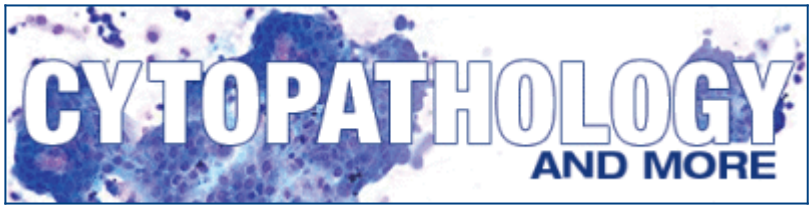
Aptima HPV and Aptima genotype assays for triage of borderline squamous (ASCUS) cytology: CLEAR study



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May 2015—The characterization of the HPV genome and development of techniques that have the ability to detect nucleic acids in cytologic specimens has had a major impact on patient management. The Hybrid Capture 2 High-Risk HPV DNA Test, or HC2 (Qiagen, Gaithersburg, Md.), which uses probes designed to target the entire HPV genome, was cleared by the FDA in 1996.[1,2] It was soon realized that determination of clinical sensitivity and specificity was essential to fully characterize assay performance and understand and classify correlation with cervical disease. An early large clinical trial, the ASCUS/LSIL Triage Study (ALTS), led to FDA clearance of the HC2 test for qualitative determination of HPV low- and high-risk types.[3] The data from the ALTS study also led to the conclusion that low-risk HPV types play no role in cervical carcinogenesis and testing for such is not clinically useful. The HC2 test received another FDA clearance in 2003 for triage of borderline squamous abnormality (ASCUS) and as an adjunctive cotest with routine Papanicolaou testing of women age 30 and older.[2]

The emergence of these data ignited brisk collaborative efforts of the commercial and scientific communities to further expand the breadth of diagnostic platforms available for HPV molecular testing. Several platforms subsequently emerged, including the 2009 FDA-cleared Cervista HPV HR test and Cervista HPV 16/18 tests (Hologic, Bedford, Mass.), which target the conserved L1 gene. The Cervista HPV HR test was approved for indications similar to those for which HC2 was approved. Indications for Cervista HPV 16/18 include follow-up of a positive Cervista HPV HR test in women age 30 and older and for triage of ASCUS results.[2] The ATHENA (Addressing the Need for Advanced HPV Diagnostics) clinical trial led to FDA clearance of the Cobas HPV Test (Roche Molecular Diagnostics, Pleasanton, Calif.) in 2011.[2] This test is performed using a Cobas 4800 instrument, which performs nucleic-acid extraction and polymerase chain reaction analysis followed by concurrent detection of HPV types 16 and 18 along with a pool of 12 other high-risk HPV genotypes and a human beta-globin gene to control for nucleic-acid amplification inhibitors which may be present in the specimen.

The most recent test to enter the U.S. market is the Aptima HPV assay (AHPV) by Hologic. This test targets E6/E7 mRNA transcripts of 14 high-risk HPV types. The clinical sensitivity and specificity were established during the CLEAR (Clinical Evaluation of Aptima mRNA) clinical trial, with the data published this year.[4] The test received FDA clearance in 2011 for ASCUS triage and for screening of women age 30 and older and as an adjunctive test with cytology screening.[2] The data obtained from use of this test for ASCUS triage were reported in 2013.[5] This prospective study focused on the clinical performance of the Aptima HPV assay with the HC2 test as a comparator for 939 women with ASCUS cytology, of which 394 (42 percent) were positive for high-risk HPV mRNA. All women underwent colposcopy with biopsy of the target lesion and had random biopsies of all four quadrants and endocervical curettage. The prevalence of CIN2+ and CIN3+ was 9.7 percent and 4.4 percent, respectively. The sensitivity and specificity of the Aptima HPV assay in women with ASCUS cytology was 86.8 percent and 90.2 percent for CIN2+ and CIN3+ biopsy results. The corresponding specificity for CIN2+ and CIN3+ was 62.9 percent and 60.2 percent, respectively, using results from all biopsies with the Aptima assay, and 55.8 percent and 53.3 percent for the HC2 assay.[4]

The Aptima HPV 16 and 18/45 Genotype test (Aptima-GT) received FDA clearance in 2012 with claims for the triage of Aptima HPV assay positive results for the patient population from the CLEAR study. These data demonstrate that of 354 women with ASCUS cytology and positive Aptima HPV findings, 121 (34.2 percent) showed positive results following analysis with the Aptima-GT assay.4 The risks for CIN2+ and CIN3+ were 37 percent and 20.5 percent, respectively, for HPV-16–positive women, 15.9 percent and 9.1 percent for HPV-18/45–positive women, and 14.3 percent and 4.3 percent for patients who were positive for high-risk HPV types other than 16, 18, and 45. Additionally, the corresponding risks for ASCUS women negative by the Aptima HPV assay were 2.2 percent and 0.7 percent. The overall absolute risk of CIN2+ was reported to be nine percent for the CLEAR patient population and five percent for Cobas HPV-positive women in the ATHENA trial. One possible explanation for increased disease detection, according to the authors, may be due to obtaining four-quadrant biopsies and endocervical curettage on all patients even when no lesions were identified on colposcopic examination.[4] The outcomes data from age-defined HPV-positive/cytology-negative women will be published shortly and the outcomes data appear similar to those of the ATHENA trial (MH Stoler, personal communication, March 18, 2015).

In summary, HC2, Cervista HPV, Cobas HPV, and Aptima HPV are the four FDA-cleared testing platforms for high-risk HPV testing of women age 30 and older in conjunction with cytology and for reflex testing of ASCUS cytology results. Three of these systems (Cervista 16/18, Cobas HPV, and Aptima-GT) are available for detection of HPV 16 and HPV 18 in the aforementioned scenarios. It should also be pointed out that all HPV detection systems are to date approved only for specimens collected in specific transport media and PreservCyt media (Thin Prep).

Finally, based on ATHENA trial data, the Cobas HPV test was approved for primary screening of women age 25 and older. Two professional societies (Society of Gynecologic Oncology and ASCCP), along with input from representatives of the CAP and ACOG, ACS, ASCP, and ASC, have published an interim clinical guidance document as an addition to 2012 guidelines. It reads: "This document aims to provide information for the healthcare providers who are interested in primary hrHPV testing and an overview of the potential advantages and disadvantages of this strategy for screening as well as to highlight areas in need of future investigation."[6]

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