Cobas HPV test for first-line screening for cervical cancer

On April 24, 2014, the cobas HPV Test was approved by the US Food and Drug Administration for use as a first-line primary screening tool in women aged 25 years or older to assess risk of cervical cancer based on the presence of clinically relevant high-risk human papillomavirus (HPV) DNA. It is the first and only HPV test indicated as the first-line primary screen for cervical cancer in the United States. The test simultaneously provides pooled results for high-risk (HR) genotypes (HPV-31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) and individual results for HPV-16 and HPV-18, the highest-risk genotypes.

The approval was based on the results of the ATHENA trial in which HPV testing and liquid-based cytology were performed in 47,208 women aged 21 years or older during routine cervical screening. Analysis of HPV testing was performed in those women with atypical squamous cells of undetermined significance (ASC-US) who underwent colposcopy and had valid HPV testing and cervical biopsy results. Participants had to be not pregnant, willing to undergo colposcopy and biopsy within 12 weeks if required, and could not have received treatment for cervical intraepithelial neoplasia (CIN) in the preceding 12 months. Clinical validation of the test was achieved by determining its performance characteristics for the detection of CIN grade ≥ 2 and CIN grade ≥ 3 and by comparing its performance with that of the Hybrid Capture 2 test, which detects 13 HR-HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68).

Of the total, 1,923 women (4.1%) had ASC-US cytology. Of those, 1,578 (82.3%) underwent colposcopy and had valid HPV tests and cervical biopsy results. The percentages of women with ASC-US who underwent colposcopy were similar for HR-HPV-positive (86.4%) and HR-HPV-negative women (83.5%). Overall, the mean age was 37.1 years, 23.1% of women were postmenopausal, 4.3% had received the HPV vaccination, and 0.3% were immunocompromised. Most of the patients were non-smokers, and the racial distribution of the study population reflected that of the overall US population.

The prevalence rates of overall HR-HPV (all 14 genotypes), HPV-16, and HPV-18 detected with the test were 32.6%, 8.2%, and 2.9%, respectively, with the prevalence of each decreasing with increasing age; in the 21-29-year age group, rates were 54.1%, 16.1%, and 5.6%, respectively. The prevalence of HR-HPV detected with the Hybrid Capture 2 test was 31.5% and also decreased with increasing age; in the 21-29-year age group, the overall HR-HPV rate was 52.3%.

Among women with ASC-US, biopsy-confirmed CIN 1, CIN 2, and CIN 3 were identified in 10.0%, 2.2%, and 2.9%. No cases of invasive cervical cancer or adenocarcinoma in situ were found. The prevalence of CIN ≥ 2 was 5.1%, and the prevalence of CIN ≥ 3 was 2.9%. HPV genotype 16 or 18 was detected in 8% of women without CIN, 18% of women with CIN 1, 44% of women with CIN 2, and 61% of women with CIN ≥ 3.

The cobas test had performance comparable to the
Hybrid test. For CIN ≥ 2, sensitivity was 90.0% vs 87.2%, respectively; specificity was 70.5% vs 71.1%; positive predictive value was 14.0% vs 13.7%; and negative predictive value was 99.2% vs 99.1%. For CIN ≥ 3, sensitivity was 93.5% vs 91.3%, specificity was 69.3% vs 70.0%, positive predictive value was 8.4% vs 8.5%, and negative predictive value was 99.7% vs 99.6%. The 2 tests were 90.6% concordant for CIN < 2, and 96.2% concordant for CIN ≥ 2.

The absolute risk of CIN ≥ 2 by the cobas test results was 14.0% for HR-HPV-positive (all 14 genotypes), 24.4% for HPV-16/18-positive, 31.5% for HPV-16-positive, 4.3% for HPV-18-positive, 8.6% for HR-HPV-positive for the 12 other HR genotypes (excluding HPV-16 and -18), and 0.75% for HR-HPV-negative. The risk for CIN ≥ 2 was 18.6-fold higher in women who were HR-HPV-positive (14 genotypes) compared with those who were HR-HPV-negative (relative risk [RR], 18.6, 95% confidence interval [CI], 9.0-38.4). RRs for CIN ≥ 2 for HPV-16-positive women were 42.0 (95% CI, 20.1-87.5) compared with HR-HPV-negative women, and 3.7 (95% CI, 2.4-5.7) compared with women who were positive for the 12 other HR-HPV types (excluding HPV-16 and -18). The RR for CIN ≥ 2 for HPV-18-positive women was 5.8 (95% CI, 1.3-26.5) compared with HR-HPV-negative women, and for women who were HR-HPV-positive for other HR genotypes (excluding HP-16 and -18), the RR was 11.4 (95% CI, 4.6-54.0) compared with HR-HPV-negative women.

The absolute risk of CIN ≥ 3 by the cobas test results was 8.4% for HR-HPV-positive, 15.9% for HPV-16- or -18-positive, 20.0% for HPV-16-positive, 4.3% for HPV-18-positive, 4.4% for HR-HPV-positive for the 12 other HR genotypes (excluding HPV-16 and -18), and 0.28% for HR-HPV-negative. The absolute risk of CIN ≥ 3 was nearly 30-fold higher in women who were HR-HPV-positive (14 types), compared with HR-HPV-negative women (RR, 29.7; 95% CI, 9.3-95.2). RRs for CIN ≥ 3 for HPV-16-positive women were 70.9 (95% CI, 21.8-231.1) compared with HR-HPV-negative women, and 4.5 (95% CI, 2.5-8.2) compared with women positive for the 12 other HR-HPV types (excluding HPV-16 and -18). The RR for CIN ≥ 3 for HPV-18-positive women was 15.4 (95% CI, 2.6-90.1) compared with HR-HPV-negative women. The RR for women who were HR-HPV-positive for other HR genotypes (excluding HP-16 and -18) was 15.7 (95% CI, 2.6-90.1) compared with HR-HPV-negative women.

The cobas HPV Test is marketed by Roche Molecular Systems.

Reference