pap test, and development of emerging technologies.

The use of particular cell collection devices has minimal effect on smear quality. Instead, training for smear takers and feedback on their performance from laboratories would significantly improve smear quality. A significant impact would result from dialogue between smear takers and cytotechnologists to reach consensus as to the components of an adequate smear. Automated methods of monolayer preparation that produce cleaner, more evenly dispersed smears appear to improve detection of abnormal cases. However, further analysis is required to balance this gain with the high cost of equipment and interpretive training of staff.

Automated devices for the rescreening of slides previously examined by humans are more effective, but also more costly than manual rescreening. Both of the automated systems compared in the economic evaluation appear to be of similar efficacy, but dissimilar cost. Sensitivity analyses over the range of values for each key variable revealed that the cost-effectiveness ratios for these systems were sensitive to the per rescreening cost by automated device.

The potential role of human papillomavirus (HPV) testing in screening for cervical cancer depends upon clarification of the link between HPV infection and invasive disease, and the ability to overcome cost and technical barriers.
OBJECTIVES

The following four objectives were identified for study:

1. To examine the effectiveness of the Pap test.
2. To consider different strategies for improving the effectiveness of the Pap test.
3. To compare the cost-effectiveness of automated rescreening strategies.
4. To consider emerging technologies.
I INTRODUCTION

Cervical cancer is uncommon in Canada, with an estimated incidence of 1,350 cases and 390 deaths in 1996.\(^1\) This relatively low incidence and mortality is largely attributed to the effectiveness of cytologic screening by the Papanicolaou test (Pap test).\(^2\) Based on self-reported data from provincial and national surveys, it is estimated that over 4 million smears are taken annually in Canada, of which approximately eight percent (or over 320,000 smears) will have an abnormality requiring follow-up.\(^3\) Despite its low incidence and mortality in Canada, given that it is a potentially preventable disease, cervical cancer is still the eleventh most common malignancy amongst females.\(^1\)

Although cervical cancer can occur in a wide range of ages, it usually occurs in the fifth or sixth decade of life. A long latency period normally exists between the detection of precursor lesions in cervical epithelium and the development of invasive disease. Precursor lesions occur more frequently in younger women (often under 35 years of age).\(^4\) Several factors that increase the risk for cervical cancer have been identified, including sexual intercourse at an early age, multiple male sexual partners, immunodeficiency, and smoking.\(^4\)

Cervical cancer screening can be performed within organized programs (programmatic screening) or opportunistically.\(^5\) The latter comprises screening which is carried out by suggestion from a physician (when women present for consultations for other health matters) or upon “demand” (upon a woman’s request outside a planned system of invitation). The contribution of the Pap test to reduction in cervical cancer in Canada has been through opportunistic screening. Programmatic screening, on the other hand, implies a mechanism to identify the target population and invite all members of the target population to participate. To date, in Canada, only British Columbia (BC) and Nova Scotia (NS) have most of the components of an organized screening program: a recruitment/retention strategy, a comprehensive quality management program that spans all steps in the screening pathway, and information systems to facilitate the first two components and to provide a mechanism for monitoring and program evaluation. Complete coverage of the target population is still lacking in Canada.

Screening for cervical cancer began in 1949 in BC, and has gradually spread across the country.\(^6\) In 1976 the Canadian Task Force on Cervical Cancer Screening Programs (“the Walton report”) recommended the development of organized screening programs designed to detect precursors of the disease.\(^7\) The National Workshop on Screening for Cancer of the Cervix in 1989 estimated that an organized screening program could save $20 million annually in laboratory costs alone across Canada, in addition to a reduction in the cost of invasive cases and deaths.\(^8\) In the 20 years since the first recommendation of “the Walton report”, and despite its reinforcement by subsequent reports, there has been little progress toward implementation of organized screening programs in most provinces. As of this writing, in addition to BC and NS, only Newfoundland and Prince Edward Island (PEI) have established provincial registries,\(^2,9\) one component of an organized screening program.

In response to renewed concern about the prevalence of cervical cancer among Canadian women, a workshop (Interchange ‘95: A Canadian Forum to Collaborate on Cervical Cancer Screening Program Implementation Strategies)\(^10\) was held in Ottawa on February 27\(^{th}\)-March 1\(^{st}\) 1995, in order to identify the barriers to the implementation of the 1989 National Workshop recommendations. Provincial and territorial representatives involved in cervical cancer screening on a clinical or programmatic level participated in the workshop along with policymakers from the provincial and federal governments and other relevant national organizations.
The Interchange 95' workshop concluded with suggestions that the federal government continue to encourage and facilitate information exchange between the provinces and to provide some direction and leadership in the areas of standards and quality of care.\textsuperscript{2,10} In this regard, all provinces and territories were invited to participate in the Cervical Cancer Prevention Network, an informal association of provincial and federal representatives with the relevant professional bodies.\textsuperscript{2,10} The challenge for the network was to overcome the barriers to the implementation of the 1989 recommendations and for the provinces to emerge with comprehensive, organized programs that use the technologic innovation and advances in knowledge that have occurred since 1989.\textsuperscript{2,10}

In March, 1995, following Interchange ‘95, CCOHTA was requested to undertake a technology assessment on cervical cancer screening by a provincial health ministry. Other provincial ministries were consulted with to determine the value/interest of undertaking this project. Based on comments from the representatives of the various health ministries around the country, and a clinical advisory committee convened for the project, the four objectives stated in the previous section were identified for study.

Section II summarizes the methodological aspects of the report, and the four study objectives are addressed sequentially in Sections III, IV, V, and VI. The conclusions of the assessment are in Section VII.
II METHODOLOGY

Published literature was obtained using a number of bibliographic databases. These databases and the search strategies are listed in Table 1.

Searches were limited to English language articles and to human studies. Secondary references were also identified and retrieved. Information on automated Pap-smear screening systems and related cost estimates were obtained from manufacturers through a mail questionnaire (Appendix 1), personal communication, and from the literature. The clinical advisory committee provided advice on the project, and helped to identify emerging technologies. The committee included a gynecologic oncologist, a medical consultant, and a pathologist.

The methodology for the economic evaluation of the rescreening strategies is detailed in Section V. Where appropriate, the reporting structure for the economic evaluation is in accordance with the “Guidelines for economic evaluation of pharmaceuticals: Canada”.
III  EFFECTIVENESS OF THE PAP TEST

Several cytologic classifications of Pap-smear findings have been proposed, with the Bethesda classification currently the most widely used. The most common significant lesions detected by the Pap smear are squamous cell abnormalities. The Bethesda classification recognizes two categories of squamous intraepithelial lesions (SIL). The first category, termed “low-grade” SIL (LSIL), encompasses cellular changes associated with human papillomavirus (HPV) as well as cervical intraepithelial neoplasia 1 (CIN 1), a lesion that usually undergoes spontaneous resolution. The treatment and follow-up of patients with LSIL is controversial (there is currently a landmark study under way in the United States through the National Cancer Institute that may serve to elucidate this issue). Although the finding of LSIL usually indicates the presence of a low-risk lesion, colposcopy and biopsy are indicated for persistent LSIL.

The second category of abnormal findings on the Pap smear that suggests the presence of an intraepithelial lesion is termed “high-grade” SIL (HSIL). A Pap-smear finding of HSIL suggests the presence of CIN 2 or 3 on biopsy. These are serious lesions that call for colposcopic evaluation.

In addition to LSIL and HSIL, the Bethesda classification includes a group of lesions termed “atypical squamous cells of undetermined significance” (ASCUS). The ASCUS category refers to cells that are more abnormal than cells seen in reactive or inflammatory lesions, but do not fulfill all the criteria for LSIL or HSIL. The management of patients in this category remains controversial since a Pap-smear finding of ASCUS may turn out to be SIL on follow-up.

The purpose of a Pap smear is to screen for intraepithelial lesions before they progress to invasive disease. Patients have come to expect the Pap test to have 100% sensitivity: a false-negative result must mean someone made a mistake. Many women (and unfortunately many clinicians) fail to realize that a Pap test is a screening test and therefore subject to limitations: it makes the promise of reducing the incidence of cervical (squamous-cell) cancer, but it makes no promise to detect all abnormalities in all women.

Despite its demonstrated efficacy as a screening test, false-negative results do occur for a number of reasons. False-negative Pap smears may result from sampling errors (failure to obtain a smear representative of the biologic abnormality), screening errors within the laboratory (failure to locate the biologic abnormality), or interpretative errors (failure to interpret the biologic abnormality correctly when found). Consensus suggests that screening and interpretative errors are responsible for about a third of false-negative Pap smears. The remaining two-thirds of false-negative Pap smears are attributed to sampling errors, primarily related to inadequate collection of cells from the transformation zone (see section on sample collection below). The reported false-negative results in the literature vary widely, from 1% to about 90%, with the most comprehensive studies showing results between 20% and 30%. This corresponds to sensitivity rates of 70% to 80%. Variability in interpretation (depending on the severity of the lesion) of abnormal Pap smears may contribute to the wide variation in false-negative results. In this regard, the Pap test works best when lesions have progressed further than desirable.
The incidence of cervical cancer decreased by 85%, and mortality by 80%, in BC between 1955 and 1988, with the implementation of a provincial screening program.\textsuperscript{6} Also, comparisons among the Scandinavian countries have demonstrated contrasting trends both in incidence and in mortality from the disease. On the one hand, sharp reductions were observed in Finland, Sweden, and Iceland, which implemented nationwide (70-80\% coverage) screening programs in the mid-1960s, whereas during the same ensuing 20 years, the incidence and mortality in Norway, where screening was performed in only one county, did not change.\textsuperscript{18} Although not the results of randomized trials, these comparisons point to the efficacy of the Pap test in reducing the incidence of cervical cancer, and associated mortality.
IV STRATEGIES TO IMPROVE THE EFFECTIVENESS OF
THE PAP TEST

The use of the Pap test is part of a broader process that involves several discrete steps. These include recruitment of the patient, collection of cervical cells and preparation of a Pap smear, processing, screening and interpreting the smear, reporting the findings, possible treatment, and follow-up. Strategies to increase recruitment of unscreened and underscreened women, improvements in the methods of obtaining the Pap smear, preparation techniques, the screening of smears, and quality assurance in the laboratory can each impact, in varying degree, on the results of the Pap test and the screening process.

(i) Recruitment

All women who have ever been sexually active are at risk for cervical cancer and are encouraged to have regular Pap smears. In the absence of an organized program, as stated above, the usual method of recruitment for Pap smears is by suggestion from a physician or upon “demand”. This method is adequate for women who regularly visit their physicians or are educated about their own health care. However, many women who develop invasive disease have never been screened. Canadian studies of invasive cervical carcinoma cases revealed that in PEI and BC, 65% and 49% of these women, respectively, either never had a smear or failed to have a smear in recent years.\textsuperscript{19,20} These women could be targeted for recruitment to further reduce fatalities from cervical cancer.

Women do not have regular contact with the health care system or do not have regular Pap smears for various reasons. Barriers that prevent these women from participating in screening include fear of gynecological examination, fear of cancer, concern about the gender of the smear taker, and loss of confidence in the health care system in general.\textsuperscript{18,21} Language and communication barriers may exist and lack of transportation or child care can prevent women from initial screening or follow up of a “positive” test.\textsuperscript{10} Canadian studies found that in particular, women who had a low level of education, whose mother tongue was not English or French, Native women, recent immigrants and women over 60 yrs, were found to be very low users of the Pap smear.\textsuperscript{20,22} The absence of screening in women over 60 yrs is especially serious since abnormalities are more advanced by the time they are detected, resulting in more invasive cases and higher mortality rates than in younger women.\textsuperscript{19,23}

In order to be successful, methods to encourage cervical cancer screening need to be sensitive to cultural factors. In addition, there is a need for awareness that women have other health, social, and economic needs that may interfere with recruitment.\textsuperscript{8} Approaches such as health visitors in the home, that reach beyond the physician’s office, could recruit women missed by traditional methods.\textsuperscript{24} Other women may gain access to the health care system through venereal disease clinics or penal institutions.\textsuperscript{25}

A registry linked to a population-based information system would have the potential to increase recruitment through the consistent recall and retesting of women. It would facilitate follow-up of cases diagnosed as ‘abnormal’ and recall of women for regular Pap smears.\textsuperscript{10}

At present, the best methods of health promotion and recruitment are still being investigated in Canada,\textsuperscript{8,26} but both systematic follow-up and the targeted screening of women never tested have been consistently raised as main strategies to reduce the number of invasive cases.
(ii) **Sample Collection**

The quality of the smear has a large impact on the sensitivity of the Pap test and can significantly influence the false-negative rate. This can be influenced by the quality of the sample collected, the instrument used to take the sample, and the skill of the sampler.

Controversy exists between smear takers and cytotechnologists over the composition of an adequate sample. It is acknowledged that the transformation zone, the junction between the squamous and columnar epithelia, is the origin of most squamous epithelial abnormal changes and is therefore the main target area for cell collection. Typically, the presence of endocervical cells has been used to indicate that the transformation zone has been sampled. However, the location of the transformation zone varies with individual anatomy, moves towards the ectocervix after childbirth, and is indrawn into the endocervix with menopause.\(^\text{27}\) In addition, women who are post-menopausal, pregnant, or using oral contraceptives may show very few endocervical cells in a smear.\(^\text{18}\) Also it is possible for a sample to have abnormal cells without the presence of endocervical cells.\(^\text{28}\) It has been suggested that the presence of squamous metaplastic cells may be a more accurate indicator that the transformation zone has been sampled, although these cells may be more difficult to identify.\(^\text{27,29}\)

The quality of a smear may also be reduced by the presence of inflammatory cells, necrotic debris, or blood which may obscure the viewing of cancer cells.\(^\text{16}\) Further cooperation is required between smear takers and the laboratories to determine what is indicative of an adequate sample.

The appropriateness of the sampling instrument is best determined by the characteristics of the individual cervix and the location of the transformation zone.\(^\text{27,29}\) A device is desired that will sample both the endocervical canal and the ectocervix to ensure sampling of the transformation zone. A variety of instruments are available that can be used alone or in combination, however, results of comparative studies are inconsistent as to whether these methods differ in their ability to detect neoplasia (CIN).\(^\text{28,30-36}\) Within the context of a screening program with regards to cost and ease of sampling, a simple technique would be preferred.

*It is essential that health care workers be provided with training on the proper technique of obtaining a cervical smear. Several studies have demonstrated that theoretical and practical training can significantly improve the quality of cervical smears taken.*\(^\text{37-40}\)

(iii) **Preparation Techniques**

Despite adequate collection of cervical cells for a Pap smear, poor transfer of the cells to the slide may result in a sample too thick or uneven for accurate viewing. Additionally, the cervical cells may be obscured by blood, mucus or inflammatory cells. In an attempt to improve the quality of the slide sample, new automated methods of monolayer preparation have been introduced. (ThinPrep, CYTYC Corp., Marlborough, MA, USA, and CytoRich, Roche Image Analysis Systems, Inc., Elon College, NC, USA).\(^\text{41,42}\) The collection of cervical cells remains the same, but the cells are rinsed from the collection device into a vial of preservative solution. Automated processors gently disperse the sample, then separate cervical epithelial cells from debris by filtration (ThinPrep) or density gradient centrifugation (CytoRich). The monolayer is prepared automatically from the diagnostic cells onto a glass slide and stained for viewing. An evaluation of these two devices has been recently reported by McGoogan & Reith (1996) from the University of Edinburgh (Scotland) Department of Pathology.\(^\text{43}\)
Investigators have compared the automated monolayer preparation systems with the conventional cervical smear mainly using patients that were high risk or with known abnormalities. In these cases agreement in diagnosis between the two methods is high, being in the range of 88.3% - 99%. The enhanced cellular preservation and even distribution of cells unobscured by other material makes slides prepared by monolayer easier to view and the review time is decreased substantially; however, fatigue sets in more quickly. There is inconsistency in the amount of endocervical cells reported in monolayer preparations, but the reduced total number of cells can increase the number of unacceptable slides. Overall, many studies report that monolayer preparation slightly improves detection of low and high grade disease, perhaps due to the superior cell preservation and distribution. However, to attain accurate diagnosis, substantial training for cytotechnologists and pathologists is required to interpret the unfamiliar patterns and enhanced nuclear detail in monolayer samples. These monolayer preparation systems are not routinely used in Canada due in part to their high cost.

(iv) Screening

The process of screening Pap smears is a time-consuming task, even for the most experienced cytotechnologist. Considering that each smear contains as many as 300,000 epithelial cells and careful screening requires a minimum of 5 minutes per slide, even under optimal circumstances, no cytotechnologist can adequately screen more than 90 smears in a average working day. (Many factors, however, influence how many slides are screened by a cytotechnologist. These factors include, for example, the patient population, specimen quality, and individual abilities of a cytotechnologist). Faulty interpretation may be attributable to professional fatigue and habituation (the preconceived notion that a smear will be normal because only a small number of smears is actually abnormal) during screening, among other factors.

In 1988, the Clinical Laboratory Improvement Amendments (CLIA ’88) mandated rescreening of at least 10% of all gynecologic cases initially interpreted as “negative” by the cytotechnologist, as a means of quality control in laboratories across the United States. This review was to include “negative” cases selected at random as well as cases from patients classified as “high-risk” by clinical history. Despite criticism of its appropriateness as a quality control tool, ten percent random rescreening is a common practice in the United States. In the panoply of rescreening strategies, targeted rescreening of preselected cases (e.g., previous history of SIL) and rapid (30-second) rescreening of “negative” smears, for example, have been proposed as alternative manual candidates for more efficient quality control in cytopathology laboratories.

Research into automation of the visualization and diagnosis of Pap smears has increased in recent years in an attempt to reduce false-negative interpretations resulting from human error. Improvements in the price-to-performance ratio of electronics, shortages of cytotechnologists, and in the United States, the increased scrutiny by the mass media as false-negative cases have been made public and the associated legal liability, have combined to increase interest in the development of automated techniques for cervical cancer screening. Automated screening devices can be used for prescreening (primary screening) or rescreening of Pap smears (Table 2). These two modes have different implications for cytopathology laboratories, although the automated device may be doing essentially the same thing in both situations.

The Food and Drug Administration (FDA) of the United States has approved two automated devices for quality assurance rescreening of cervical cytologic smear slides. The first system to be approved “as an automated cervical cytology rescreening device intended for use in the quality control and rescreening of previously screened Papanicolaou smear slides”, the AutoPap 300 QC Automatic Pap Screener (NeoPath
Inc., Redmond, Washington, U.S.A.), is designed to process all “negative” slides from primary cytotechnologist screening, and to select 10 percent or more of the most “abnormal” fraction for manual review. The second system which has received FDA approval in an “adjunctive” capacity in the quality control process, the PAPNET Testing System (Neuromedical Systems Inc., Suffern, New York, U.S.A.), is also designed to process all “negative” slides from primary cytotechnologist screening; however, 27 percent of the most “abnormal” fraction would be selected (human selection based on examination of “tiles” processed by the system) for manual review. It is important to note that even with these automated devices, cytotechnologists are still required for interpretation of smears. Two other systems, the AUTOcyte Interactive Screening System (Roche Image Analysis Systems, Inc., Elon College, North Carolina, U.S.A.), and the Cyto-Savant (Xillix Technologies Corp., Richmond, British Columbia, Canada), are currently undergoing clinical trials as part of FDA clearance. Another automated system, the CYMET A40 (Morphometrix Technologies Inc., Toronto, Ontario, Canada), will be in clinical trials through summer, 1997 (personal communication, Gordon Rosenblatt, February 11, 1997) (Table 2).

Regarding Health Protection Branch (Health Canada) notification status, AutoPap is “in clinical trials” as of 3/6/94; PAPNET, AUTOcyte, and Cyto-Savant, on the other hand, have received notification (“normal status”) (Table 2). To date, none of the automated screening devices are being utilized in practice for primary Pap smear screening. An advisory committee to the FDA recently reviewed the AutoPap system for this purpose and recommended that additional studies are needed on its effectiveness in the laboratory setting prior to recommendation for clearance to market the system as a primary screener for Pap smears. The AutoPap system is to date the only primary automated screener to be reviewed by the FDA panel, although other systems mentioned above are under investigation.

(v) **Quality Assurance**

Quality assurance is essential for all aspects of a cervical cancer screening program and can be integrated into each component from sampling and screening to treatment.

As stated above, a major source of error in missed invasive cases is due to poor samples, but training of the sampler can significantly improve the quality of smears. Laboratories could work with clinicians by monitoring smears from specific clinicians and offering feedback on their quality.

The importance of laboratory quality control was recognized by the 1989 Canadian National Workshop on Cervical Cancer Screening which advocated the 1989 revised guidelines for quality assurance programs in cytopathology produced by the Canadian Society of Cytology. In addition, some provinces have developed their own quality assurance measures such as those recommended by the Laboratory Quality Assurance Subcommittee of the College of Physicians and Surgeons of Saskatchewan and the Laboratory Proficiency Testing Program in Ontario.

However, there is not yet consistent, systematic guidelines for cervical cytopathology laboratories in Canada as in other countries, such as in Scotland and in Australia. These guidelines address issues such as workload and training of cytotechnologists, consistency of diagnostic terminology, rescreening methods, the correlation of cytology and histology, and standard record keeping, as areas for the development of internal and external quality assurance. Guidelines are also required for consistent management, treatment and follow-up by clinicians and specialists.
V  COST-EFFECTIVENESS OF AUTOMATED RESCREENING STRATEGIES

(i)  Type of Analysis, Viewpoint, Cost Measurement, & Outcome Measurement

A ‘cost-effectiveness’ analysis from the perspective of a third party payer, comparing AutoPap 300 QC (AutoPap) and PAPNET, with a strategy of 10 percent manual random rescreening was conducted. As acknowledged earlier, despite being generally discredited as a QC practice, ten percent random rescreening has been used as the standard against which to measure the cost-effectiveness of the automated strategies in this analysis to facilitate comparison between the strategies. AutoPap and PAPNET have been selected as comparators for this analysis due to availability of published clinical trials. Both devices have been available for use by the cytopathology community in the United States following clearance by the FDA for rescreening of slides previously examined by humans (In Canada, PAPNET is offered for QC purposes through private clinics). At present there is a lack of sufficient published clinical data for the other automated devices identified in the previous section, for purposes of this economic evaluation.

Decision analysis was used to calculate the expected total direct laboratory costs of screening under each of the three strategies, and to derive the cost per additional abnormal case discovered. The cost estimates were derived from values quoted in the relevant literature, and in addition, for the automated strategies, from a mail questionnaire (Appendix 1) to the respective manufacturers. Clinic and follow-up (colposcopy and treatment) costs were excluded from this analysis. The costs to patients (e.g., productivity loss, anxiety) have not been included, due to the perspective taken for the analysis.

(ii)  Analysis

A decision-analysis model was constructed to compare the direct laboratory costs of the alternative rescreening strategies for cervical cancer (Figure 1). The three options (10% Manual, upper branch; AutoPap, middle branch; PAPNET, lower branch) are located at the square decision node. For either of the three strategies, circular nodes represent events that may occur by chance, and rectangles represent total costs for each pathway. All three options enter the subtree depicted to the right of the bracket. For all options, the subtree has a similar structure. The first chance node represents the true rate of abnormal cases (pRate) in the screening population (Table 3). Subsequent nodes represent chance events in terms of routine practice in a cytopathology laboratory where the three rescreening strategies are operational. In the process, every smear is examined by a cytotechnologist and is interpreted to be either negative or positive, with all positive interpretations being reviewed by a pathologist. If both a cytotechnologist and a pathologist interpret the smear to be positive, it is given a final interpretation of positive. Alternatively, the pathologist may revise a positive interpretation from the cytotechnologist to a final result of negative. Under the ten percent manual rescreening strategy, a random 10% of all negative determinations from initial cytotechnologist screening will undergo review by the cytotechnologist. Under each of the automated strategies, on the other hand, all negative determinations from the cytotechnologist are submitted to the automated device in question. If the automated device determines the smear to be suspect (“review”), then the smear is routed back to the cytotechnologist for review and then, if determined to be positive, to the pathologist. Any smears that the automated device accepts as negative, or redirects as “review” but the cytotechnologist still classifies as negative, are given the final determination of negative. The decision analysis model was constructed and evaluated using the software program DATA™ 2.6.
Seven major assumptions were made in the decision model: 1) the number of Pap smears to be screened is 4,000,000. This number is derived from the estimated number of Pap tests performed per year in Canada, based on data from national and provincial surveys;\(^3\) 2) the proportion of true abnormal Pap smears is 10%. This percentage is derived from the proportion of women having an abnormality on the first Pap test (8%),\(^3\) and an estimate of 25% for the false-negative rate of current screening programs;\(^{16,17}\) 3) the initial screening and review sensitivity of the cytotechnologist is 75%.\(^{16,17}\) In practice, in comparison to initial sensitivity, it may be reasonable to assume a higher review sensitivity of the cytotechnologist, for example due to increased vigilance;\(^{74}\) 4) the pathologist review sensitivity is 100%. This ideal sensitivity rate is assumed for the pathologist in order to accurately interpret the cost/additional abnormal case within the laboratory; 5) the cytotechnologist initial screening and review specificity is 95%.\(^{71}\) Similar to the case of sensitivity, in practice, a heightened vigilance may increase the review specificity of the cytotechnologist (and/or pathologist). However, it may also be reasonable to assume, for example due to a tendency to “believe the machine”, a lower specificity for redirected smears;\(^{74}\) 6) the direct cost estimates per slide for cytotechnologist screening is Can$8, and Can$5 for either cytotechnologist or pathologist review. These estimates were derived (adjusted for overhead) from the Ontario Ministry of Health Schedule of Benefits, under services listed under Laboratory Medicine;\(^{73}\) 7) the direct cost estimates per slide for rescreening by AutoPap is Can$7, and Can$14 for rescreening by PAPNET (Appendix 1). The baseline values used in the decision model are summarized in Table 3.

(iii) Results

For each additional abnormal case found by 10% random rescreening, the cost would be $250 (Table 4). For each additional case found by the least expensive automated strategy (AutoPap) the cost rises to over $400 (Table 4). PAPNET is marginally more effective (rescreening sensitivity 83% vs. 80%), but the cost to find an abnormal case, in comparison to AutoPap is very high: over $10,000 (Table 4). This result highlights the fact that both automated rescreening strategies are virtually equal in efficacy, but quite different in cost, and it is this cost difference which accounts for the difference in economic attractiveness of the two strategies.

There is no widely accepted threshold for cost-effectiveness analysis at which programs become economically attractive. It may well be the case that society is willing to pay $10,000 to find an additional abnormal result. However, given the precision of our estimates of screening efficacy (low), we suggest that the data be interpreted as follows: Automated rescreening methods are more effective, but also more costly than manual rescreening. The cost per case found for AutoPap appears to be reasonable. The automated programs appear to be of similar efficacy, but dissimilar cost. Given these estimates, the marginal cost difference for PAPNET does not appear justified.

(iv) Uncertainty

Values used in the decision model were varied widely from the baseline case to examine the impact of uncertainty of these values (Table 5). 10% random rescreening was found to have a better cost-effectiveness ratio than either AutoPap or PAPNET over a wide range of values for key variables under one-way sensitivity analysis (Table 5). The baseline result in terms of a favorable cost-effectiveness ratio of the 10% manual route in comparison to the automated devices, however, is sensitive to the per rescreening cost by automated device, and to the per review cost by a cytotechnologist or pathologist. Assuming each of the remaining variables constant, 10% random rescreening would, for example, be less cost-effective than AutoPap if the per rescreening cost under AutoPap falls below $4, or the per review cost exceeds $7.
The cost-effectiveness ratios for each of the automated devices are sensitive to the *per rescreening cost by automated device*. Assuming each of the remaining baseline variables constant, AutoPap will be less cost-effective than PAPNET if the per rescreening cost under each automated device begins to exceed $5 (for example, at a per rescreening cost by automated device of $6, the cost-effectiveness ratio for AutoPap is $359 and for PAPNET $358; at a per rescreening cost of $10, the cost-effectiveness ratio for AutoPap increases to $594 and for PAPNET $584).

(v) Related Studies

In a recent analysis of these automated strategies with alternative methods of manual rescreening, Hutchinson (1996), using a conventional mathematical model considering overall sensitivity in a three-stage screening algorithm (cytotechnologist screening, rescreening by the automated device, and cytotechnologist review) reported that the most effective route for recovering false negatives in the “negative” pool would be 100% manual rescreening. In comparison to a no rescreen strategy, Hutchinson estimated that the incremental cost per additional abnormal case (LSIL+: prevalence, 2.50%) discovered by AutoPap (US $2,197) was twice as high than that discovered by 100% rescreening (US$ 1,049), and the incremental cost per additional abnormal case discovered by PAPNET (US$ 4,486) was four times that of 100% rescreening. Despite being the least favorable of all rescreening strategies (manual and automated) in terms of effectiveness, ten percent random rescreening was reported to have the same cost-effectiveness ratio as that of 100% manual rescreening.

One hundred percent manual rescreening of all “negative” slides, however, is an unrealistic goal in the current climate of fiscal constraints and shortage of human resources in cytopathology laboratories. Of the remaining manual rescreening strategies, Hutchinson reports that rapid rescreening shows the greatest benefit per unit of cost (US $348 per additional abnormal case discovered). Rapid rescreening has recently been proposed as an alternative strategy for quality control of “negative” slides by Baker et al (1995): Under this proposal, all “negative” slides are rescreened by an ‘experienced’ cytotechnologist for a 30-second period. Based on over 100,000 “negative” slides over a period of four years, Baker et al. reported a fivefold increase in the pickup of false-negatives in comparison to 10% random rescreening. Concerns, however, over both cytotechnologist fatigue and the high false-positive rates (“alarms”) of the screening cytotechnologists, at least during the initial stages of utilization, need to be addressed before adoption of rapid rescreening in cytopathology laboratories.

(vi) Limitations

Two broad limitations of the current analysis need to be highlighted. The first limitation relates to the difficulty in deriving estimates of the operating characteristics of the automated devices. These devices have generally been evaluated under controlled conditions (small sample, selected group of lesions) by manufacturer-sponsored researchers as opposed to independent analysis in routine practice. The comparator (and study design) against which each of the devices have been measured, moreover, varies between studies making it difficult to compare studies and assess the performance (screening efficacy) of the devices. Related to this latter point is to date the lack of a common definition of the gold standard for Pap-smear rescreening. Second, the downstream costs and effects of the competing rescreening strategies were not considered in this analysis. This may dramatically change the economic attractiveness of all of these competing strategies. For example, while automated devices are designed to decrease false-negative Pap smears, it is too early to tell if they will significantly increase the number of false positives, thereby increasing patient anxiety and suffering and adding still more unnecessary costs to screening programs.
VI EMERGING TECHNOLOGIES

In addition to recruitment, sampling, preparation and screening techniques, two other strategies which could impact on cervical cancer screening in the future may include screening for HPV in asymptomatic women and flow cytometry.

(i) HPV Testing

There is a strong body of evidence to associate epithelial cell transformation by human papillomaviruses with cervical cancer; although there is evidence that the presence of other social, sexual or nutritional factors can further increase the risk of cervical cancer. HPV infection may be observed visually by colposcopy as the presence of raised plaques on the cervix (condylomas), or microscopically as the presence of epithelial cells with enlarged atypical nuclei and perinuclear clearing (koilocytosis). Recent methods more precisely identify HPV through the detection of its DNA, although there may be no other visible signs of HPV infection.

HPV is sexually transmitted and over 70 types have been identified. Specific types of HPV (e.g., types 16 and 18), designated 'high risk' types, are found more frequently in invasive neoplasia and carcinoma. Low risk’ HPV types (e.g., types 6 and 11) are most often associated with condyloma or mild dysplasia which do not usually progress to invasive disease. It is well established that the frequency of HPV in cervical cells is directly related to the severity of CIN. The occurrence of HPV is about 9-27% in normal smears, 18-31% in atypical smears, and 48.6-92% in CIN diagnosis. The prevalence is highest in biopsy (46-92%) and carcinoma (88%) samples. This connection was substantiated in an international study by Bosch et al. (1996) who found that 93% of invasive-disease samples from patients in 22 countries were HPV positive.

In Canada, HPV testing methods are still confined to the research arena due to their complexity and cost. These methods include either gene amplification (polymerase chain reaction, PCR), hybridization against specific DNA probes (dot blot, Southern blot, or in situ hybridization) or the use of RNA probes (hybrid capture test). Direct comparison studies show that PCR is the most sensitive test compared to dot blot, Southern blot, and in situ hybridization tests (34%, 68.4% and 72.7% detection of HPV as compared to PCR, respectively), but this high sensitivity requires careful skill to avoid false-positives from external DNA contamination. The Southern blot technique offers both high sensitivity and specificity, but is labour intensive and not suited for routine clinical use. In situ hybridization is used most commonly, and like hybrid capture techniques, it is more economical and can be used on fixed specimens. Studies are constantly emerging that improve methods to increase flexibility, sensitivity, specificity and ease of performance. For example, PCR can be adapted to fixed tissue samples, combined with enzyme immunoassay and there is a move to automate in situ methods.

Although these tests can separate HPV types associated with lower or higher risk of invasive neoplasia, the clinical predictive applications are uncertain. Many researchers have suggested a predictive role for HPV testing in conjunction with cytology or colposcopy to identify abnormal cases that are more likely to progress to cervical cancer. Long term studies show that type HPV 16 infections are more persistent and more likely to progress to an invasive stage, but a high percentage will regress spontaneously in both normal patients (83.7%) and patients with CIN 1 or 2 (55.7-84%). Also, patients positive for HPV can show normal cytological diagnosis. Since a positive HPV test does not confidently predict the development of cervical cancer, identification of women who may be at higher risk for cervical cancer by present HPV testing...
methods may lead to unnecessary aggressive treatment. In 1995, the Canadian Task Force on the Periodic Health Examination recommended that HPV screening not be performed on asymptomatic women which reinforced a similar recommendation of the 1989 National Workshop.⁸

Presently, a large trial at National Cancer Institute (U.S.A.), is evaluating whether HPV testing can distinguish which women diagnosed as ASCUS (mildly atypical) should undergo colposcopy or close observation.¹⁴ Since an ASCUS diagnosis is often unclear, this would be a potentially important role for HPV testing. However, through a mathematical model Jenkins et al (1996)¹⁰⁷ project that HPV testing of women with mildly abnormal diagnoses would only minimally reduce the number of cancers detected. They reason that the greater number of undetected invasive cancers occur in women who have never been screened or who are inadequately screened.

The reliability of HPV testing as a screening method would require further research on the natural history of HPV infections and the clarification of the link between HPV presence, HPV type, and the subsequent development of cervical cancer. In addition, until the cost and complexity of HPV testing is reduced, the practical benefits of HPV testing in cervical cancer screening are questionable.

(ii) Flow Cytometry

Flow cytometry (FCM) is a well established method in pathology for detection and quantification of different types of cells.¹⁰⁸ FCM is capable of rapidly evaluating large numbers of cells and is accorded with a measure of objectivity because its results are reported as graphic displays.¹⁰⁹ FCM can rapidly quantitate cell size, nuclear size, nuclear:cytoplasmic ratio, and the expression of cellular antigens.¹¹⁰ FCM is widely used for measurement of cellular DNA content, which 1) provides an estimate of a tumor’s proliferative activity, and 2) identifies populations of cells with abnormal amounts of DNA.

DNA analysis by FCM requires a fluid suspension of single cells or nuclei.¹⁰⁹ The suspended cells are stained with a DNA-specific dye (e.g., propidium iodide), and then examined by a flow cytometer as they flow in single file past a narrowly focused beam of light, the source of which is usually a laser or a mercury arc lamp. The stained cells will emit a fluorescent pulse, the height of which will be proportional to the amount of DNA in the cell. The pulse heights of thousands of cells can be measured in minutes, and the data displayed as a DNA histogram. The nature of the peaks (diploid/aneuploid) will determine the (ab)normality of the cells.¹⁰⁹

Attempts have been made to screen cervical samples using FCM DNA analysis in a research context. There have been claims in earlier published studies of 94-97% sensitivity¹⁰⁸,¹¹¹ and 82-88% specificity¹⁰⁸,¹¹¹ of FCM in detection of cervical abnormalities. Sample preparation times are longer than for the Pap test and there can be difficulties in disaggregating cells.¹¹² FCM, at present, is still seen as demanding (problems of standardization, complex S-phase analysis) for routine pathology services, and expensive (>50 per test) in the context of screening.¹⁰⁸
VII CONCLUSIONS

The above techniques for cervical cancer screening may increase the effectiveness of the Pap test for those women presently screened, but will not affect detection in women who are rarely or never screened. Barriers that prevent these women from participating in screening may put them at a higher risk for cervical cancer. Opportunistic screening leads to over screening of younger, affluent, lower-risk women and under-screening of older, less affluent and minority group women. The targeted recruitment of women in coordination with an information system that would allow regular follow-up and recall of women could significantly reduce the number of cervical cancer cases.

It is essential that promotion of technological improvements does not divert resources and effort from the implementation of the main recommendations of the 1989 National Workshop, namely recruitment, information systems, and training and quality-control requirements for laboratories and programs.
### Table 1: Databases Searched and Description of Searches

<table>
<thead>
<tr>
<th>DATABASE</th>
<th>DESCRIPTION OF SEARCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDLINE</td>
<td>(Vaginal Smears or Cervix Neoplasms) + Terms below in various strategies. Instrumentation; (Economics or Cost-Benefit Analysis); (Mass Screening or Screening); Barrier*; (Histocytochemical Preparation Techniques or Cytodiagnosis or Cytological Techniques); (Equipment Failure or Equipment Design); Education, Medical; (Physicians, Family or Nurses or Nurse Practitioners); Automat*; DNA Probes, HPV and Flow Cytometry); Staining, Quality, Sensitivity or Specificity; Review</td>
</tr>
<tr>
<td>Cancerlit</td>
<td></td>
</tr>
<tr>
<td>Hlth.Plan&amp;Admin</td>
<td></td>
</tr>
<tr>
<td>EMBASE</td>
<td></td>
</tr>
<tr>
<td>Pascal</td>
<td></td>
</tr>
<tr>
<td>• 1985-1997</td>
<td></td>
</tr>
<tr>
<td>MEDLINE</td>
<td>1. ((Cervix Neoplasms or Vaginal Smears) or Intraepithelial Neoplasia or Vaginal Neoplasms; Cervix)) 2. (Flow Cytometry or DNA Probe? or Pap smear? or Cervicograph?) and (Screen? or Test? or Diagnosis or Lab?) 3. 1 or 2 and Review Literature or Meta-Analysis</td>
</tr>
<tr>
<td>• 1985-1997</td>
<td></td>
</tr>
<tr>
<td>DIALOG PTS Newsletter</td>
<td>Search for recent news on cervical cancer screening.</td>
</tr>
<tr>
<td>FDA Online Database</td>
<td>The Gray Sheet for new approvals of tests, instruments, etc. Slide Preparation techniques</td>
</tr>
<tr>
<td>ECRINet</td>
<td>1. Cervix and Screening 2. Vaginal smears</td>
</tr>
<tr>
<td>CURRENT CONTENTS</td>
<td>Searches conducted as a current awareness service. (Vaginal Smears or Cervix neoplasms) and Screening</td>
</tr>
<tr>
<td>Clinical Medicine</td>
<td></td>
</tr>
<tr>
<td>CCOHTA Library Database</td>
<td>All relevant terms</td>
</tr>
</tbody>
</table>

* or ? = truncated term
### Table 2: Automated Pap-smear Screening

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NeoPath, Inc.</td>
<td>AutoPap 300 QC</td>
<td>QC†</td>
<td>conventional</td>
<td>US $5</td>
<td>FDA- 9/29/95</td>
</tr>
<tr>
<td>Redmond, Wash., USA</td>
<td>AutoPap Primary Screener</td>
<td>prescreen‡</td>
<td>conventional</td>
<td>-</td>
<td>HPB- in clinical trials as of 3/6/94</td>
</tr>
<tr>
<td>Neuromedical Systems, Inc., Suffern, NY, USA</td>
<td>PAPNET</td>
<td>QC†</td>
<td>conventional</td>
<td>US $10</td>
<td>FDA- 11/8/95</td>
</tr>
<tr>
<td>Roche Image Analysis Systems, Inc., Elon College, NY, USA</td>
<td>AUTOcyte</td>
<td>prescreen‡</td>
<td>monolayer</td>
<td>-</td>
<td>FDA- in clinical trials through 9/96</td>
</tr>
<tr>
<td>Morphometrix Technologies Inc., Toronto, ON, Canada</td>
<td>CYMET A40</td>
<td>prescreen‡</td>
<td>monolayer</td>
<td>-</td>
<td>HPB- “normal status” as of 3/20/95</td>
</tr>
<tr>
<td>Xillix Technologies Corp., Richmond, BC, Canada</td>
<td>Cyto-Savant</td>
<td>prescreen‡/ QC†</td>
<td>conventional/ monolayer</td>
<td>-</td>
<td>FDA- in clinical trials</td>
</tr>
</tbody>
</table>

* FDA = Food and Drug Administration (U.S.A.); HPB = Health Protection Branch (Health Canada)

† In the QC mode, slides would first be screened by cytotechnologists, then “negative” cases would be rescreened by the automated device (refer to text)

‡ In the prescreening mode, slides are examined first by the automated device and subsequently by the cytotechnologist
## Table 3: Baseline Values used in the Decision Model

<table>
<thead>
<tr>
<th>VARIABLE:</th>
<th>INTERPRETATION:</th>
<th>BASELINE VALUE:</th>
<th>STUDY (Ref no.):</th>
</tr>
</thead>
<tbody>
<tr>
<td>pRate</td>
<td>True rate of abnormal Pap smears</td>
<td>0.10</td>
<td>(3,16,17)</td>
</tr>
<tr>
<td>pSens1</td>
<td>Cytotechnologist screening sensitivity</td>
<td>0.75</td>
<td>(16,17)</td>
</tr>
<tr>
<td>pSens2</td>
<td>Pathologist review sensitivity</td>
<td>1.00</td>
<td>(*)</td>
</tr>
<tr>
<td>pReview</td>
<td>Review rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10% random</td>
<td></td>
<td>0.10</td>
<td>(53)</td>
</tr>
<tr>
<td>AutoPap</td>
<td></td>
<td>0.10</td>
<td>(68)</td>
</tr>
<tr>
<td>PAPNET</td>
<td></td>
<td>0.27</td>
<td>(69)</td>
</tr>
<tr>
<td>pSens3</td>
<td>Rescreening sensitivity</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>10% random</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>AutoPap</td>
<td></td>
<td>0.80</td>
<td>(68,70)</td>
</tr>
<tr>
<td>PAPNET</td>
<td></td>
<td>0.83</td>
<td>(71)</td>
</tr>
<tr>
<td>pSens4</td>
<td>Cytotechnologist review sensitivity</td>
<td>0.75</td>
<td>(*)</td>
</tr>
<tr>
<td>pSens5</td>
<td>Pathologist review sensitivity</td>
<td>1.00</td>
<td>(*)</td>
</tr>
<tr>
<td>pSpec1</td>
<td>Cytotechnologist screening specificity</td>
<td>0.95</td>
<td>(*),.71)†</td>
</tr>
<tr>
<td>pSpec2</td>
<td>Rescreening specificity</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>10% random</td>
<td></td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>AutoPap</td>
<td></td>
<td>0.80</td>
<td>(70)</td>
</tr>
<tr>
<td>PAPNET</td>
<td></td>
<td>0.80</td>
<td>(*,.71,72)†</td>
</tr>
<tr>
<td>pSpec3</td>
<td>Cytotechnologist review specificity</td>
<td>0.95</td>
<td>(*)</td>
</tr>
<tr>
<td>pSpec4</td>
<td>Pathologist review specificity</td>
<td>1.00</td>
<td>(*)</td>
</tr>
<tr>
<td>N</td>
<td>Number of Pap smears</td>
<td>4,000,000</td>
<td>(3)</td>
</tr>
<tr>
<td>cScreen</td>
<td>Per screening cost by a cytotechnologist</td>
<td>8</td>
<td>(73)</td>
</tr>
<tr>
<td>cRescreen</td>
<td>Per rescreening cost by automated device</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AutoPap</td>
<td></td>
<td>7</td>
<td>(‡)</td>
</tr>
<tr>
<td>PAPNET</td>
<td></td>
<td>14</td>
<td>(‡)</td>
</tr>
<tr>
<td>cReview</td>
<td>Per review cost by a cytotechnologist or pathologist</td>
<td>5</td>
<td>(73)</td>
</tr>
</tbody>
</table>

* authors’ estimate
† authors’ estimate based on cited studies
‡ mail questionnaire (Appendix 1)
Table 4: Baseline Analysis

<table>
<thead>
<tr>
<th>STRATEGY:</th>
<th>COSTS: (1,000$):</th>
<th>TOTAL ABNORMAL CASES:</th>
<th>ADDITIONAL ABNORMAL CASES:</th>
<th>COST/ADDITIONAL ABNORMAL CASE ($)</th>
<th>A:*</th>
<th>B:†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No rescreen</td>
<td>34,400</td>
<td>300,000</td>
<td>0</td>
<td>Base case</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10% rescreen</td>
<td>36,283</td>
<td>307,500</td>
<td>7,500</td>
<td>251</td>
<td>251</td>
<td></td>
</tr>
<tr>
<td>AutoPap</td>
<td>59,469</td>
<td>360,000</td>
<td>60,000</td>
<td>418</td>
<td>442</td>
<td></td>
</tr>
<tr>
<td>PAPNET</td>
<td>84,846</td>
<td>362,250</td>
<td>62,250</td>
<td>810</td>
<td>11,278</td>
<td></td>
</tr>
</tbody>
</table>

* incremental cost/additional abnormal case in comparison to a no rescreen strategy.
† incremental cost/additional abnormal case in comparison to the next most expensive strategy.
### Table 5: One-way Sensitivity Analysis on Key Variables

<table>
<thead>
<tr>
<th>VARIABLE:</th>
<th>INTERPRETATION:</th>
<th>BASELINE VALUE:</th>
<th>RANGE OF VALUES:</th>
<th>COST/ADDITIONAL ABNORMAL CASE* 10% random:</th>
<th>Threshold VALUE:†</th>
</tr>
</thead>
<tbody>
<tr>
<td>pRate</td>
<td>True rate of abnormal Pap smears</td>
<td>0.10</td>
<td>0.01-0.20</td>
<td>2,645-118, 4,468-193, 8,658-374</td>
<td>Not found‡</td>
</tr>
<tr>
<td>pSens1</td>
<td>Cytotechnologist screening sensitivity</td>
<td>0.75</td>
<td>0.50-0.99</td>
<td>131-5,997, 215-10,137, 418-19,644</td>
<td>Not found‡</td>
</tr>
<tr>
<td>pSens3</td>
<td>Rescreening sensitivity</td>
<td>0.80</td>
<td>0.50-0.99</td>
<td>668-338, 1,343-680</td>
<td>Not found‡</td>
</tr>
<tr>
<td>AutoPap</td>
<td>PAPNET</td>
<td>0.83</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pSens4</td>
<td>Cytotechnologist review sensitivity</td>
<td>0.75</td>
<td>0.50-0.99</td>
<td>374-191, 626-317, 1,215-614</td>
<td>Not found‡</td>
</tr>
<tr>
<td>pSpec1</td>
<td>Cytotechnologist screening specificity</td>
<td>0.95</td>
<td>0.50-0.99</td>
<td>138-261, 226-435, 439-843</td>
<td>Not found‡</td>
</tr>
<tr>
<td>pSpec2</td>
<td>Rescreening specificity</td>
<td>0.80</td>
<td>0.50-0.99</td>
<td>427-412, 834-796</td>
<td>Not found‡</td>
</tr>
<tr>
<td>AutoPap</td>
<td>PAPNET</td>
<td>0.80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pSpec3</td>
<td>Cytotechnologist review specificity</td>
<td>0.95</td>
<td>0.50-0.99</td>
<td>354-242, 420-418, 817-810</td>
<td>Not found‡</td>
</tr>
<tr>
<td>cRescreen</td>
<td>Per rescreening cost by automated device</td>
<td>7</td>
<td>2-20</td>
<td>(251), 124-1,180, 132-1,150</td>
<td>5</td>
</tr>
<tr>
<td>AutoPap</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cReview</td>
<td>Per review cost by a cytotechnologist or pathologist</td>
<td>5</td>
<td>2-20</td>
<td>100-1,004, 413-439, 799-866</td>
<td>Not found‡</td>
</tr>
<tr>
<td>PAPNET</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Incremental cost/additional abnormal case in comparison to a no rescreen strategy.
- † The threshold (77) value is a value where the two automated devices have equal expected cost-effectiveness ratios. If a given variable has a value less than a threshold, than one strategy is more cost-effective; if the variable has a value greater than a threshold, than the alternative strategy is more cost-effective.
- ‡ AutoPap is more cost-effective than PAPNET over all the given range of values (no threshold).
Figure 1. Decision Model for Rescreening Strategies of Cervical Cancer

- **10% Manual**
  - **ABNORMAL**
    - **pRate**
      - **Rescreen**
        - **pReview**
          - **Positive**
            - **pSens1**
              - **Positive**
                - **pSens2**
                  - **N(cScreen+cReview)**
              - **Negative**
                - **#**
            - **Negative**
              - **#**
          - **Negative**
            - **#**
        - **Rescreen**
          - **pSpec1**
            - **Negative**
              - **#**
          - **Positive**
            - **pSpec4**
              - **Positive**
                - **#**
              - **Negative**
                - **#**
        - **Rescreen**
          - **pSpec3**
            - **Negative**
              - **#**
          - **Positive**
            - **pSpec4**
              - **Positive**
                - **#**
              - **Negative**
                - **#**
        - **Rescreen**
          - **pSpec2**
            - **Negative**
              - **#**
          - **Positive**
            - **pSpec3**
              - **Negative**
                - **#**
              - **Positive**
                - **#**
          - **Rescreen**
            - **pSens4**
              - **Positive**
                - **pSens5**
                  - **Positive**
                    - **N(cScreen+cRescreen+2(cReview))**
                  - **Negative**
                    - **#**
              - **Negative**
                - **#**
          - **Rescreen**
            - **pReview**
              - **Positive**
                - **N(cScreen+cRescreen+2(cReview))**
              - **Negative**
                - **#**
          - **Rescreen**
            - **pSens3**
              - **Positive**
                - **N(cScreen+cRescreen+2(cReview))**
              - **Negative**
                - **#**
          - **Rescreen**
            - **pSpec3**
              - **Positive**
                - **N(cScreen+cRescreen+2(cReview))**
              - **Negative**
                - **#**
        - **Rescreen**
          - **pSens4**
            - **Positive**
              - **N(cScreen+cRescreen+2(cReview))**
            - **Negative**
              - **#**
        - **Rescreen**
          - **pReview**
            - **Positive**
              - **N(cScreen+cRescreen+2(cReview))**
            - **Negative**
              - **#**
        - **Rescreen**
          - **pSens3**
            - **Positive**
              - **N(cScreen+cRescreen+2(cReview))**
            - **Negative**
              - **#**
        - **Rescreen**
          - **pReview**
            - **Positive**
              - **N(cScreen+cRescreen+2(cReview))**
            - **Negative**
              - **#**
        - **Rescreen**
          - **pSens2**
            - **Positive**
              - **N(cScreen+cRescreen+2(cReview))**
            - **Negative**
              - **#**
        - **Rescreen**
          - **pReview**
            - **Positive**
              - **N(cScreen+cRescreen+2(cReview))**
            - **Negative**
              - **#**
        - **Rescreen**
          - **pSens1**
            - **Positive**
              - **N(cScreen+cRescreen+2(cReview))**
            - **Negative**
              - **#**

- **AutoPap**
  - **NORMAL**
    - **pRate**
      - **Rescreen**
        - **pReview**
          - **Positive**
            - **pSens1**
              - **Positive**
                - **pSens2**
                  - **N(cScreen+cReview)**
              - **Negative**
                - **#**
            - **Negative**
              - **#**
          - **Rescreen**
            - **pSpec1**
              - **Negative**
                - **#**
            - **Positive**
              - **pSpec2**
                - **Positive**
                  - **#**
                - **Negative**
                  - **#**
            - **Rescreen**
              - **pSpec3**
                - **Negative**
                  - **#**
              - **Positive**
                - **pSpec4**
                  - **Positive**
                    - **#**
                  - **Negative**
                    - **#**
            - **Rescreen**
              - **pSens4**
                - **Positive**
                  - **pSens5**
                    - **Positive**
                      - **N(cScreen+cRescreen+2(cReview))**
                    - **Negative**
                      - **#**
                - **Negative**
                  - **#**
            - **Rescreen**
              - **pReview**
                - **Positive**
                  - **N(cScreen+cRescreen+2(cReview))**
                - **Negative**
                  - **#**
            - **Rescreen**
              - **pSens3**
                - **Positive**
                  - **N(cScreen+cRescreen+2(cReview))**
                - **Negative**
                  - **#**
            - **Rescreen**
              - **pReview**
                - **Positive**
                  - **N(cScreen+cRescreen+2(cReview))**
                - **Negative**
                  - **#**
            - **Rescreen**
              - **pSens1**
                - **Positive**
                  - **N(cScreen+cRescreen+2(cReview))**
                - **Negative**
                  - **#**
            - **Rescreen**
              - **pReview**
                - **Positive**
                  - **N(cScreen+cRescreen+2(cReview))**
                - **Negative**
                  - **#**

- **PAPNET**
  - **NORMAL**
    - **pRate**
      - **Rescreen**
        - **pReview**
          - **Positive**
            - **pSens1**
              - **Positive**
                - **pSens2**
                  - **N(cScreen+cReview)**
              - **Negative**
                - **#**
            - **Negative**
              - **#**
          - **Rescreen**
            - **pSpec1**
              - **Negative**
                - **#**
            - **Positive**
              - **pSpec2**
                - **Positive**
                  - **#**
                - **Negative**
                  - **#**
            - **Rescreen**
              - **pSpec3**
                - **Negative**
                  - **#**
              - **Positive**
                - **pSpec4**
                  - **Positive**
                    - **#**
                  - **Negative**
                    - **#**
            - **Rescreen**
              - **pSens4**
                - **Positive**
                  - **pSens5**
                    - **Positive**
                      - **N(cScreen+cRescreen+2(cReview))**
                    - **Negative**
                      - **#**
                - **Negative**
                  - **#**
            - **Rescreen**
              - **pReview**
                - **Positive**
                  - **N(cScreen+cRescreen+2(cReview))**
                - **Negative**
                  - **#**
            - **Rescreen**
              - **pSens3**
                - **Positive**
                  - **N(cScreen+cRescreen+2(cReview))**
                - **Negative**
                  - **#**
            - **Rescreen**
              - **pReview**
                - **Positive**
                  - **N(cScreen+cRescreen+2(cReview))**
                - **Negative**
                  - **#**
            - **Rescreen**
              - **pSens1**
                - **Positive**
                  - **N(cScreen+cRescreen+2(cReview))**
                - **Negative**
                  - **#**

= decision  ○ = chance event  # = complementary probability  = costs for each pathway
APPENDIX

Appendix 1: Cervical Cancer Screening - Questions re: Automatic Screeners of Pap Smear

1. Name of screener (e.g. AutoPap 300)

2. Is it to be used for prescreening of slides ☐ or for quality assurance ☐?

3. What is it’s sensitivity? specificity?
   and rates of false positives? false negatives?

4. What are the hardware and software requirements?

5. Do the slides to be read require special preparation? Yes ☐ No ☐
   If yes, please elaborate.

6. Would it be possible for you to send any product information sheets that you might have? Yes ☐ No ☐

7. What is the cost of the system?

8. Do you know what the cost/slide will be approximately?

9. What is the current status of this system? (e.g. still being studied, routine clinical use, etc.)

10. May I contact you again if I require further information? Yes ☐ No ☐
REFERENCES


