



Hot Topic



HPV Testing Update: The 2006 ASCCP Consensus Guidelines

Edward J. Wilkinson, MD, FACOG, FCAP

The American Society for Colposcopy and Cervical Pathology (ASCCP) recently released updated consensus guidelines for HPV testing and its applications in screening for cervical cancer and management of women with a Pap test interpreted as ASCUS or LSIL. The recommendations involve several key issues: HPV testing methods, HPV testing in routine cervical screening, HPV testing in evaluation of a Pap test interpreted as ASCUS or LSIL, and modified indications for HPV testing in

adolescents and postmenopausal women with LSIL.

HPV Testing Methods

Over 100 HPV types infect humans, but only about 20 are associated with cervical neoplasia. These are considered oncogenic, or high-risk HPV (HR HPV) types, in contrast to the other types that are classified as nononcogenic or low-risk types. Of the oncogenic types, HPV types 16 and 18 account for approximately 70% of all cervical carcinomas. Although the term “HPV testing” is often used in a non-specific way, within the recent 2006 ASCCP guidelines—which were developed in conjunction with the National Cancer Institute (NCI) and in collaboration with representatives of 29 national organizations involved in women’s health care—HPV testing specifically refers to testing for HR HPV types. The 2006 ASCCP Conference confirmed the prior 2001 ASCCP guidelines, as well as those currently issued by the American Cancer Society (ACS) and American College of Obstetrics and Gynecology, that only oncogenic HPV types are to be tested for in either the screening for, or the management of women with, cervical neoplasia. Nononcogenic HPV viral testing is not of value in this situation and is not recommended.

The HPV test findings have a significant influence on clinical management, both when used for screening or for management of women with ASCUS or LSIL Pap test findings. To be useful for screening or management, the method of testing for oncogenic HPV types must be sufficiently vetted through clinical trial and demonstrate sensitivity and specificity for HR HPV infection. A test’s sensitivity must also have been clinically validated in terms of false-positive and false-negative fractions. For an HPV test to meet these requirements, sufficiently large clinical trial data are needed to provide evidence of the robustness of the test, as well as to validate the methods of sample collection and preservation. The 2006 guidelines reaffirm the need for clinical validation for the use of oncogenic HPV testing.¹

Applications in Cervical Screening

Currently, the FDA has approved only one test for oncogenic HPV.² This FDA-approved test can be used as a supplement to cytologic screening in women 30 years of age or older. It can also be used as a reflex test in women with a Pap test interpreted as “atypical squamous cells of uncertain clinical

Editors:

Thomas F. Purdon, MD, FACOG

Clinical Professor of Obstetrics and Gynecology
Department of Obstetrics and Gynecology
University of Arizona Health Sciences Center, Tucson, Arizona
Consultant, United Community Health Centers of Arizona

Kenneth D. Hatch, MD

Professor, Obstetrics and Gynecology
Head, Division of Gynecologic Surgery
University of Arizona College of Medicine
Tucson, Arizona

Edward J. Wilkinson, MD, FACOG, FCAP

Professor and Vice Chairman
Director, Cytopathology Fellowship, Department of Pathology and Laboratory Medicine, University of Florida College of Medicine
Medical Director, Quantitative Pathology Laboratory, University of Florida Diagnostic Reference Laboratories
Adjunct Professor, Department of Obstetrics and Gynecology, University of Florida College of Medicine

Dr. Edward J. Wilkinson is Professor and Vice Chairman in the Department of Pathology at the University of Florida College of Medicine, where he also

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significance" (ASCUS). Some laboratories offer non-FDA-approved types of oncogenic HPV testing and, if so, carry the burden to demonstrate that their test is equivalent.

The ACS initially recommended HR HPV testing as a supplement to cytologic screening for women 30 years of age or older.³ Combined cytology and HR HPV testing has been proven effective in large clinical trials.^{4,5} In women 30 years of age or older the prevalence of oncogenic HPV infection is relatively low, and in one large clinical trial of over 200,000 women conducted by Fetterman and colleagues, 6.5% of women had oncogenic HPV. With this relatively low prevalence rate, the use of HR HPV testing becomes useful to distinguish those who have oncogenic HPV infection from those without and to develop appropriate management strategies. Even if oncogenic HPV is detected, the concurrent Pap test may be negative, as demonstrated in 58% of patients in the same study. Clavel and colleagues observed in a prospective study that 60% of women who test positive for oncogenic HPV with a concurrent negative Pap test have no evidence of HPV on follow-up at 6 months.⁶ In addition, the estimated prevalence of high-grade CIN, CIN 2 or CIN 3—in cytology negative, HPV-positive women 30 years of age or older—is low with reported frequencies under 5.2% (ranging from 2.4 to 5.1%).^{7,8,9}

Based on these data, the 2006 ASCCP consensus recommendation for management of women 30 years of age or older with a negative Pap test and a positive HR HPV test is to return the patient for additional screening and repeat both tests at 12 months. If she shows the same pair of test results after additional screening, she should be referred for colposcopy. When a woman aged 30 or older has a negative Pap test and a negative HR HPV test, the prior recommendation of the ACS to return for screening in three years continues to be supported by the evidence.

Women with a Pap Test Interpreted as ASCUS

The updated 2006 ASCCP consensus guidelines differ from the 2001 guidelines in following women with Pap results interpreted as ASCUS. Women with ASCUS cytology and a positive HR HPV test should be referred directly to colposcopy. Women with ASCUS cytology and a negative HR HPV test should return for screening in 12 months. The 2001 ASCCP consensus guidelines offered alternate management approaches for women with ASCUS cytology and positive HR HPV tests that are no longer recommended, which are: (1) immediate referral to colposcopy and (2) follow-up with a repeat Pap test at 6 months. The 2006 consensus guidelines continue to recommend referral to colposcopy for any woman with a Pap interpreted as or more severe than ASCUS. The 2001 ASCCP guidelines also recommended using the remainder of the aliquot in the Pap vial for HR HPV testing if a liquid-based Pap collection method was used. This was a preferred management recommendation because it did not require that the patient return for additional sample collection, and this recommendation carries forward into the 2006 guidelines. An alternate approach when using conventional Pap testing is co-collection of the HPV test sample at the time the Pap test is performed. Both samples can be sent to the laboratory, and if the Pap test is ASCUS, the HPV sample can be sent for testing.

Adolescent Patients

Oncogenic HPV exposure and transient infection in women 20 years of age or under has a high prevalence rate—over 50% of women within this age group are HR HPV positive. The evidence shows that most HPV infections in younger women are transient and will clear without treatment. The 2001 ASCCP guidelines did not make any specific recommendations for managing young women. The new 2006 ASCCP guidelines make separate recommendations for adolescents, specifically women who are 20 years of age or younger. For younger women with an ASCUS Pap test, HR HPV testing is not recommended because it is now understood that the frequency of HR HPV is significantly higher in this population compared to women 21 years of age or older. The incidence of cervical cancer in younger women is also significantly lower.^{10,11}

HPV testing in young women with a Pap test interpreted as ASCUS would result in a high rate of colposcopy with a very low probability of cervical carcinoma compared to the older women. The 2006 ASCCP guidelines have addressed this issue and recommend that HR HPV testing not be performed in adolescents—women 20 years of age or younger—but rather, that the repeat Pap testing be performed at 12 months. The patient should be referred to colposcopy only if the repeat Pap test is interpreted as HSIL, AGC, or a more severe finding.¹²

directs the Cytopathology Fellowship program and is the Medical Director of the department's Quantitative Pathology Laboratory. As prior president of the American Society for Colposcopy and Cervical Pathology, he initiated the first Consensus Conference on the Management of Women with Abnormal Cervical Cytology in 2001, and served as the Chairman of the Steering Committee and Chair of the LSIL Committee directing this evidence-based conference. For the second 2006 ASCCP Consensus Conference he served on the Steering Committee and as Chairman of the Human Papillomavirus Testing Committee. Dr. Wilkinson is also a past president of the International Society for the Study of Vulvovaginal Disease and the Florida Society of Pathologists. He is editor-in-chief of the *Journal of Lower Genital Tract Disease*, and serves as a member of the editorial boards of the journals *Human Pathology*, *International Journal of Gynecological Pathology*, *The Breast Journal*, and *The Journal of Gynecological Surgery*. He also serves as a special reviewer for several other leading medical journals. He is listed in *Who's Who in Medicine and Health* and *Who's Who in the World*, and he is in the *Best Doctors in America* (gynecological pathology), listed in the first and all subsequent publications for the past 15 years. In a career spanning more than 40 years, he has researched and published on cancers and pre-neoplastic lesions of the cervix, vulva, vagina, endometrium, ovary, and breast. He has been awarded funding from the National Cancer Institute (NCI) and the American Cancer Society, and served as a member of the Data and Safety Monitoring Committee of the NCI's ALTS trial.

Notable scientific contributions include: First to directly measure

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Postmenopausal Women with a Pap Test Interpreted as LSIL

A major change in the 2006 ASCCP guidelines is in the management of postmenopausal women with LSIL. For these women, reflex HPV testing is an acceptable option, as is colposcopy or repeating the Pap test at 6 and 12 months. Two large studies show that the prevalence of HR HPV declines in postmenopausal women. However, those with CIN 2/3 or cervical cancer will have persistent HPV.^{13,14} With HPV testing as the option, if the HPV test demonstrates HR HPV, the patient is referred to colposcopy; if negative the patient can return for repeat Pap testing at 12 months.

When Not to Test for HPV

Continuing with the 2001 ASCCP management guidelines, the 2006 guidelines recommend colposcopy for nonpregnant adult women of reproductive age with a Pap result interpreted as LSIL. For these women, the risk of an associated CIN 2 or more severe lesion is between 12 and 16%.^{15,16} In addition, HR HPV testing is not recommended for these women because over three-fourths will test positive for HR HPV.¹⁷ The high prevalence of HR HPV also supports the guideline that HPV testing is not recommended for adolescents or pregnant women with LSIL.

In regard to women vaccinated against HPV, ASCCP did not develop separate management guidelines for these patients. HPV testing is not recommended prior to vaccination. If a vaccinated woman were to have an abnormal Pap result, the 2006 consensus management guidelines apply as written. Only time will tell if there is a need to modify current screening guidelines for this population.

Additional details about the 2006 ASCCP consensus guidelines are available online at <http://www.asccp.org/consensus.shtml>.¹⁸

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- 2 Hybrid Capture 2 FDA approval letter. 2006. Digene Corporation, Gaithersburg, MD.
- 3 Saslow D, Runowicz CD, Solomon D, et al. American Cancer Society guideline for the early detection of cervical neoplasia and cancer. *CA Cancer J Clin*. November-December 2002;52(6):342-362.
- 4 Cuzick J, Mayrand MH, Ronco G, et al. Chapter 10: New dimensions in cervical cancer screening. *Vaccine*. August 21, 2006;24 Suppl 3:S90-97.
- 5 Koliopoulos G, Arbyn M, Martin-Hirsch P, et al. Diagnostic accuracy of human papillomavirus testing in primary cervical screening: a systematic review and meta-analysis of non-randomized studies. *Gynecol Oncol*. January 2007;104(1):232-246.
- 6 Clavel C, Masure M, Bory JP, et al. Human papillomavirus testing in primary screening for the detection of high-grade cervical lesions: a study of 7932 women. *Br J Cancer*. June 15, 2001;84(12):1616-1623.
- 7 Ronco G, Segnan N, Giorgi-Rossi P, et al. Human papillomavirus testing and liquid-based cytology: results at recruitment from the new technologies for cervical cancer randomized controlled trial. *J Natl Cancer Inst*. June 7, 2006;98(11):765-774.
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- 9 Clavel C, 2001.
- 10 Arbyn M, Sasieni P, Meijer CJ, et al. Chapter 9: Clinical applications of HPV testing: a summary of meta-analyses. *Vaccine*. August 21, 2006;24 Suppl 3:S78-89.
- 11 Boardman LA, Stanko C, Weitzen S, et al. Atypical squamous cells of undetermined significance: human papillomavirus testing in adolescents. *Obstet Gynecol*. April 2005;105(4):741-746.
- 12 Kulasingam SL, Kim JJ, Lawrence WF, et al. Cost-effectiveness analysis based on the atypical squamous cells of undetermined significance/low-grade squamous intraepithelial lesion Triage Study (ALTS). *J Natl Cancer Inst*. January 18, 2006;98(2):92-100.
- 13 Evans MF, Adamson CS, von Walstrom GM, Cooper K. Use of multiple displacement amplification in the investigation of human papillomavirus physical status. *J Clin Pathol*. October 2007;60(10):1135-1139.

and quantitate alpha fetoprotein in ovarian endodermal sinus tumor. First to document, through retrospective sectioning and detailed analysis of 525 stage 1 breast carcinoma cases initially interpreted as having negative lymph nodes, that occult micrometastasis can be detected and occur in over 15% of cases and that these micrometastases do not significantly decrease survival as compared to cases with negative lymph nodes. First to develop a mathematical model to estimate probabilities of missing micrometastasis in lymph nodes by histopathologic study when using various sectioning intervals. Pioneered in defining a subset of minimally invasive vulvar carcinomas as carrying essentially no risk for lymph node metastases. Instrumental in working with the International Society for the Study of Vulvovaginal Disease, the International Society of Gynecological Pathologists, and the International Federation of Gynecology and Obstetrics in establishing stage IA vulvar carcinoma as a tumor stage, and a stage of tumor that can be managed by less than radical surgery. First to describe and define endometrial well-differentiated papillary adenocarcinoma (subsequently called villo-glandular adenocarcinoma) and distinguish this tumor as having a relatively good prognosis as compared to papillary serous adenocarcinoma. First to report and document, with family linkage, congenital cirrhosis in the newborn due to S-Z phenotype alpha-1-antitrypsin deficiency. First to define and document acquired columnar cell metaplasia of the squamous mucosa of the vagina. Developed the first comprehensive etiologic classification of vulvar Paget disease based on histopathologic, immunohistochemical, and clinical features.

For more information, see E.J. Wilkinson in faculty member listing at www.pathology.ufl.edu.

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- ¹⁶Chute DJ, Covell J, Pambuccian SE, et al. Cytologic-histologic correlation of screening and diagnostic Papanicolaou tests. *Diagn. Cytopathol.* July 2006; 34(7):503-506.
- ¹⁷Arbyn M, 2006.
- ¹⁸Wright TC Jr, et al. 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests. *American Journal of Obstetrics and Gynecology.* October 2007;197: 346-355.

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