

Human Papillomavirus Testing for Precancerous Lesions of the Cervix

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Introduction

Human papillomavirus (HPV) infection is the most common sexually transmitted viral infection. An estimated 20 million Americans are currently infected with HPV and approximately 6 million new cases develop each year with the majority occurring in the adolescent age group.¹ The annual burden of cervical HPV-related diseases in the United States is estimated to cost between \$2.25 billion and \$4.6 billion, and the annual burden of cervical cancer is approximately \$181.5 million to \$393 million.² Persistent HPV infection is the most important risk factor for the development of cervical cancer and constitutes the basis for screening. The incidence of cervical cancer has decreased in every country that instituted mass screening for the disease.

Until recently, screening for cervical cancer was predominantly cytology based, relying on the detection of dysplasia, or cellular abnormalities, which are a precursor to cervical cancer. Screening with conventional smears has a sensitivity ranging from 50% to 60%. Despite this poor sensitivity, it was responsible for a 75% reduction in the incidence of cervical cancer in the United States since its introduction as a screening test in 1949.³ With the advent of liquid-based cytology, where the sample is suspended in a fixative solution instead of smeared on a slide, cytologic screening is not only more sensitive, but also more versatile. Liquid-based cytology enables cytotechnologists to perform further tests on the specimen in solution, such as HPV DNA testing, which cannot be performed on the slide. Recent well-controlled clinical trials with verification of positive and some negative results have found sensitivities of 70% to

80% for conventional cervical cytology and 85% to 95% for liquid-based cytology.^{4,5} Despite this, even the liquid-based methods can miss between 15% and 35% of high-grade dysplasia or cancer.⁶ Unfortunately, given the current health care dollars spent on HPV infections, even small imperfections in the screening process can have significant financial implications.

Computer-Assisted Screening Technology

Liquid-based screening was first introduced over a decade ago. It is now the preferred method of screening, and its versatility has paved the way for other advancements in cervical cancer screening. The specimen in suspension can be filtered and sprayed evenly on a slide, allowing for less artifact and a more consistent specimen to evaluate, which results in fewer false negatives. The uniformity and clarity also enable the use of computer-assisted screening using an automated microscope to further decrease false negative results and increase the ability to identify the truly abnormal Pap test.

There are currently 2 Food and Drug Administration (FDA) approved automated systems: the Focal Point™ Slide Profiler (FPSP) and the ThinPrep® Imaging System (TPIS).^{7,8} They both use the principle of morphometry, the appearance and size of the cells, and both use slides created with the liquid-based technology. However, the FPSP is also approved for screening conventional Pap test slides.

The FPSP system is only approved for screening specimens from a defined low-risk population of patients. The slides are evaluated using FPSP image analysis software and assigned to

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one of following groups: (1) *negative for intraepithelial lesion or malignancy*, needing no further review; (2) *review*, requiring manual review by a cytotechnologist; (3) *quality control*, requiring manual review of slides with the highest probability of having an abnormality; and (4) *process review*, requiring manual review of slides that cannot be successfully processed by the FPSP system. This system limits the amount of manual review by a cytotechnologist and focuses him/her on the slides of concern. It can use any of the currently available liquid-based systems.

The TPIS system can only evaluate slides that use the liquid-based thin layer technology, but it can be used in both low- and defined high-risk patient populations. It scans every slide and identifies cells of interest and the 22 fields that contain them. The cytotechnologist reviews these fields using an automated microscope and assigns them as no intraepithelial lesions if all fields are judged to be normal or, if any cell is suspicious, the entire slide is reviewed and abnormal cells are evaluated by a pathologist. With this technology, all slides are reviewed, but the computer directs the cytotechnologist to the areas of concern.

HPV Testing

The ability to detect HPV DNA in the liquid-based Pap vial has led to a paradigm shift in cervical cancer screening. Instead of just looking for cellular abnormalities, the current technology allows for the assessment of the causative agent, HPV. However, there are over 100 different types of HPV and each has a different oncogenic risk. For clinical simplicity, they are usually stratified into two groups: low and high risk for the development of cervical cancer. In 2001, the results of the landmark *Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesions Triage Study (ALTS)* were published.⁶ They compared three different methods of triaging patients with equivocal Pap testing results, atypical cells of uncertain significance (ASCUS). The results indicated that women with an ASCUS Pap test can undergo high-risk HPV DNA testing from the same liquid-based Pap test vial to evaluate for the presence of high-risk DNA. If high-risk DNA is present they should undergo further diagnostic evaluation. But, if a woman was high-risk HPV DNA negative, she had less than a 1% chance of developing a high-grade lesion within the year and could undergo routine screening the following year. The reported sensitivity of this combination of tests was 96%. As a result, fewer women were referred for costly diagnostic tests and reflex high-risk HPV DNA testing became the recommended management for women with ASCUS Pap test results.

As a result of numerous studies confirming the low prevalence of HPV in women over the age of 30, high-risk HPV DNA testing can be offered to women in addition to the liquid-based Pap test.⁹ This is different than reflex testing because it is done in conjunction with, rather than as a result of, the liquid-based Pap test. If both Pap test and HPV test are negative, the woman can be rescreened in three years because she is at very low risk of developing a high-grade lesion during this time. Unfortunately, this is only cost effective in the 30 and older age group because the prevalence of HPV in the younger age group is so high.

HPV Vaccine

In June of 2006, the FDA approved the first HPV vaccine, Gardasil®, a quadrivalent vaccine against HPV 6 and 11, the low-risk types associated with 90% of anogenital warts and low-grade lesions, as well as HPV 16 and 18, the high-risk types responsible for 70% of high-grade lesions and cervical cancer.³ Cervarix®, a vaccine against HPV 16 and 18, was also developed, but is not yet approved by the FDA. Both vaccines approach 100% efficacy in the prevention of HPV 16 and 18 associated high-grade lesions in the patients that received vaccination before contact with either virus. Gardasil® is also effective at preventing the low-grade lesions and anogenital warts associated with HPV types 6 and 11.¹⁰ Based on available data, the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices suggested routine vaccination for girls as young as 9 years of age.¹¹ Several other groups such as the American College of Obstetricians and Gynecologists have also supported these recommendations.¹² Patients that are HPV naïve (ie, women who have never been exposed to the virus) will be best served by this vaccine because they have the most to gain. Although its utility in males is still not proven, if efficacy is shown, vaccination for males may be recommended as well. The true impact of the HPV won't be realized for several years, but its impact on the low-grade lesions may be apparent sooner.

Summary

As new technologies are introduced that increase the sensitivity of detecting patients at risk and the incidence of cervical cancer continues to decrease in the US, annual screening for this disease may actually be overscreening. It has been shown that the screening interval can safely be increased to every 2 years if liquid-based testing is performed with reflex HPV testing in patients under 30 and can be increased to every three years in patients over the age of 30 if they are done together and both are negative.^{13,14} As we move into the age of risk stratification as a screening tool with HPV testing and liquid-based screening, it is imperative that the aforementioned recommendations are followed in order to keep the costs of screening at a minimum. Unfortunately, despite data confirming its safety and efficacy, many patients are unconvinced.¹⁵ The overwhelming respondents in one series would still seek to obtain annual screening. In order to complete the paradigm shift in the screening for cervical cancer using the current technologies, more education will be required of the public and health care community to understand and accept the differences, most notably the increased screening interval. The true effects of the HPV vaccine will not be known for some time. Therefore, appropriate screening is still imperative even for those vaccinated because it does not offer complete protection from other strains of the HPV virus. **NCMJ**

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