A SUPPLEMENT TO
Ob.Gyn. News®

The Changing Landscape of Cervical Cancer Screening and Implications for the Clinician

Implications of Computer-Assisted Cervical Screening for the Ob.Gyn. Clinician

Comparison of Manual and Imaging-Directed Screening of Liquid-Based Cervical Cytology in a Large Metropolitan Cytology Practice

Performance of a Computer-Assisted Imaging System in Detecting High-Grade Squamous Intraepithelial Lesions

Evaluation of a Computer-Assisted Imaging System in Diagnosing Uncommon Malignancies

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Introduction

A trend in decreasing mortality rates from cervical cancer began 60 years ago when George Papanicolaou first published his findings and conclusions in his groundbreaking monograph Diagnosis of Uterine Cancer by the Vaginal Smear. *For 50 years, Papanicolaou's smear was the standard of care.*

In only the past decade, the drive for better patient care, along with the need to further reduce cervical cancer incidence and mortality, has led to continued improvement, first by the introduction of liquid-based cytology and then by the advent of the computer-assisted imager to screen slides.

Despite the widespread acceptance of cervical cancer screening and declining incidence and mortality rates, much confusion remains with regard to optimal screening strategies. The landscape for cervical cancer screening is ever-changing and the need to stay informed is pressing.

The first article is a comprehensive overview of computer-assisted cervical screening, prepared by two prominent gynecologic oncologists who are the faculty co-chairs: Thomas J. Herzog, MD (Director, Division of Gynecologic Onocology, Columbia University College of Physicians and Surgeons, New York, N.Y.) and Randall K. Gibb, MD (Assistant Professor, Division of Gynecologic Onocology, Washington University School of Medicine, St. Louis, Mo.). Pathologists Bruce R. Dziura, MD (Chief of Pathology, New England Pathology Associates, Mercy Medical Center, Springfield, Mass., and Andrea E. Dawson, MD (Staff Pathologist, Cleveland Clinic Foundation, Cleveland, Ohio), and veteran cytotechnologist Fern S. Miller, MSM, CT (ASCP) (Cytology Manager, Cytology Department, Metropath Laboratories, Denver, Colo.) —all of whom have experience using the latest generation computer-assisted imager—have paired to write the remaining three articles with practicing ob.gyns., who provide insight on how the new technology may affect various types of clinical practice. The participating physicians are Timothy Kelly Fitzpatrick, MD, who is on the medical staff at Mercy Medical Center, Springfield; Holly L. Thacker, MD, Director, Women's Health Center at the Cleveland Clinic, with joint appointments in ob.gyn. and internal medicine; and James R. Lingle, MD, who has a private practice in Denver, Colo.

Implications of Computer-Assisted Cervical Screening for the Ob.Gyn. Clinician

Co-Chairs: Randall K. Gibb, MD, and Thomas J. Herzog, MD

Dr Herzog: Several major developments have occurred in the past decade that have dramatically affected the way that we view cervical cancer screening. Some of the more significant changes include the 2001 update of the Bethesda System terminology for reporting cervical cytology results and new patient management guidelines developed by the American Society for Colposcopy and Cervical Pathology.[1,2] We continue to learn more about the molecular genetics of preinvasive and invasive cervical cancer, which has provided yet another research initiative and expanded knowledge base that we did not have heretofore.

Development of liquid-based cytology has been another significant milestone in cervical cancer screening. The fluid-based, thin-layer preparation technique was first approved by the US Food and Drug Administration (FDA) in 1996 in an attempt to improve upon the 60-year-old Papanicolaou (Pap) smear method.

Different approaches for liquid-based cytology have emerged during the past decade. FDA-approved methodologies include ThinPrep Pap Test and the SurePath method. The published literature on the ThinPrep method illustrates how liquid-based cytology can be superior to conventional smears in several aspects. It has been shown to dramatically reduce the number of unsatisfactory slides because abnormal cells are not obscured by blood, inflammation, mucus, or other debris.[3,4] A 2001 meta-analysis by Bernstein et al[5] demonstrated that the ThinPrep test was as good as, or superior to, the conventional Pap in detecting cervical abnormalities and also improved sample quality. A 2003 review by Abulafia et al[6] of 17 comparative studies concluded that ThinPrep tests are both more sensitive and more specific than are conventional smears, resulting in increased diagnosis of cervical atypia, low-grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesions (HSIL), and invasive carcinoma.

Another benefit of liquid-based cytology is that cells from the sampling device are preserved and thus can be used for adjunct testing, such as detecting human papillomavirus (HPV) or chlamydia or gonorrhea infections.

Dr Gibb: One of the chief weaknesses of the conventional Pap is its false-negative rate, which has been reported to range from 1.5% to 55%.[7] It has been estimated that nearly two thirds of false negatives on conventional Pap tests are caused by sampling and preparation errors: failure to collect representative cells on the sampling device, to transfer the cells to the slide in an even manner, or to preserve the cells properly.[7,8] The remaining one third of false-negative errors with conventional

Paps are attributed to screening and interpretive errors, ie, abnormal cells are overlooked or misclassified. Liquid-based cytology has been shown in numerous studies to reduce the false-negative rate.[7,9,10]

Computer-Assisted Imaging for Cervical Cytology

Dr Herzog: Presumably this false-negative reduction has occurred largely in the "two-thirds" error category, with the liquid-based cytology technology leading to improved sampling/slide preparation.

This brings us to another significant advancement in cervical cytology—computer-assisted imaging. This technology attempts to improve the cytotechnologists' accuracy in reading cervical slides. The first computer-assisted imaging device was developed for use with conventional Pap smears. A device known as PapNet received FDA approval for quality-control rescreening of previously interpreted negative slides.

Dr Gibb: Because the device was designed for conventional Paps, it scanned slides that had cells stacked atop one another, not the uniform thin-layer distribution of cells of liquid-based cytology. It proved unsuccessful and is no longer being manufactured.

The next major computer-assisted device was a slide profiler now known as FocalPoint, which can be used with both conventional smears and SurePath liquid-based cervical cytology. The profiler uses algorithms to assign scores to slides based on the probability that they contain abnormal cells. It sets aside up to 25% of slides as normal, needing no further review. The remaining slides are reviewed manually.

Fields of View

A new-generation computer-assisted imager rapidly scans a cervical cytology slide and measures the integrated optical density of each cell's nucleus. It uses this information to identify 22 fields of view (FOV), or areas of interest, for the cytotechnologist to review. If the cytotechnologist finds any abnormalities, the entire slide, representing approximately 120 FOV, is screened. But for the 95% of slides that are normal*, the cytotechnologist need only screen approximately one fifth of the slide.

*Solomon D, et al. *J Natl Cancer Inst.* 2001; 93:293-299.

> **"[Computer-assisted imaging] attempts to improve the cytotechnologists' accuracy in reading cervical slides."**
>
> ***—Dr Herzog***

Dr Herzog: The question with this device is, how much does it help the cytotechnologist who still must screen 75% of the slides, plus do quality-control assessment on some of the 25% sorted as negative? As Dr Dziura notes in his article (page 9), the slide profiler does not do anything to improve the cytotechnologist's ability to interpret the slides that he or she must screen manually.

Still another approach was taken in designing the latest computer-assisted imager, the ThinPrep Imaging System, approved by the FDA in 2003 for use on ThinPrep liquid-based cytology. It is very different from the previous technology because it reviews every slide and out of approximately 120 fields of view (FOV) determines 22 fields for the cytotechnologist to examine. Twenty of the fields detect individual cells or small groups; the remaining two look at cell clusters or large groups. The computer-assisted imager uses algorithms to determine which cells look the most abnormal, based on cell nuclear morphology and DNA content. If the cytotechnologist finds any abnormalities in these 22 FOV, he or she screens the entire slide. Then it is reviewed by a pathologist. If no abnormalities are found, the slide is signed out as normal.

This approach has importance for the ob.gyn. because (1) it reduces cytotechnologist fatigue, (2) it decreases turnaround time for test results, and (3) it ensures that every slide has the potential to be screened up to three times—by the imager, the cytotechnologist, and, if necessary, the pathologist, which will result in diagnostic accuracy.

Dr Gibb: Another unique aspect of the new imager is that it uses a quantitative stain to denote cell nuclei. Dysplastic and cancerous cells have denser nuclei and thus absorb more of the stain, making it easier for the computer to measure their DNA content and provide areas of interest for the cytotechnologist to review and make an informed diagnosis.

Computer-Assisted Imaging Tested in the Laboratory

Dr Herzog: Clinical data submitted to the FDA showed that for a threshold of atypical squamous cells of undetermined significance (ASCUS) and higher, the ThinPrep Imaging System demonstrated a statistically significant improved sensitivity, as well as a statistically significant improved specificity for HSIL and higher, compared to manual review of ThinPrep slides.[11]

Now we are beginning to see the impact that this imager has under "real-world" laboratory conditions and how it may impact the ob.gyn. with studies such as the one conducted by Miller et al ("Comparison of Manual and Image-Directed Screening of Liquid-Based Cervical Cytology in a Large Metropolitan Cytology Practice," page 7). In this study, disease detection rates of nearly 86,000 manually screened liquid-cytology Paps were compared to rates of nearly 20,000 imaged Paps. Statistically significant improvements in LSIL and HSIL detection were seen, without a significant increase in ASCUS. Of note, a second study by Miller et al[12] used biopsy and/or HPV data to demonstrate improvement in specificity as well as sensitivity with the imager.

Dr Gibb: This study is important for three reasons: (1) a large number of slides were looked at, (2) it is from a large metropolitan area, which means it is likely to represent a mixed population, and (3) there was no difference in ASCUS rates between the two arms. That's something, as practicing clinicians, we want to see—no increase in equivocal results.

Dr Herzog: Also, the increase in the HSIL detection rate was 43%. HSIL is the diagnosis that we are most interested in, since a majority of low-grade lesions regress without treatment. A second study ("Performance of a Computer-Assisted Imaging System in Detecting High-Grade Squamous Intraepithelial Lesions," page 9) was designed to look specifically at HSIL. Detection rates of approximately 11,000 imaged slides were compared with those of more than 28,000 manually screened slides. Biopsy correlations of HSIL diagnoses were calculated when available. Seventy-four cases of HSIL in the imaged slide were detected (0.68%) compared to 140 HSIL in the nonimaged slides (0.49%). Biopsy results were not available for all the HSIL cases, but of the patients who had gone on to biopsy, imaged slides had a higher correlation rate (85% vs 77% of nonimaged slides).

Dr Gibb: A strong point of this study is the biopsy correlation, so we know we are picking up real disease, not false-positives. I think any ob.gyn. would agree that detecting 8% more cases of HSIL is worthwhile.

Dr Herzog: A third study looked at the imager's ability to select areas of interest for the cytotechnologist to review and ultimately detect lesions such as endocervical adenocarcinoma in situ and invasive carcinomas ("Evaluation of a Computer-Assisted Imaging System in Diagnosing Uncommon Malignancies," page 11).

In this study, which involved 70,000 processed slides, the imager identified areas of interest to aid the cytotechnologist in detecting 13 cases of uncommon malignancies. What's important about this study is that there were no false-negatives.

Dr Gibb: The strength of this study is biopsy confirmation of real disease. It is heartening that even though these entities are rare, the imager identified areas of interest where the cytotechnologist detected sufficient abnormal cells on its 22 FOV to trigger a full review of the slide.

Dr Herzog: These results go hand in hand with earlier studies showing that ThinPrep is superior to conventional Paps in picking up glandular lesions.[13,14] Also, HPV testing most likely would not have aided in detecting some of the cancers picked up by the imager, including six endometrial and two ovarian adenocarcinomas. Finally, there is no known utility for HPV testing in abnormal atypical glandular cells of undetermined significance results.[15]

> **"The most exciting aspect of this new imaging technology to me, as a clinician, is that it appears to be able to further reduce false-negatives."**
>
> ***—Dr Gibb***

Liquid-Based Cytology and HPV Testing

Dr Gibb: HPV testing has been shown to be valuable in triage/reflex testing of ASCUS patients,[16] but its utility as a primary screening tool remains controversial. The American College of Obstetricians and Gynecologists (ACOG) and the American Cancer Society have revised their screening guidelines to state that women older than 30 years of age who receive both cervical cytology and a genetic test for HPV and who have negative results on both tests may not need to be rescreened for 3 years.[17,18] (It should be noted that ACOG's recommendations were based on what it considered limited and inconsistent scientific evidence.)

Some societies recommend extending the interval between Paps because, on average, it takes at least 2 years for significant cervical dysplasia to develop when an HPV infection occurs. The rationale behind increasing intervals is cost savings. Yet there appears to be a number of clinicians who are using both tests but are not increasing the screening interval when both are negative, so they are, in fact, adding cost to the system. Goldie et al[19] concluded in their cost-savings analysis that annual cytology screening combined with HPV DNA testing added very few hours of life-expectancy gained but had an overall negative cost-effectiveness ratio of more than $2 million per year of life saved.

Dr Herzog: It should also be emphasized that because of the extremely high prevalence of HPV in women younger than 30 years of age, much of which will resolve without treatment, the HPV DNA test is not recommended for screening in this population. The guidelines state this, but there is still confusion among clinicians about how to correctly utilize these tests.

Dr Gibb: It is true that the sensitivity of the HPV DNA test is excellent—nearly 100% in one study—for detecting biopsy-confirmed HSIL. But far more important is the positive predictive value of the HPV DNA test. This has been reported to range from 8% to 20%.[20-22] In other words, we're finding a lot of false-positives.

A second important issue is the negative predictive value of both tests. Several studies have shown the negative predictive value of ThinPrep and the HPV DNA test to be virtually identical. According to Ferreccio et al,[21] both technologies had a 99.8% negative predictive value for ASCUS or higher. So why subject the medical health care system to the additional cost of two tests when the second may be no better than the first?

Dr Herzog: I agree that the real question is whether combining two tests (liquid-based cytology and HPV DNA) is better than liquid-based cytology alone. There are still some concerns that need to be answered relative to using an HPV DNA test as a primary screening tool. Researchers don't really understand, for example, how viral load or the interaction of different HPV types may impact disease progression. HPV testing shows us only who has been infected, not who will get the disease. And now, as the abstracts reviewed in this supplement illustrate, there appear to be emerging data suggesting that accuracy of liquid-based cytology is further improved by computer-assisted imaging.

Dr Gibb: Primary screening with HPV DNA tests raises other concerns as well, such as how to manage the patient who tests positive for high-risk HPV but who has a normal Pap. And if we extend the intervals between Pap tests, are we going to lose that woman who ought to be coming in for annual pelvic and breast examinations and lose a chance to relay diet, exercise, lifestyle, and smoking cessation advice to her?

Dr Herzog: I agree that these secondary issues are indeed a concern. With the state of today's health care system, it is common for patients to switch health plans frequently. Physicians are forced to rely on a patient's recall of her last Pap test, which is notoriously unreliable. So a planned 2- to 3-year screening interval could in fact become a 4- to 5-year interval, and we don't know the implications of prolonged screening intervals on cervical cancer incidence using these new technologies.

Computer-Assisted Imaging: The Future

Dr Herzog: The benefit of this newest imager is that it is not trying to replace the cytotechnologist. The computer has the ability to assess a large number of cells in a short period, but it lacks interpretive skill. That's where the human being steps in, after being guided by the imager to the areas of interest.

Dr Gibb: It appears that the imager may have applications in areas beyond cervical cytology. The liquid cell preservation medium is already being used to produce thin-layer slides from lymph node, lung, breast, thyroid, and other tissue collected via fine-needle aspiration or from mucoid or body fluid specimens. The next step may be to have these slides similarly imaged.

Conclusion

Dr Herzog: In summary, the three studies presented here demonstrate that using the new imaging system results in increased sensitivity for HSIL with no increase in equivocal ASCUS Pap results. The imager also may help the cytotechnologist more accurately identify glandular abnormalities. By focusing in on 22 FOV, the imager also spares the cytotechnologist from scanning the entire slide when he or she identifies no abnormalities (and approximately 95% of Paps are normal[16]), thus reducing fatigue and hastening turnaround time for results.

Dr Gibb: The most exciting aspect of this new imaging technology to me, as a clinician, is that it appears to be able to further reduce false-negatives. Liquid-based cytology reduces sampling errors; this technology now will aid in reducing screening errors.

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Comparison of Manual and Image-Directed Screening of Liquid-Based Cervical Cytology in a Large Metropolitan Cytology Practice

James R. Lingle, MD, and Fern S. Miller, MSM, CT(ASCP)

Miller, MSM, CT(ASCP): When a new technology is introduced, scientists are required to validate its capability to replace existing methods. To do so, our laboratory conducted a study to compare disease detection rates of approximately 20,000 slides imaged using the ThinPrep Imaging System that our laboratory had processed in the first quarter of 2004 with approximately 86,000 slides manually screened in 2003 (see box below). I would describe the study population as mostly low-risk women who receive regular Papanicolaou (Pap) tests and are dependable about returning for follow-up when results are abnormal. There is a mix of racial backgrounds one would expect to find in a large metropolitan practice.

Dr Lingle: The population served by my suburban Denver practice is similarly stable and reliable about follow-up, representing a full spectrum of age groups. The women are primarily Caucasian but also include Hispanics, Asians, and African Americans. We have a moderate-sized subset of women 16 to 30 years of age who would be considered higher risk for abnormal Paps and for human papillomavirus (HPV) infection.

What were the results of your study?

Miller, MSM, CT(ASCP): We found that the imager helped identify areas for the cytotechnologist to focus on, therefore, helping the cytotechnologist to detect 25% more low-grade squamous intraepithelial lesions (LSIL) and 43% more high-grade squamous intraepithelial lesions (HSIL), with no significant increase in atypical squamous cells of undetermined significance (ASCUS). These rates appear to be similar to those that other laboratories are finding with the imager, although the data are not yet published. We also found that the imager could properly assess the endocervical component and the imager has the potential to reduce the false-negative fraction for the laboratory.

Specimen Adequacy Issues

Dr Lingle: Although the conventional Pap smear was one of the best screening tests developed in the past half-century, one of its weaknesses was its high rate of false-negatives. The liquid-based cytology has been shown to reduce false-negatives[1] and the imaging system is the logical progression of that technology, taking interpretation of Paps to an even higher level of accuracy.

Beyond the increased LSIL and HSIL detection rates, I think the significance of the findings of Miller et al, is that the imager does not increase ASCUS rates, which are equivocal results, or the number of slides deemed inadequate because of lack of cells. In my practice, that's likely to mean that I'll spend less time having to repeat Pap tests because of inadequate specimens, which is an inconvenience for the patient as well as the clinician.

Miller, MSM, CT(ASCP): The presence of endocervical cells lets the cytotechnologist know that the clinician has gotten high enough into the endocervical canal when obtaining the specimen—ie, the sample comes from the right place in the transformation zone, which is where many precancerous lesions originate. Thus, in our study we wanted to make sure the imager was showing these cells.

Dr Lingle: We certainly look at endocervical cells as a measure of the adequacy of the specimen we've obtained. However, some recent studies have indicated that lack of endocervical cells has not really made a difference in the detection of clinical disease.[2-4]

Natural History of Cervical Neoplasia

Dr Lingle: Going back to the improved sensitivity and specificity of liquid-based cytology compared to that of conventional Paps, the reason the accuracy issue is paramount in the minds of clinicians today is that there have been suggestions that patients should undergo primary screening for HPV DNA. Obviously, this would require further clinical data since the current HPV DNA test is not approved to be used without cervical cytology. Its current approval is as an adjunctive test to cervical cytology.[5]

I think this approach has its shortcomings, in part because of the high preva-

Title of Study: Comparison of Manual and Image-Directed Screening of the ThinPrep Pap Test in a Large Metropolitan Cytology Practice

Investigators: Fern S. Miller, MSM, CT(ASCP); Lynn Nagel, BS, CT(ASCP); and Mary Kenny-Moynihan, MD

Purpose: To assess disease detection rates using a computer-assisted imager compared to manual screening of ThinPrep Pap tests.

Description: Disease detection rates of 19,936 imaged cervical cytology slides were compared to rates of 85,921 manually screened ones.

Summary of Results: The imager detected significantly more low-grade squamous intraepithelial lesions (25% more, $P<0.0001$) and high-grade squamous intraepithelial lesions (43% more, $P<0.002$) without a significant increase in atypical squamous cells of unknown significance.

Investigators' Conclusion: The imager has the potential to aid the cytotechnologist in detecting more disease and reducing false-negative results in the laboratory.

Adapted from *Acta Cytol.* 2004;48:701-702.

lence of HPV in the population, particularly among younger women. According to a 1998 study by Ho et al,[6] 60% of college-age women had an HPV infection during a 3-year period. Of these HPV-infected women, 70% had cleared the virus after 1 year and 92% had cleared the virus after 2 years. We know that infection is often transient, and persistent infection is more likely to lead to HSIL and invasive cancer. While women have the virus, their Paps are more likely to be abnormal, but if the infection is transient, cytology results may revert to normal.

And what about the woman who tests positive for high-risk types of HPV, which are more likely to persist? In a UK study, Woodman et al[7] showed that only 5.5% of women positive for high-risk HPV went on to develop cervical intraepithelial neoplasia (CIN) 2 or CIN 3.[8] In a Netherlands study, 10% of high-risk HPV-positive women followed for 6½ years developed CIN 3.[8] Yes, a woman is at increased risk for cervical cancer if she is high-risk HPV positive—ob.gyns. should not take this risk lightly—but universal HPV screening is likely to turn up a high number of positives from transient infections. This might cause undue anxiety in the woman who tests positive and then gets on the Internet and starts reading about HPV. The test will create a lot of unnecessary follow-up. Not all physicians are comfortable or familiar with the guidelines for managing the patient who is HPV positive but who has a normal Pap. Some clinicians may want her to repeat the Pap in 6 months; others may refer her to colposcopy. This leads to unnecessary procedures for patients and added costs to the system.

"In my opinion, HPV testing has its place, such as reflex testing when ASCUS results are obtained, but the liquid cytology combined with the imager is superior to using HPV DNA testing as a primary screening tool."

—Dr Lingle

Increasing screening intervals to 2 to 3 years in patients who have three consecutive negative Pap results using liquid cytology, or who have negative Paps and negative HPV results, may be appropriate in some patients, such as the monogamous married woman in a stable relationship, but I'm not comfortable yet taking this approach with patients in other circumstances.

In my opinion, HPV testing has its place, such as reflex testing when ASCUS results are obtained, but the liquid cytology combined with the imager is superior to using HPV DNA testing as a primary screening tool.

As I stated earlier, accuracy of Pap results is paramount in the minds of clinicians today because if a Pap test is highly sensitive and specific, conducting an HPV DNA does not improve upon it. Now we have this new imager which appears to help cytotechnologists make even more accurate Pap screening evaluations.

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Performance of a Computer-Assisted Imaging System in Detecting High-Grade Squamous Intraepithelial Lesions

Bruce R. Dziura, MD, and Timothy Kelly Fitzpatrick, MD

Dr Dziura: The 2001 revision of the Bethesda System of reporting cervical cytology results has given us new terminology for some types of abnormalities, but it maintains the category of HSIL for high-grade squamous intraepithelial lesions.[1] HSIL comprises the subcategories of cervical intraepithelial neoplasia (CIN) 2 and CIN 3, or moderate to severe dysplasia and carcinoma in situ.

It was once thought that cervical cancer was a progression from mild to moderate to severe dysplasia, to carcinoma in situ, and finally to invasive carcinoma. Later research appears to indicate that a majority of HSIL originate as such.

Dr Fitzpatrick: This is an important distinction because approximately 60% of mild dysplasias will resolve without treatment. Approximately 40% of moderate dysplasias will spontaneously resolve. However, only a third of severe dysplasias will.[2] That means more than 60% will progress to more severe lesions. The chances of CIN 3 progressing to invasive cancer is greater than 12%.[2,3]

Dr Dziura: Because we now know that most low-grade squamous intraepithelial lesions (LSIL) regress and most HSIL do not, emphasis has shifted in recent years to detecting and treating HSIL.

Imager Identifies Areas of Interest

Dr Fitzpatrick: Can you describe your study, Dr Dziura?

Dr Dziura: First, let me describe how the new imager we used in the study works. The ThinPrep Imaging System is a computer-assisted Pap screening system that scans a microscopic slide and identifies 22 fields of view (FOV) for the cytotechnologist to examine. This process is distinctly different from the stand-alone file sorter Pap screening device described by Drs Herzog and Gibb (page 3), in which the machine determines that a certain percentage of cases are negative and are not reviewed by the cytotechnologist. If a computer says that 25% of slides are negative and passes the remaining 75% of slides on for manual screening, the cytotechnologist is still going to make the same percentage of mistakes he or she would make on any manual screen. However, the ThinPrep Imaging System is designed to improve accuracy by directing the cytotechnologist to diagnostically relevant areas of the slide. Another difference between the two devices is that the slide profiler is not intended to be used on slides designated by the laboratory as high risk,[4] whereas the imager can be used on any slide.

The real advantage of this integrated system is that it takes advantage of what a computer brain does well and combines it with what a human brain does well. The imager is incredibly efficient at picking up small random events, such as one or two tiny abnormal cells on the slide. It's easy for a human to miss something like that.

The goal of our study comparing imaged screening versus manual screening of ThinPrep slides in detecting HSIL (see box, below) was to assess the imager's performance in picking up the events that we have noted are most likely to progress to invasive cancer. Ours was a retrospective study comparing imaged slides from the first quarter of 2004 to nonimaged slides from the preceding 11 months. Retrospective studies can sometimes be problematic because of differences in cohorts, but our clinician base was the same in both arms of the study, as was our cytotechnology staff. In addition, I was the only cytopathologist to sign out cases in both the manually screened and the imaged slide periods of the study. The nearly 40,000 slides analyzed in both arms represented a mixed population of primarily low-risk women, but there was a significant subset of high-risk patients as well.

Interestingly, while we were conducting this study, our cytotechnologists said they thought they were passing on more HSIL

Title of Study: The ThinPrep Imaging System in the Detection of High-Grade Squamous Intraepithelial Lesions (HSIL) of the Uterine Cervix

Investigators: Kathleen Richard, CT(ASCP), CT (IAC); Bruce R. Dziura, MD, and Sarah Quinn, CT(ASCP)

Purpose: To assess the ThinPrep Imaging System's ability to detect HSIL compared to manual screening of ThinPrep cervical cytology slides.

Description: Rates of atypical squamous cells of unknown significance, low-grade squamous intraepithelial lesions, and HSIL were calculated from 10,858 imaged slides and 28,410 manually screened slides. Biopsy results of HSIL diagnoses were correlated.

Summary of Results: Seventy-four HSIL diagnoses, or 0.68%, were made from imaged slides, 140 HSIL diagnoses (0.49%) from nonimaged ones. Of the slides for which biopsy results were available, 85% (46 of 54) of the imaged slides had positive tissue diagnosis for HSIL; 76% (91 of 119) of the manually screened slides did.

Investigators' Conclusion: The ThinPrep Imaging System detected a significantly higher number of HSIL than did manual screening of ThinPrep Paps.

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slides to me for review. I also felt that I was signing out more HSIL slides. When we reviewed the data, we saw indeed that that was true. But the obvious question is, are these real HSIL or are these false-positives?

The way to determine that is with follow-up biopsies. Biopsy correlations were available for 54 of the imaged HSIL cases and 119 of the manually screened ones. These biopsies confirmed HSIL in 85% of the imaged cases and 77% of the nonimaged ones. This shows that not only were we diagnosing more HSIL but we also were detecting true disease. The imaging system is significantly more sensitive than manual screening in the detection of HSIL of the uterine cervix.

Data from the multicenter clinical trial for US Food and Drug Administration approval for the imager demonstrated a statistically significant improvement for specificity for HSIL-positives compared to manually screened slides.[5] Although our numbers are small, our biopsy correlation of HSIL also supported increased specificity.

Dr Fitzpatrick: With these new technologies—first the thin-layer Pap and now the new imager—we have more confidence in the results coming out of the cytopathology lab. There doesn't seem to be any question that we have identified more people with cervical dysplasia. These technologic advances, combined with the more recent addition of human papillomavirus reflex testing on ASCUS results, have made triage of very difficult pathologic problems easier for us.

Detecting HSIL

- ***50 million Pap tests conducted annually in the United States***
- ***3.5 million are abnormal***
- ***>2 million of the abnormal Paps are ASCUS***
- ***200,000 to 300,000 of abnormal Paps are HSIL, the majority of which will progress to more severe lesions***

ASCUS-atypical squamous cells of undetermined significance; HSIL-high-grade squamous intraepithelial lesions.

Sources: Solomon D, et al. *J Natl Cancer Inst.* 2001;93:293-299. Jones BA, Davey DD. *Arch Pathol Lab Med.* 2000;124:672-681.Ostor AG. *Int J Gynecol Pathol.* 1993;12:186-192.

> **"When I see a biopsy-proven increase in HSIL detection rate with the use of the new imaging system, that's extremely exciting, because this is precisely the core group of patients on whom we should be focusing our cervical cancer screening."**
>
> ***—Dr Fitzpatrick***

Although the Pap test is a screening test, not a definitive diagnosis, we gynecologists live in fear of missing someone with HSIL who goes on to develop invasive cancer. Much of our patient management hinges on our confidence that the cytopathologist genuinely sees something on the slide.

HSIL Detection Maintained

Dr Fitzpatrick: When liquid-based cytology was first introduced, we saw a phenomenon in which cells could be seen so clearly that it was actually difficult for cytotechnologists to decide whether they were looking at high-grade lesions. ASCUS readings actually rose slightly at first before dropping. In other words, there was a learning curve for cytotechnologists to adjust to the clearer slides. Is there a similar learning curve for the imager?

Dr Dziura: That is an interesting question. We expected an initial rise in ASCUS because of the psychology of being directed by the system to 22 FOV and being asked to decide whether the cells were abnormal. Our laboratory did report a rise in ASCUS the first 3 months, but then it began dropping. It is now where it was prior to using the imager. However, with HSIL findings, we saw an immediate increase in HSIL identification that has been maintained.

Dr Fitzpatrick: With liquid-based cytology, the number of either metaplastic or endocervical cells needed for a slide to be deemed adequate is fairly small. Is the imager making it easier for your cytotechnologists to qualify a slide as adequate or showing endocervical cells?

Dr Dziura: The imager's algorithms are not designed to pick up metaplastic or endocervical cells per se. However, we have found if endocervical or metaplastic cells are not found in the 22 FOV, we're fairly confident signing the slide out as "no endocervical component." Some of the cytotechnologists will take an additional manual slice to make sure. But we haven't seen a significant rise in "no endocervical component" findings.

Dr Fitzpatrick, with these preliminary data indicating the computer-assisted imager is reducing false-negatives, can you describe what type of impact this device might have for ob.gyns. such as yourself?

Dr Fitzpatrick: As clinicians, we understand that if a low-grade lesion is missed on a Pap, it may very well be picked up a year or two later. But if a high-grade lesion is missed, a small percentage of those patients will have an invasive cancer within 2 to 3 years. When I see a biopsy-proven increase in HSIL detection rate with the use of the new imaging system, that's extremely exciting, because this is precisely the core group of patients on whom we should be focusing our cervical cancer screening.

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Evaluation of a Computer-Assisted Imaging System in Diagnosing Uncommon Malignancies

Andrea E. Dawson, MD, and Holly L. Thacker, MD

Dr Dawson: It has been estimated that 15% to 24% of cervical cancers are adenocarcinomas or adenosquamous carcinomas.[1,2] Although these types of cancer are uncommon compared to squamous cell carcinomas, they appear to be increasing in incidence. According to Smith et al,[2] from 1973 to 1996 the proportion of adenocarcinomas increased by 107.4% relative to all cervical cancer. It is unclear whether this is a true increase or simply that squamous cell cancer incidence is decreasing because of better screening methods.

Dr Thacker: Also, an annual 3% increase in invasive cervical cancer among white women younger than 50 years of age has been noted over the past few decades.[3]

Not only are endocervical adenocarcinomas uncommon, they are also very hard to detect, both clinically and by cervical cytology. Patients are usually asymptomatic. Adenocarcinomas may be missed on Papanicolaou (Pap) tests because they typically originate higher in the endocervical canal, where it is harder for the clinician to sample. For the same reason, these lesions can be hard to detect during colposcopy as well. Fortunately, liquid-based cytology has been shown to be more effective at detecting these types of cancers than are conventional Pap tests.[4,5]

Imager Evaluated in Study of Other Rare Cancers

Dr Dawson: Our clinic evaluated approximately 70,000 slides in an 8-month period using the computer-assisted imager (see box, below). We wanted to assess the imager's ability to identify uncommon lesions—endocervical adenocarcinomas in situ (AIS) and invasive carcinomas, including adenocarcinomas. We identified 18 cases during that period that had biopsy-confirmed diagnoses.

> **"Not only are endocervical adenocarcinomas uncommon, they are also very hard to detect, both clinically and by cervical cytology."**
>
> ***—Dr Thacker***

Of the 13 imaged cases, biopsy showed two were AIS and high-grade squamous intraepithelial lesions (HSIL), six were endometrial, two were ovarian, two were metastatic breast, and one was squamous carcinoma. We then had a cytotechnologist blinded to the diagnoses examine the slides. A preliminary diagnosis was made by looking at only the 22 fields of view (FOV) pinpointed by the imager as containing the most abnormal cells. The cytotechnologist then reviewed the entire slide and made a second diagnosis based on a full screening. We then compared the two diagnoses for each case.

The point of the comparison was to see if the 22 FOV were picking up enough abnormalities to trigger a manual review. Of the FOV isolated by the imager, 20 are of individual cells and two are of cell clusters. We were concerned that if the imager was picking up abnormalities only in the cell cluster fields, it might be difficult for the cytotechnologist to spot them and trigger a review of the entire slide—these glandular lesions are notoriously difficult to detect.

We found that the average number of fields per slide containing abnormal cells in the imager's 22 FOV was 10.31. The average number of fields outside the original 22 FOV that contained abnormal cells was 10.58. Thus, the imager's 22 FOV were very representative of the slide generally, and one can infer that it wasn't just picking up cluster features. When the cytotechnologists' preliminary and final diagnoses were compared, they were

Title of Study: ThinPrep Imager System Performance in the Diagnosis of Uncommon Malignancies

Investigators: Debbie Sabo, CT(ASCP); Julie Shorie, CT(ASCP), and Andrea E. Dawson, MD

Purpose: To evaluate the performance of a computer-assisted imager in detecting uncommon lesions such as endocervical adenocarcinomas in situ (AIS) and invasive carcinomas on ThinPrep cervical cytology.

Description: Of all cervical specimens screened from October 2003 to April 2004 in a laboratory, 18 cases of biopsy-confirmed AIS, adenocarcinoma, and squamous carcinoma were identified. These specimens were put through the imager for review. A cytotechnologist evaluated the 22 fields of view (FOV) selected by the imager and made a diagnosis based on only those fields, then reviewed the entire slide and made a diagnosis based on those findings.

Summary of Results: The imager rejected five slides. Of the 13 remaining cases, there were no false-negative original diagnoses made by the cytotechnologist based on the 22 FOV.

Investigators' Conclusion: The imager showed excellent performance in identifying abnormal cells that would trigger a full slide review in this small number of cases.

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equivalent in eight cases and resulted in a slight upgrade in five cases. There was no case of going from a negative to a positive diagnosis; in each case, the imager identified areas to trigger a full review by the cytotechnologist.

We felt comfortable that the imager is identifying areas for the cytotechnologist to detect even these rare abnormalities.

Dr Thacker: Human papillomavirus (HPV) plays an important role in the pathogenesis of cervical cancer, but it's important to note that HPV DNA testing would not have aided in detecting any of the nonendocervical cancers in this study. HPV testing has not been approved by the US Food and Drug Administration for testing in cases of abnormal atypical glandular cells of undetermined significance (AGUS) results.[6]

In my practice, I do not perform a liquid cytology Pap and HPV DNA test at the same time on a patient unless she is more than 30 years of age and someone I am not likely to see again soon. In my opinion, cytology and pathology remain our gold standard for diagnosis of cancer, not detecting viral load or viral infection. If a woman is HPV negative, she might still have a significant lesion, as Dr Dawson's study has demonstrated. An HPV test does not significantly improve the sensitivity and specificity of a liquid cytology Pap. Incidentally, the Pap provides a lot of other information besides cervical cancer neoplasia. Trichomoniasis, candidiasis, actinomycosis, and other infections are revealed on Paps.

Management of Women with Glandular Abnormalities

Dr Thacker: When a clinician gets a report of atypical glandular cells (AGC) on a Pap test, it is imperative that some type of follow-up be done. AGC represent a substantially greater risk for cervical neoplasia than do atypical squamous cells of undetermined significance (ASCUS) or low-grade squamous intraepithelial lesions.[7] Colposcopy and endocervical sampling are the recommended course of action, according to the most recent patient management guidelines.[8] If disease is not identified during the initial workup, women with AGC-favor neoplasia or AIS cytology should undergo a diagnostic excisional procedure such as cold-knife conization. Women with AGC-not otherwise specified cytology but negative biopsy should repeat a Pap test in 4 to 6 months.

> **"...it appears that the imager will continue to lower our false-negative rate and has been demonstrated in this small study to detect even these hard-to-identify lesions."**
>
> ***—Dr Dawson***

Dr Dawson: The Pap test was really designed to detect precursor lesions on the ectocervix, not adenocarcinomas. That said, we are finding, as Dr Thacker has noted, that ThinPrep cytology has better sensitivity and specificity for detecting these lesions than do conventional Pap smears. But sometimes reparative lesions or inflammatory lesions can mimic glandular lesions.[9] Also, a number of cases called AGUS on cytology are found to be HSIL on biopsy.

The data aren't in yet, but it appears that the imager will continue to lower our false-negative rate and has been demonstrated in this small study to detect even these hard-to-identify lesions.

Dr Thacker: Because one of my areas of expertise is menopause, I treat a lot of older women who have cervico-vaginal atrophy. The cervical cells in many women who are estrogen-deficient undergo a change that can lead to an ASCUS diagnosis. Liquid-based cytology has already reduced the number of ASCUS diagnoses in my practice, which has been hugely beneficial, and it appears that the imager may lower the number of cases still further.

Perhaps most important to me clinically in Dr Dawson's study is that there were no false negatives using the imager, even with these rare glandular cancers. This means we are not missing real disease.

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