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[1] 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 tests 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 nonsmokers, 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

What's new, what's important

The FDA approved the first HPV DNA test last month. The cobas HPV test detects DNA from 14 high-risk HPV types, including HPV-16 and HPV-18, the highest-risk HPVs. Based on this test, health care professionals can decide if a patient should undergo further testing, such as colposcopy. The test was approved in 2011 as a cotest with Pap smear. Based on results from the ATHENA trial, the FDA has now approved the test for primary screening.

There are significant controversies surrounding the approval of this test. If we don't use it according to the evidence, it could lead to overuse, over-diagnosis, and over-treatment, which would result in significant long- and short-term side effects for patients and unnecessary health care expenditure and patient anxiety. The FDA has responded to the concerns by patient advocacy groups and other bodies by stating that it "does not to establish US guidelines for clinical use or reimbursement of cervical cancer screening. Those decisions properly rest with recommending bodies, such as professional societies or the US Preventive Services Task Force and payers such as Centers for Medicare and Medicaid Services." The Society of Gynecologic Oncology and the American Society of Colposcopy and Cervical Pathology have endorsed this testing.

More than 90% of patients with HPV infection will not develop any long-term problems. At this point, we have a well-established, validated, time-tested screening tool available – the Pap smear. It is important that we support and embrace new advances in medicine, but we need to make sure that these tests are used in the proper context.

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News angle

The Food and Drug Administration on April 24 approved the cobas HPV test as a first-line screening test for primary cervical cancer. The test uses a sample of cervical cells to detect DNA from 14 high-risk human papillomavirus types.

The agency recommended that women who test positive for HPV 16 or HPV 18 using the cobas HPV test have a colposcopy. Those who test positive for one or more of the 12 other high-risk HPV types should have a Pap test to determine the need for a colposcopy. The results should be used along with patient screening history and risk factors, and current professional guidelines when making clinical decisions, the FDA advised.

The test was first approved in 2011 for use in conjunction with or as a follow-up to a Pap test. With the current approval, it can now be used as the primary cervical cancer screening test.

The approval means women will have more screening options, said Alberto Gutierrez, PhD, director of the FDA Office of In Vitro Diagnostics and Radiological Health. "Roche Diagnostics conducted a well-designed study that provided the FDA with a reasonable assurance of the safety and effectiveness when used as a primary screening tool for cervical cancer," he said in a statement.

Despite some concerns about the potential for confusion and its off-label use, the FDA's Microbiology Devices Advisory Committee voted unanimously on March 12 to support expanding the approval of the cobas HPV test to include first-line use for primary cervical cancer screening. Some panelists noted that it will be up to professional societies to integrate the new test into their practice guidelines and to educate physicians and patients about its use. The decision to approve the test was based on the results of the ATHENA trial (see p. 156).

– Mary Ellen Schneider

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

1. Stoler MH, Wright TC Jr, Sharma A, et al. High-risk human papillomavirus testing in women with ASC-US cytology. Results from the ATHENA HPV study. Am J Clin Pathol. 2011;135:468-475.