

JOURNAL REVIEW

High-risk human papillomavirus testing in women with ASC-US cytology: results from the ATHENA HPV Study

Stoler MH, Wright TC Jr, Sharma A, *et al.*
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For some time the Hybrid Capture 2™ (HC2) Test (QIAGEN, Gaithersburg, MD, USA) was really the only commercially available test for high-risk human papillomavirus (HR-HPV) detection. However, as the application of HPV testing for cervical disease management became increasingly evidenced, this led to a rapid increase in other major commercial entities producing HPV tests for their diagnostic portfolios. The majority (like HC2) detect a pool of common high-risk types in aggregate; however, some, like the Cobas™ 4800 HPV Test (Roche Molecular Systems, Pleasanton, CA, USA), also offer limited genotyping. The ATHENA trial was designed to assess the clinical performance of this test and this article describes its performance in the context of low-grade cervical disease management/triage. Of particular interest is the fact that this study assessed the potential usefulness of a (geno)type-specific result.

Although the article reports on the Cobas test performance *a priori*, it is of note that two additional HPV tests (also Roche assays) were applied to the samples. In addition, a second sample was

taken from women for the HC2 test, so that comparisons could be performed. ATHENA was a large study: 47 208 women were recruited; however, the triage component was confined to 1578 women (mean age 37.1 years) who were diagnosed with ASC-US (atypical cells of undetermined significance) cytology and had colposcopy and biopsy. The Cobas test exhibited sensitivity of 90%, specificity of 70.5%, positive predictive value of 14% and negative predictive value 99.2% for cervical intraepithelial neoplasia Grade 2+ (CIN2+). According to these performance measures, Cobas exhibits equivalent performance to the HC2. When the type-specific analysis was performed, the absolute risk (number of subjects with disease/number of subjects with positive test results) for CIN2+ among women who were HPV16+ was 31.5% (95% CI 24.2–40.0), compared to a 14.0% (95% CI 11.3–17.3) for those who were positive by the assay irrespective of type and 8.6% (95% CI 6.0–12.1) in those who were positive for types other than 16 or 18. This reviewer found it quite difficult to extricate the HPV 18 information; however, it would appear HPV 18 (in the absence of HPV 16) confers a lower risk than HPV 16, although the wide CIs reflect the relatively small number of women who were HPV 18-positive (2.9%).

The data on HPV 16 consolidate what has been observed in longitudinal cohort studies, in that the prognosis associated with HPV 16 is significantly worse compared to other HR-HPV types. The authors do not follow-up their observations with a defined type-specific management

algorithm; rather they suggest “consideration should be given to more aggressive disease ascertainment and more intensive follow-up” for HPV 16-positive women. How practicable this will be in the wider context will be determined by a number of factors, not least of which will be education and training for care providers unused to negotiating type-specific results.

There is clearly a lot more to be published from the ATHENA project; it is notable that the performance of the other Roche assays was not presented. Furthermore, it will be interesting to see how the Cobas test performs in a non-triage, screening context where data are scarcer.

The increased market competition in the HPV diagnostics world can only be positive for users who have an increased choice of platforms. Given similar overall performances, standard business processes will be influential for user-preference in addition to the ‘extra’ capacity for genotyping. However, ‘riskiness’ of HPV 16 has been established for some time now and this behoves the scientific and clinical community to better define recommendations for typing in practice.

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