

New Tests for Cervical Cancer Screening

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The Papanicolaou (Pap) smear has been used to screen women for cervical cancer since 1940. Recently, a number of new technologies have been developed to improve the detection of cervical cancer and its precursors. However, there is substantial controversy about whether the new tests offer meaningful advantages over the conventional Pap smear. Ideally, these new tests will increase the early detection of meaningful Pap smear abnormalities, reduce the number of unsatisfactory smears and provide fewer ambiguous results. It is also hoped that these new screening methods will not increase the number of false-positive results, but will improve the productivity of cytology laboratories without substantially increasing costs. The new tests include liquid-based/thin-layer preparations to improve the quality and adequacy of the Pap smear; computer-assisted screening methods to improve Pap smear interpretation; and new-generation human papillomavirus testing methods that may be useful in triaging patients with atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesions. Evidence on these new tests is reviewed and the advantages and disadvantages of their use are discussed. (*Am Fam Physician* 2001;64:780-6.)

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on page 729.

Over the years, the Papanicolaou (Pap) smear has proved to be one of the most successful methods of cancer detection available. Once a common disease, invasive cervical cancer is now a relatively rare event in developed countries.¹ Of the 13,000 women who develop cervical cancer annually in the United States, approximately 50 percent have never had a Pap smear, and another 10 percent have not had a Pap smear within five years of their diagnosis (*Table 1*).² While the majority of these women are uninsured, nonadherence to screening recommendations has been observed even among women who have comprehensive preventive care coverage.³ Inappropriate triage and follow-up of an abnormal Pap smear account for 10 percent of women who develop cervical cancer. Given this information, improved access to care, adherence to screening recommendations and appropriate follow-up for women with an abnormal Pap smear should

have the greatest impact on decreasing morbidity and mortality from cervical cancer.

The remaining 30 percent of cervical cancers result from errors in sampling and interpretation.² Examples of such errors include incomplete sampling of the transformation zone, a poorly prepared slide with drying artifact or clumping of cells, and failure of the

TABLE 1
Estimated Annual Contributions
to Cervical Cancer Screening Failures
in the United States

Characteristic	Number of women (%)
Not screened	6,280 (50)
Poorly screened	1,260 (10)
Errors in follow-up	1,260 (10)
Errors in sampling and interpretation	3,770 (30)
Total	12,560 (100)*

*—Subcategories do not add up to 12,560 due to rounding.

Adapted with permission from Sawaya GF, Grimes DA. New technologies in cervical cytology screening: a word of caution. *Obstet Gynecol* 1999;94:307-10.

Of the 13,000 women who develop cervical cancer annually in the United States, approximately 50 percent have never had a Papanicolaou smear.

cytotechnologist to detect the presence of abnormal cells on the slide. The effort to reduce the number of cancers missed because of these errors has served as the catalyst for the development of new screening technologies.

Concerns for False-Negative Pap Smears

Estimations of the false-negative rate of Pap smears vary substantially among studies. Based on studies in which the Pap smear was performed under optimal conditions, a previous estimate of the false-negative rate ranged from zero to 29.7 percent.⁴ A 1999 technology assessment⁵ on the evaluation of cervical cytology screening was prepared for the Agency for Health Care Policy and Research (now known as the Agency for Healthcare Research and Quality). The study involved an exhaustive review of the accuracy of cervical cytology and new technologies. Unfortunately, the reviewers could not meet their objectives because of the lack of high-quality research. Sufficient precautions were taken to avoid bias in only three of 84 studies on cervical cytology. The researchers found that while the sensitivity of the Pap smear in these three studies was relatively low (56, 53 and 29 percent), the test performed best in the detection of high-grade dysplasia, which is more likely to progress to cancer if left untreated.⁵

MEASURES TO REDUCE ERRORS

A number of specific measures have been implemented to correct the problem of false-negative Pap smears. These have included recommendations on the optimal technique in performing a Pap smear and improved methods to harvest cells from the entire transformation zone (e.g., using a cytobrush with a plastic Ayre spatula). Cytopathology laboratories have been mandated to establish procedures to optimize quality assurance. For example, nationally implemented workload limitations require a cytotechnologist to screen no more than 100 slides per day. Furthermore, 10 percent of all Pap smears read as "normal" must be manually re-screened.

TABLE 2
Criteria for a Desirable Pap Test

An increase in the early detection of meaningful Pap smear abnormalities
A reduction in the number of "unsatisfactory" and "satisfactory but limited by..." Pap smears
Fewer ambiguous results from the laboratory
No substantive increase in the false-positive rate
Acceptable costs per life-year saved
Improved productivity of the cytology laboratory

Pap = Papanicolaou

Adjunctive Tests/Technologic Approaches

Ideally, an improved, more readable Pap smear or a technique that ensures that cytotechnologists do not miss important findings will improve patient outcomes and reduce morbidity and mortality from cervical cancer. Criteria for a desirable test are listed in *Table 2*.

Furthermore, technologic advances that facilitate the productivity of cytopathology laboratories should be valuable. The number of cytotechnology schools has decreased in the past several years, resulting in the graduation of fewer technologists. Backlogs are common in many laboratories and turnaround may be several weeks. Automation and computerization offer an opportunity to extend human resources and decrease fatigue in this labor-intensive profession.

New Technologies Under Investigation

New technologies for cytology screening have been promoted to physicians and the public. These technologies are intended to reduce the false-negative rate, improve sensitivity and specificity of screening, improve the adequacy of the Pap smear and potentially improve laboratory productivity. These new technologies include methods to

Advantages of the liquid-based preparation method include improved transfer of cells from the collection device and uniformity of the cell sample on each slide.

improve the quality and adequacy of the Pap smear (liquid-based/thin-layer preparations); methods to improve Pap smear interpretation (computer-assisted screening); and methods potentially useful in the triage of patients with atypical squamous cells of undetermined significance (ASCUS) or low-grade squamous intraepithelial lesions (LSIL), testing for the presence of high-risk human papillomavirus (HPV). *Table 3* presents a summary of each test including its goals, advantages and disadvantages.

LIQUID-BASED/THIN-LAYER PREPARATIONS

Interpretation of Pap smear slides may be hindered by poor sampling, uneven cell distribution or improper fixation of the slide. Important findings may be obscured by uneven sample distribution, cellular clumping and debris. The liquid-based/thin-layer preparation system (ThinPrep and AutoCyte Prep) is designed to correct this problem. The Pap smear is obtained with either a cytobrush and Ayre spatula or a cervical “broom” device. The clinician does not smear the sample directly onto a glass slide. Instead, the sample is placed in a small bottle containing fixative solution. The sample is sent to the cytology laboratory where it is filtered or centrifuged to remove excess blood and debris. The cells are then transferred to the slide in a “mono” layer.

TABLE 3
New Tests for Cervical Cancer Screening

<i>Test</i>	<i>Goals</i>	<i>Advantages</i>	<i>Disadvantages</i>
Liquid-based/thin-layer preparations (e.g., ThinPrep, AutoCyte Prep)	Improve the quality of the Pap smear Decrease unsatisfactory Pap smears Increase detection of cancer precursors	High-quality smear for review Improved transfer of cells from collection device Residual material may be used for HPV testing	Cost Increased detection of low-grade lesions in initial studies* Retraining of cytotechnologists
Computer-assisted screening (AutoCyte Screen)	Improve Pap smear interpretation Increase laboratory productivity Increase detection of cancer precursors	Increase cytotechnologist productivity May decrease false-negative reports	Cost From studies on PAPANET, increased detection of low-grade lesion*
HPV testing (e.g., Hybrid Capture II)	Potential use in triage of patients with ASCUS or noncorrelating colposcopy	Detect presence of high-risk HPV types	Cost ASCUS/LSIL Triage Study Group indicated lack of utility for LSIL Studies on ASCUS are ongoing

Pap = Papanicolaou; HPV = human papillomavirus; ASCUS = atypical squamous cells of undetermined significance; LSIL = low-grade squamous intraepithelial lesion.

*—There is controversy about whether this significantly benefits patients.

The slide is stained and examined manually in the conventional way.

Advantages of the liquid-based technique include improved transfer of cells from the collection device and uniformity of the cell population in each sample. These should improve the quality of the report and limit the number of smears read as “unsatisfactory” or “satisfactory but limited by...” Furthermore, this method provides representative residual material in collection media that can be used for additional/adjunctive testing (e.g., HPV testing).^{6,7}

COMPUTER-ASSISTED SCREENING

One of the factors that can influence the false-negative rate of Pap smears is whether abnormalities that exist on the slide are identified and interpreted accurately by the cytotechnologist. The cytotechnologist is typically challenged with slides containing many cells of which only a small proportion may demonstrate significant abnormalities. Even with improved quality assurance methods, abnormalities may be overlooked. Newly available techniques that use primary computer-assisted screening may improve detection.⁶⁻¹⁰ This screening method uses a video microscope to help detect abnormalities.

Two methods of computer-assisted screening are currently available: AutoPap and AutoCyte Screen. With AutoPap, the device reviews the material on the slide and, based on an algorithm, “scores” the slide as to the likelihood of an abnormality being present. This algorithm includes a variety of visual characteristics, such as shape and optical density of the cells. The device typically does not show the cytotechnologist which of the cells are likely to be abnormal.

The AutoCyte Screen device presents cell images to a human reviewer who then determines whether manual review is required. After the human reviewer has entered an opinion, the device reveals its determination based on a ranking as to whether manual review is warranted. When the human

reviewer and the computer agree that no review is needed, a diagnosis of “within normal limits” is given. Manual review is required for any case if designated by either the cytologist or the computer ranking.

HPV TESTING

A strong relationship exists between infection with HPV and occurrence of cervical cancer and its precursors. Approximately 80 different types of HPV exist. These can be divided into high-risk HPV types (e.g., HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56 and 58) and low-risk types (e.g., HPV 6, 11, 42, 43 and 44). A number of studies have shown that women infected with HPV 16 or 18 have a higher rate of progression of cervical squamous intraepithelial lesions (SILs) to cancer.⁶ It has been hoped that the ability to identify patients with oncogenic HPV types will lead to improved detection in women more likely to have SILs. The potential value of HPV testing for cervical cancer and its precursors is based on this association.

Hybrid Capture II is the latest refinement of HPV tests and has been described as having enhanced sensitivity. It can detect 13 high-risk types of HPV. The sample is collected with a cervical swab of the transformation zone and placed into transport medium. The test may also be performed from residual material collected in liquid-based medium for monolayer preparation. In the laboratory, cellular DNA is denatured and mixed with a ribonucleic acid probe that binds only to HPV DNA. The DNA “hybrid” is then captured by antibodies coating the sides of the tube. Next, a chemical is added, causing a chemoluminescent reaction. The amount of light that is measured can be used to determine the presence of HPV and the viral load.⁵⁻⁷

Studies Assessing the New Technologies

THINPREP

In initial studies on ThinPrep, most of the increased sensitivity can be accounted for by an increase in the diagnosis of LSIL. There is

Preliminary results indicate that computer-assisted screening can reduce the manual screening load in a laboratory by almost 60 percent.

controversy about whether patients significantly benefit from the detection of more low-grade lesions, which frequently regress without treatment.^{6,7}

AUTOCYTE SCREEN

The focus of technologies involving computer-assisted screening has shifted to primary screening because these devices may offer the greatest efficiency and benefit in this area. The AutoCyte Screen System was developed for primary screening and has been approved by the U.S. Food and Drug Administration. Preliminary results suggest that it can effectively select those cases that require manual screening from those that do not, and significantly reduce the manual screening load in a laboratory by almost 60 percent.^{8,10}

HPV TESTING FOR LSIL

Current findings of recent reports indicate a lack of utility for HPV testing in women with

LSIL. The ASCUS/LSIL Triage Study (ALTS) Group is a randomized trial including 3,600 women who were recently diagnosed with ASCUS and 3,600 who were recently diagnosed with LSIL.¹¹ All of the women underwent HPV testing with the Hybrid Capture II assay. HPV DNA was detected in 82.9 percent of the women with LSIL. Because of this high percentage, HPV testing in this group has limited potential to assist in the clinical management of these patients.

HPV TESTING FOR ASCUS

The results of the ALTS trial for women with ASCUS are still under investigation.¹¹ A recent study¹² reported the usefulness of HPV testing in women with ASCUS. HPV testing was done by reflex testing from ThinPrep fixative. Women who had ASCUS were selected from a large cohort who had routine Pap testing. All of the women had liquid-based cytology, HPV testing and subsequent repeat Pap tests and colposcopy including histologic evaluation. Of the 973 women who were eligible, 65 (6.7 percent) had histologic high-grade squamous intraepithelial lesions or cancer. In these women, the HPV test had a sensitivity of 89.2 percent and a specificity of 64.1 percent. Other studies have shown sensitivities of approximately 90 percent or more for the second-generation HPV test.¹³ However, concern has been raised about its false-positive rate, which has ranged from 5 to 20 percent.

Another study¹⁴ analyzed the results of nine studies that used Hybrid Capture II. The authors found no advantage of HPV testing over repeat Pap smear follow-up, although the analysis did not directly compare repeat cytology and HPV testing. This analysis also includes an analysis of HPV Profile testing, which has been shown to have low sensitivity and is not used.

Costs

Each of the new techniques will increase the costs of routine Pap smear testing. Whether these costs are justifiable is controversial. A

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cost-effectiveness analysis¹⁵ of ThinPrep, AutoPap and Papnet was recently performed. The reviewers applied the results of previous studies to a hypothetical cohort of 20- to 65-year-old women representative of the U.S. population. Notable findings included the following: (1) all three technologies increased the cost per woman screened by \$30 to \$257; (2) the new technologies increased mean life expectancy by five hours to 1.6 days and (3) there was an impact of the Pap smear screening interval with the cost per life-year saved. For example, the cost per life-year saved rose from \$7,777 with every four-year screening to \$166,000 with annual screening. They concluded that these technologies are more cost effective when incorporated into an infrequent screening interval.

Authors of another review⁵ found a substantial increase in costs with implementation of these newer technologies. The cost-effectiveness of conventional Pap smear screening every three years compared with no Pap smear screening was \$4,079 per life-year saved. The addition of new screening technology every three years had an incremental cost of \$22,010, which was less than the usually accepted threshold of \$50,000 per life-year saved.

Application to Clinical Practice

How should the clinician respond to these proposed measures to improve the detection of cervical cancer and its precursors? Specific recommendations for practicing clinicians are listed in *Table 4*. First, clinicians should ensure that the technique of specimen collection and slide preparation is done appropriately. Smears should be obtained before digital examination is performed. The ectocervix and endocervical canal should be sampled. The sample should be smeared and fixed immediately to avoid air-drying artifact. The use of lubricants should be avoided. Screening should be rescheduled in the presence of infection or bleeding.

Second, the issue of reaching the unscreened population must be addressed. Most women

Efforts to improve compliance with cervical cancer screening include physician and patient reminders and screening at visits not specifically intended for health care maintenance.

with cervical cancer have never had a Pap smear or have not had one in the past three to five years.¹⁵ Measures to improve compliance with cervical cancer screening should be widely implemented. These include physician and patient reminders and opportunistic screening (e.g., offering a Pap smear during a visit not initially intended for health care maintenance), especially in high-risk groups (i.e., women attending sexually transmitted disease and family planning clinics, and older, minority women).

Finally, measures must be implemented to ensure that women with abnormal smear results are triaged according to currently recommended guidelines.

Final Comment

The Pap smear remains one of the most successful cancer screening methods developed. However, false-negative results continue to concern physicians and their patients. False-negative slides are caused by clinicians (in obtaining an adequate sample without cellular clumping or air drying artifact) and by the laboratory (in reading the slide inaccurately). New technologies have been developed to reduce the

TABLE 4
Recommendations to Improve the Detection of Cervical Cancer and Its Precursors

Ensure proper technique in sample collection.
Implement measures to improve compliance with cervical cancer screening.
Advocate for access to care for the unscreened population.
Ensure appropriate triage for women with an abnormal cytology result.
Ensure that treatment of cervical disease follows acceptable guidelines emphasizing cytologic, colposcopic and histologic correlation.

false-negative rate. They may also provide the cytopathology laboratory with an opportunity to read slides more accurately and efficiently. Nationwide, cytopathology laboratories have been under increased pressure, particularly pressure caused by successful litigation, to remove the possibility of a false-negative test, although most false-negative reports are not related to laboratory errors.¹⁶ Cytology laboratories also face a diminishing pool of cytotechnologists with a backlog of specimens to be read or re-screened.

However, the current evidence indicates that these new tests will increase the detection of lesions that may not be clinically meaningful. Specifically, most of the lesions detected are borderline or low-grade abnormalities. Unless the new technologies can reduce current labor costs associated with manual screening, the potential for increased expense is substantial. Women who already have access problems to the health care system will likely face another burden that may again decrease their opportunity for screening.¹⁷ The impact of providing better access to regular screening and consistent follow-up for patients with abnormal results is likely to be greater than implementation of these new technologies.

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