



Will Your Patient Benefit from the HPV Vaccine?



By Gordon L. Love, MD

Expanded HPV Testing Would help provide the answer.

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HUMAN PAPILOMA VIRUS genotyping is needed, and future HPV vaccines may offer greater flexibility for use in patients with, or without, previous HPV exposure.

Merck's human papilloma virus (HPV) vaccine, Gardasil™, is recommended for women between the ages of 15 and 26. It is most effective in women without sexual experience. However, women with a history of sexual activity may also benefit if they have not been exposed to the HPV types the vaccine covers - HPV 6 and 11 but particularly HPV 16 and 18, which are the most dangerous. Only HPV typing (genotyping) can determine which HPV types a woman has been exposed to. However, as of this issue's deadline, no HPV genotyping test to identify specific HPV types has been approved by the FDA for use in the United States.

Most physicians have seen the comprehensive articles on HPV in the May 10, 2007 issue of the *New England Journal of Medicine (NEJM)*. The extent of HPV infections is staggering (data drawn from Centers for Disease Control MMWR, March 23, 2007).

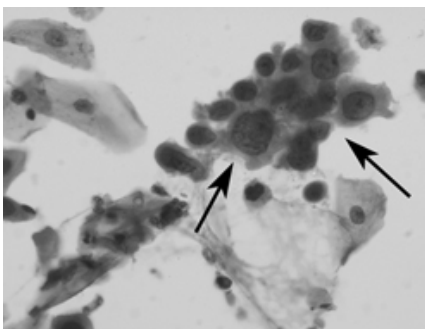
In women:

Cervical HPV newly infects an estimated 6.2 million American women every year. Of these, a small percentage will develop cervical cancer.

More than 80 percent of sexually active women may acquire genital HPV by age 50. All anogenital warts are caused by HPV. About half of all vulvar cancers are associated with HPV.

In both men and women:

Approximately 90 percent of all anal squamous cell carcinomas are associated with HPV. Women with high-grade cervical lesions or men who have sex with men are at higher risk for anal cancer.



"Low-risk" HPV 6 and 11 primarily cause respiratory tract warts and papillomas. High-risk HPV 16 has been associated with increasing numbers of oropharyngeal cancers.

No FDA approved HPV Typing Test in the U.S.

The *NEJM* articles described analysis of vaccine and placebo groups in the Gardasil vaccine trials using tests for HPV-16/18 DNA by polymerase chain reaction on vaginal/cervical samples or for serum HPV-16/18 antibodies by immunoassay. As

mentioned earlier, these tests are not approved by the FDA.

FDA-approved patient HPV testing is limited to the Digene Hybrid Capture/Nucleic Acid Hybridization/Signal Amplification method on cervical Papanicolaou smears (liquid-based) or cervical swabs. This Digene testing produces a "detected" or "non-detected" result for high-risk HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68, but does not indicate the specific high-risk HPV type.

Lack of detectable HPV antibodies in some infected people.

If serology is so helpful in other viral diseases, why isn't a HPV serology available to physicians in the United States?

Some HPV-infected patients produce no HPV antibodies. Immune response may be limited or absent when a HPV infection is confined within a cutaneous surface. However, papillomavirus L1 capsid proteins assemble into virus-like particles that are good antigens for serologic studies to detect type-specific HPV antibodies.

Unfortunately, key laboratory reagents have not been standardized, and no reference method or gold standard exists to establish positive or negative results. A helpful technique in many other viral diseases - viral culture - is useless with HPV, which cannot be propagated in vitro.

The Gardasil vaccine is only the first on the market.

HPV presents two points of attack for vaccination:

Prevention of primary infection through inducing antibodies against L1 or L2 viral capsid proteins. This vaccine type would be most effective in patients who have no previous exposure to HPV.

Modification of existing infection through inducing antibodies against the E6 or E7 viral oncoproteins to prevent malignant transformation of cervical epithelial cells. This vaccine type could be useful for patients already infected by HPV.

Gardasil is a "primary-prevention" vaccine, and at least one other similar vaccine is undergoing FDA review. It is possible that many different vaccines with differing HPV targets ultimately may become available that would be appropriate for both men and women with, or without, previous HPV exposure.

Summary

The advent of the HPV vaccine has created a situation in which HPV vaccine therapeutics has trumped available HPV testing. Making decisions for HPV vaccination using the Digene HPV test would be similar to deciding whether to vaccinate for hepatitis B using a hypothetical test for hepatitis A, B, and C that reports "detected" irrespective of the presence of one or all three hepatidides.

At least parts of this testing gap may be bridged, possibly soon. At least one major laboratory instrument manufacturer has announced FDA submission of a HPV genotyping test to enable specific detection of any of the 13 high-risk HPV types, although presumably only on Papanicolaou smear material. With FDA approval, this test could be adopted by numerous laboratories to become widely available to treating physicians.

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