More than just a test result: Molecular screening of Human Papilloma Virus for contemporary management of cervical cancer risk

CHRIS L. MCGOWIN, RODNEY E. ROHDE, GERALD REDWINE

LEARNING OBJECTIVES

1. Discuss the historical and epidemiological background of Human Papilloma Virus (HPV) infections.
2. Define current evidence based guidelines for HPV diagnosis and management.
3. Justify the epidemiological and clinical rationale for HPV testing in the management of cervical cancer.

ABBREVIATIONS:


INDEX TERMS:

Molecular diagnostics, HPV, Human Papilloma Virus, sexually transmitted disease, sexually transmitted infection, cervical cancer, co-testing, nucleic acid amplification test, NAAT.

Human Papilloma Virus (HPV) is the most common sexually transmitted infection (STI), and currently is the only vaccine-preventable etiology of urogenital disease. As an STI, HPV is an independent risk factor for virtually all cases of cervical cancer and is associated with anogenital and orolabial warts. Importantly, infection with HPV is a necessary factor in the development of squamous cervical neoplasia despite the fact that most infections and dysplastic abnormalities will not progress to malignant transformation. Over 100 genotypes of HPV have been identified of which less than 50% are transmitted sexually. Of the urogenital HPV types, several have been associated directly with the enhanced risk of cervical cancer. In 2012, updated guidelines for cervical cancer screening were put forth by the US Preventative Services Task Force (USPSTF) and the combined partnership of the American Society for Colposcopy and Cervical Pathology (ASCCP), the American Cancer Society (ACS) and the American Society for Clinical Pathology (ASCP). Collectively these guidelines lengthened the time interval between cervical cancer screens and increased the age to begin screening. These evidence-based recommendations indicate the use of either cytology alone or in combination with an FDA-approved HPV test stratified primarily by age, but also by the interval since last screen and hysterectomy status. Compared to cytological investigation alone, co-testing can more informatively direct the need for and method...
of treating precancerous lesions by more accurately assessing a woman’s risk for developing cancer. This article aims to concisely summarize the current guidelines for managing cervical cancer screening, and addresses how HPV test results are incorporated into the clinical decision making algorithms.

Role of HPV Testing in Cervical Cancer Screening

HPV plays a critical role in cancers of the lower anogenital tract. Several types of HPV are classified as high-risk (HR-HPV) due to their enhanced oncogenic potential and stronger associations with cervical cancer relative to low-risk types. FDA-approved HPV tests target HR-HPV types and so “HPV testing” in this article and in published guidelines refers to specific identification of one or more HR-HPV types; testing for low-risk types (classified as non-oncogenic) has no role in managing cervical cancer. Traditional to Papilloma viruses, HPV replication is maintained in differentiated squamous epithelia resulting in transient low-grade lesions that can lead to abnormalities in the cervical epithelium. These lesions can be detected by cytological or histologic investigation (e.g. Papanicolaou smear or biopsy, respectively). The Papanicolaou smear examines cells collected from the cervix and results are reported using the Bethesda system where squamous abnormalities are parsed into three main groups: atypical squamous cells of undetermined significance (ASCUS), low-grade or high-grade squamous intraepithelial lesions (LSIL or HSIL). In contrast to cytology, histologic evaluation of the cervix facilitates identification of architectural changes to the epithelium. Non-invasive cervical squamous cell abnormalities are graded as cervical intraepithelial neoplasia (CIN 1, CIN 2 or CIN 3) as determined by the severity of the cell changes and extent to which the normal epithelium is displaced by dysplastic cell growth.

Several studies have shown that HPV testing is more sensitive but less specific than cytological examination alone for identifying high-grade lesions. This is the case because HR-HPV infections are known to be transient in a substantial proportion of women and not all infections will lead to dysplasia. As such, HPV testing has the ability to indirectly identify high-grade CIN lesions identified initially using Pap cytology. Perhaps more importantly, it is known that most CIN1 lesions will not lead to cancer and so a balance must be managed between transient HPV infections and those associated with or likely to lead to high-grade dysplasia. This balance has been addressed epidemiologically to identify the most appropriate population of women for whom testing is performed. High HPV prevalence without a ≥CIN3 lesion is common among western populations in women up to 30 years of age. After age 30, HR-HPV prevalence declines sharply but the rate of CIN progressively increases. In addition, regardless of age, women who have no cytological abnormalities and are negative for HR-HPV are at an extremely low risk of ≥CIN3. Therefore, using data from several randomized controlled trials, the current indication for HPV nucleic acid amplification test (NAAT) screening is for women beginning at age 30 and only in combination with cytology as detailed below.

Summary of Current Cervical Cancer Screening Guidelines

The USPSTF and ASCCP/ACS/ASCP guidelines are generally consistent and summarized as follows: 1) screening of women less than 21 years of age is not recommended; 2) women 21-29 years of age should be screening with cytology alone every three years and, if ASCUS is diagnosed, HPV testing is done prior to colposcopy; 3) among women aged 30-65, cytology and HPV co-testing is recommended every five years, or cytology screening alone every three years; 4) women over the age of 65 who have had adequate negative prior screening and no recent (20 years) history of ≥CIN2 should not be screened for cervical cancer; 5) women of any age following a hysterectomy with removal of the cervix, who have no history of ≥CIN2, should not be screened for cervical cancer; and 6) cervical cancer screening practices should not change on the basis of HPV vaccination status. The guidelines summarized herein reflect only a portion of the full recommendations that are very detailed and outlined graphically in a scenario-specific manner on the ASCCP website (www.asccp.org). Special consideration is required for certain populations of women including those that are pregnant whereby surgical management of CIN can lead to pre-term delivery in some cases. Therefore, pregnant women and young women with CIN, must be counseled by their physician to weigh the risks of treating cervical dysplasia compared to the risk for cancer during observation.

Critical Considerations for HPV testing

The increase in time interval between screening visits is
arguably the most significant advantage of applying HPV testing to cervical cancer screening paradigms. Co-testing with cervical cytology and HPV NAAT is recommended every five years compared to every three years with cytology alone. This not only reduces the economic burden of annual screening, but also should serve to reduce the psychological distress when receiving HPV test results and when referred for colposcopy. The required time and associated anxiety for management of cervical abnormalities can be substantial and thus underscores the importance of accurate triage for therapy when low-grade lesions are likely to resolve. However, it remains important to continue annual 'well woman' visits since cervical cytology/HPV testing is only one component of health maintenance. In addition, properly educating the patient on the updated screening and treatment paradigm is crucial to minimize anxiety and confusion regarding these new guidelines. Many young women will be confused as to why the annual Pap smear is no longer the standard of care, why the interval for cancer screening has changed to once every three or five years, and the rationale for testing only after they reach 30 years of age. In short, the risk for cervical cancer before age 30 is low, HPV infection is extremely common in these younger women and low-grade dysplastic changes will most often resolve without intervention.

Unlike diagnostic tests such as for C. trachomatis and N. gonorrhoeae, HPV test results are only one component in the algorithm for managing cervical cancer risk and subsequent therapeutic approach. Generally speaking, laboratory screening tests are highly sensitive and developed for use on apparently healthy populations. Screening tests are characterized by a very high negative predictive value (NPV) to very accurately identify subjects who are truly negative for the target analyte. In contrast, diagnostic tests are designed to help aid in identification of an etiology of disease or condition, and as such, are geared to be more specific than sensitive and can be used secondarily to a screening test to confirm infection. Typically, diagnostic tests should be characterized by very good positive predictive value (PPV) to accurately identify true positives.

In a large trial of women over 30 years of age, cytology had a specificity of 97% compared with 94% for HPV testing. Due to transient HR-HPV infection in younger women, the specificity of HPV testing would be substantially lower among women younger 30 years of age and therefore is not recommended. It is important to remember that, in contrast to many other diagnostic tests where the primary outcome is the presence/absence of a pathogen, the HPV test’s outcome is ultimately linked to cervical dysplasia. It is known that PPV is linked directly to prevalence in a given population, and although the currently available HPV tests are designed to screen the generally healthy population at large, testing for HPV in women where precancerous lesions are more prevalent maximizes the PPV of the test. Despite focusing our screening efforts on women greater than 30 years of age (or younger women with ASCUS cytology), PPVs remain low for HPV testing (10-25%). In order to predict the usefulness of a test prior to implementation, we advise clinical laboratories to evaluate a test’s performance with data collected from subjects that most accurately reflect the population they will be testing (located in the package insert of all FDA-approved tests).

In closing, laboratorians should have expertise on the test results reported from the clinical laboratory, and therefore should understand how HPV testing fits into the cancer risk management algorithm. In the coming years, molecular HPV testing will be an exceedingly common request of clinical laboratories. It has never been more important for medical laboratory professionals to understand the changing landscape of MDx as they play a critical role in managing cervical cancer. This role will increase as MDx are even further integrated into the clinical laboratory. Importantly, the downstream procedures set into motion based on HPV test results (e.g. colposcopy, biopsy, follow-up visits, other surgical interventions, etc.) have significant ramifications for an enormous number of women regarding reproductive, sexual and psychological health. Therefore it remains imperative to closely follow the evidence-based guidelines provided by the national governing entities to accurately and effectively employ HPV testing as the powerful tool it is for cervical cancer management.

REFERENCES

The Focus section seeks to publish relevant and timely continuing education for clinical laboratory practitioners. Section editors, topics, and authors are selected in advance to cover current areas of interest in each discipline. Readers can obtain continuing education credit (CE) through P.A.C.E.* by completing the continuing education registration form, recording answers to the examination, and mailing a photocopy of it with the appropriate fee to the address designated on the form. Suggestions for future Focus topics and authors, and manuscripts appropriate for CE credit are encouraged. Direct all inquiries to the Clin Lab Sci Editorial Office, Westminster Publishers, 315 Westminster Court, Brandon MS 39047. (601) 214-5028, (202) 315-5843 (fax). westminsterpublishers@comcast.net.