

## Descriptions of New FDA-approved HPV DNA Tests

In March 2009 the FDA announced approval for clinical use in the U.S. of two new HPV DNA diagnostic tests.<sup>1</sup> One of these tests is designed to identify 14 high risk types of HPV. These include the 13 types detected by the Hybrid Capture® 2 HPV DNA Assay (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) as well as HPV 66. This test will be marketed under the name Cervista™ HPV HR. The other test is designed to specifically detect HPV 16 and HPV 18 and will be marketed under the name Cervista™ HPV 16/18. Both tests utilize an isothermal enzymatic DNA amplification process with a fluorescent read out and both are approved for use with ThinPrep® samples. They were developed by Third Wave Technologies which was acquired in 2008 by Hologic Inc., the manufacturer of the ThinPrep® Pap test.

## FDA Approved Indications

The FDA-approved clinical indications for Cervista™ HPV HR are similar to those of the Hybrid Capture® 2 HPV DNA Assay. These are:

1. *To screen patients with ASC-US cervical cytology results to determine the need for referral to colposcopy.*
2. *Used adjunctively with cervical cytology to screen women 30 years and older to assess the presence or absence of high-risk HPV types.*

The FDA-approved indications for the Cervista™ HPV 16/18 test are:

1. *In women 30 years and older the test may be used adjunctively with the Cervista™ HPV HR test in combination with cervical cytology to assess the presence or absence of specific high-risk HPV types.*
2. *Used adjunctively with the Cervista™ HPV HR test in patients with ASC-US cervical cytology results, to assess the presence or absence of specific high-risk HPV types. The results of this test are not intended to prevent women from proceeding to colposcopy.*

## ASCCP 2006 Consensus Conference Recommendations for HPV 16/18 Detection

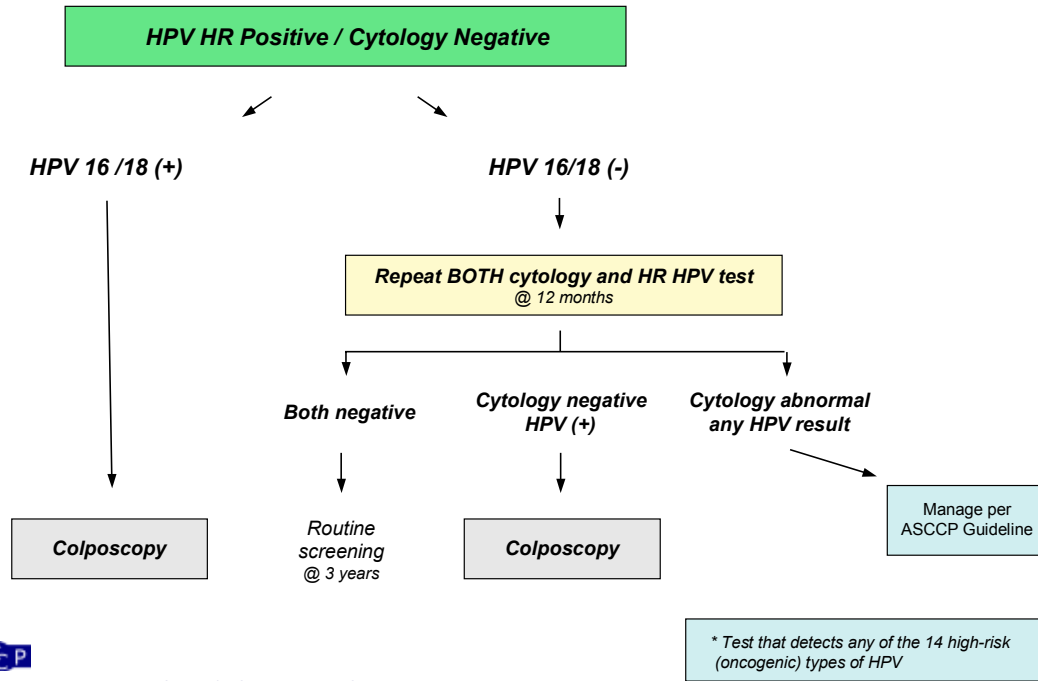
The clinical utility of HPV genotyping assays was discussed at the 2006 ASCCP Consensus Conference.<sup>2,3</sup> At the time of the conference it was recognized that molecular genotyping tests would become commercially available for routine clinical use in the near future. Therefore the data available at that time was evaluated and recommendations made that were contingent on a FDA-approved genotyping assay becoming available.

### ***Use when screening women 30 years and older***

Based on the data available in 2006, it was determined that in cytology negative women 30 years and older who are HPV DNA positive (for any of the 13 or 14 high-risk types of HPV detected by the high-risk HPV assays) molecular genotyping assays that detect HPV 16 and 18 would be clinically useful for determining which women should be referred for immediate colposcopy, and which could be followed-up with repeat cytology and high-risk HPV testing in 12 months, **Figure 1.**<sup>2</sup>

**Figure 1:** Algorithm for using HPV genotyping for HPV 16 and 18 to triage high-risk HPV positive / cytology negative women

**Use of HPV Genotyping to Manage HPV HR \* Positive / Cytology Negative Women 30 Years and Older**



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**Use for women with ASC-US**

Based on the data available as of September 2006, both the committee that reviewed atypical squamous cells and the committee that reviewed HPV DNA testing decided that HPV genotyping does not add clinical benefit to the management of women with ASC-US. This was based on the fact that only approximately 50% of CIN 2+ lesions are associated with infection with HPV 16 or 18.<sup>4</sup> The other 50% are not. In ALTS, for women 21 years of age and older with oncogenic HPV- positive ASCUS, the overall two-year cumulative risk of CIN 2+ was 25%. Stratifying by HPV genotype categories, the cumulative risk of CIN 2+ for women with HPV 16/18- positive ASCUS was approximately 40%, while the risk for women with other oncogenic (non 16/18) HPV- positive ASCUS was approximately 20%. Similar patterns were observed in women aged 21-29 and women aged 30 and older. While HPV genotyping did stratify risk to an extent, the risk of CIN 2+ among women with non 16/18 oncogenic HPV-positive ASCUS remained high enough to warrant colposcopy. **Therefore the 2006 ASCCP guidelines do NOT recommend the use of HPV genotyping in women with oncogenic HPV-positive ASC-US.** Management of women in the general population with ASC-US, who are screened using liquid-based cytology should be to perform a “reflex” test using a validated assay that detects either 13 or 14 high-risk HPV types. If the woman is high-risk HPV DNA positive, she should be referred to colposcopy, even if she tests negative for HPV 16 and HPV 18.

Data from the pivotal trial of the new HPV genotyping assay for HPV 16/18 that led to the FDA-approved indication of using 16/18 genotyping in women with ASCUS has not yet been published. Once available, this data, as well as data from the ongoing clinical trials of genotyping tests being developed by other companies, may necessitate changes in the management guidelines.



## Situations Where HPV DNA Testing and Genotyping Are Not Recommended

As HPV DNA testing becomes more widespread we need to remember that there are situations where high-risk HPV DNA testing and genotyping are NOT recommended. These include:

- *adolescents, defined as women 20 years and younger (regardless of their cytology results)*
- *women 21 years and older with ASC-H, LSIL, or HSIL cytology (note: “reflex” HPV testing is acceptable in postmenopausal women with LSIL)*
- *routine screening in women before the age of 30 years*
- *in women considering vaccination against HPV*
- *for routine STD screening*
- *as part of a sexual assault workup*
- *HPV genotyping is not recommended for women with ASC-US*
- *HPV genotyping is not recommended as the initial screening test for women 30 years and older.*

It should also be recognized that there are situations where the 2006 Consensus Guidelines recommend limits on the frequency of HPV DNA testing to avoid over-testing and unnecessary treatment. When managing women with ASC-US it is recommended that HPV DNA testing not be performed at intervals of less than 12 months. In addition, women 30 years of age and older who are negative by both cytology and high-risk HPV DNA testing should not be rescreened (using either cervical cytology or HPV DNA testing) before 3 years.

## References

1. FDA approved first DNA test for two types of human papillomavirus. 2009;<http://www.fda.gov/bbs/topics/NEWS/2009/NEW01974.html>.
2. Wright TC, Jr., Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D. 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests. *Am J Obstet Gynecol* 2007;197(4):346-55.
3. Wright TC, Jr., Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D. 2006 consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarcinoma in situ. *Am J Obstet Gynecol* 2007;197(4):340-5.
4. Smith JS, Lindsay L, Hoots B, et al. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. *Int J Cancer* 2007;121(3):621-32.
5. Cox JT, Schiffman M, Solomon D. Prospective follow-up suggests similar risk of subsequent cervical intraepithelial neoplasia grade 2 or 3 among women with cervical intraepithelial neoplasia grade 1 or negative colposcopy and directed biopsy. *Am J Obstet Gynecol* 2003;188(6):1406-12.

## Disclaimer

This Clinical Update has been designed as an educational resource and as such does not define a standard of care, nor is it intended to dictate an exclusive course of treatment or procedure to be followed. It presents methods and techniques of clinical practice that are acceptable and used by recognized authorities, for consideration by licensed healthcare professionals to incorporate into their practice. Variations of practice, taking in account the needs of the individual patient, resources, and limitations unique to the institution or type of practice, may be appropriate.