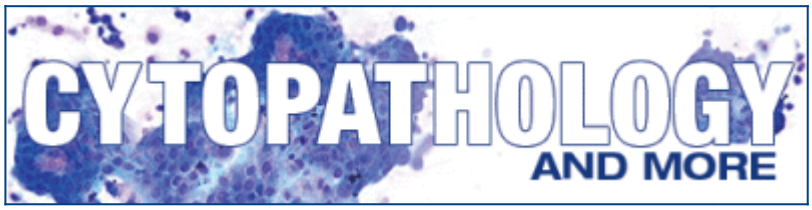
Cytopathology and More | ATHENA design, data—and the FDA's decision



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August 2014—The Food and Drug Administration Microbiology Devices Panel of the Medical Devices Advisory Committee held a hearing March 12 on a proposal by Roche Molecular Systems for a new application of human papillomavirus first-line primary cervical cancer screening for women age 25 and older.[1] The 13-member panel unanimously approved the test as safe and effective with benefits to women's health. The FDA formally approved the additional testing indication on April 24.[2]

Background: The Pap test has historically been the most effective cancer screening test ever and has demonstrated a dramatic positive impact on cervical cancer incidence and mortality. Globally, women in organized screening programs with regular screening invitations and follow-up enjoy the highest degree of protection. Screening for cervical cancer poses a special problem in that HPV infections are very common in young women but usually regress. Only a minority of women with persistent high-risk infection develop precancer (CIN3), and only a small fraction of precancers progress to cancer, generally at least 20 years after initial HPV acquisition. While the Pap test has high specificity, the lower sensitivity requires multiple screenings to detect most precancers before they progress. The introduction of liquid-based cytology and automated imaging has optimized the test and led to improvements in Pap sensitivity. HPV molecular testing was approved previously for triage of borderline Pap tests (atypical squamous cells of undetermined significance, ASC-US) and for cotesting in women age 30 and older. Based on multiple observational and clinical trial studies, an updated 2011 screening guideline of the American Cancer Society, American Society for Colposcopy and Cervical Pathology, and ASCP said that utilization of cytology and HPV cotesting was the preferred screening option in women age 30 and older, but that there was insufficient data to recommend HPV primary screening. Since then there have been multiple randomized clinical trials and observational studies in Europe. HPV DNA testing has been shown to be more sensitive than Pap testing and slightly inferior in specificity for detection of CIN3.

ATHENA study design: The ATHENA trial (Addressing THE Need for Advanced HPV Diagnostics) was a prospective U.S. trial of 47,208 women age 21 and older undergoing routine cervical screening in the U.S. using the Roche Cobas HPV test.[1,3,4] Sixty-one clinical centers in 23 states participated in this study, and the demographics were representative of the U.S. population for ethnicity and HPV positivity. Women under age 25 and those with missing results were excluded from the primary screening study, leaving 40,944 women with a median age of 41. The proportion of women in the age groups 25–29, 30–39, 40–49, and ≥50 were 16 percent, 30 percent, 29 percent, and 25 percent, respectively. Very few women had received the HPV vaccine. The rate of cytologic abnormality on the ThinPrep Pap test was 6.4 percent with an ASC-US:SIL (squamous intraepithelial lesion) ratio of 1.7:1. The overall Cobas HPV test positivity was 10.5 percent. Compared with randomized clinical trials such as the ALTS, this was an observational study with adjustment for verification bias, in that all abnormal test combinations and a subset of women with negative tests had identical disease assessment.

All eligible women who had undergone colposcopy and biopsy showing <CIN2 and a subset of women with negative cytology and HPV testing (7,642) were randomly selected for a three-year follow-up study (follow-up phase = future risk). The Cobas candidate algorithm was HPV primary screening, with women who tested positive for HPV genotypes 16/18 referred to colposcopy. Women positive for other HPV types would have reflex cytology, and those with a result of ASC-US or higher would have colposcopy. The Cobas HPV test performance was compared to cytology alone, with all women with abnormal results proceeding to colposcopy (no ASC-US triage), for several performance characteristics including sensitivity, specificity, positive and negative predictive values (PPV and NPV), and colposcopy rate. An additional comparator that includes cotesting of women age 30 and older and ASC-US triage for women under 30 years was also analyzed.

Results: After adjustments for verification bias, the sensitivity of the primary HPV screening algorithm was 45.4 percent for detection of CIN2+ (CIN2 or cancer), compared with a cytology sensitivity of 35.3 percent.[1,3] HPV sensitivity for CIN3+ threshold (CIN3 or cancer) was 58.3 percent compared with cytology, 42.6 percent, leading to a sensitivity gain of 1.37 compared with cytology screening only. The Cobas candidate HPV algorithm was statistically better than the cytology comparator in terms of PPV, NPV, sensitivity, specificity, and positive and negative likelihood ratios, and it required fewer colposcopy procedures. The comparator algorithm that included cotesting for women age 30 and older and ASC-US triage for younger women had sensitivities of 41.5 percent and 53.2 percent for CIN2+ and CIN3+, respectively. The candidate algorithm performed statistically better than the additional cotesting comparator in terms of sensitivity, predictive values, and likelihood ratios, but did not differ statistically in numbers of colposcopy procedures.

When only women age 30 and older were analyzed, the cotesting additional comparator had statistically higher sensitivity for CIN3+ lesions than the Cobas candidate algorithm (56.7 percent versus 53.6 percent). The Cobas algorithm showed a much higher gain in sensitivity (disease detection) in women ages 25–29. This age group accounted for 30 percent of CIN3+ cases. Over half of these young women had negative cytology; thus, starting HPV testing at this age would be expected to lead to more colposcopy procedures.

The study was not designed to analyze invasive carcinoma detection differences, and no statistical differences were noted. Women with unsatisfactory cytology results were excluded from the primary study analysis; however, the distribution of HPV testing results (percent HPV positive versus negative) was similar to the overall study population, suggesting the same performance and statistical conclusions.[3] The FDA presentation also discussed knowledge of HPV status on cytology performance, and concluded that knowledge of positive HPV status (HPV 16, 18, or other type) leads to about 1.3 times increased diagnoses of abnormal cytology results. This would ultimately lead to improved sensitivity of the Cobas algorithm with a slight increase in colposcopy procedures and decreases in specificity and PPV.[3]

A detailed analysis of the follow-up was also discussed by the FDA. While the baseline risk of CIN3+ was 15 percent for the 2.9 percent of women who tested positive for HPV 16/18, additional women would be found to have CIN3+ during three years of follow-up, giving a total three-year risk of about 21.1 percent. For the 7.8 percent of women testing positive for the 12 other high-risk HPV types, the current and three-year risk of CIN3+ was estimated to be 11.1 percent if cytology reflex result was abnormal, and 3.6 percent if the cytology result was negative. Women negative for all high-risk HPV types were estimated to have a three-year disease risk of 0.34 percent.

Only a few women who had received the HPV vaccine were diagnosed with disease, and these women demonstrated slightly higher age-adjusted sensitivity and lower specificity. When the issue of HPV vaccine was discussed, the sponsor and the panel concluded that both HPV and cytology positive predictive value will be negatively impacted, with perhaps a larger impact on cytology, which is more subjective.

Comments: The three years of follow-up data limit the ability to predict the long-term performance of HPV primary screening compared with other screening methods including cotesting. Additional studies will be useful in determining lifelong screening strategies. The U.S. currently has an opportunistic screening strategy and lacks the organized screening and vaccination programs found in Australia and many European countries. The total cytology abnormal rate of 6.4 percent represents the 25th percentile reporting rate for laboratories surveyed by the CAP as

published in recent Laboratory Accreditation Program checklists. This low abnormal rate may have had an impact on verification-bias–adjusted sensitivity calculations in which cytology achieved only 42.6 percent sensitivity for CIN3+ lesions. The verification-bias–adjusted sensitivity of HPV testing was 58.3 percent for CIN3+, and both cytology and HPV sensitivities were lower than much of the published literature. The FDA panel discussion included questions to sponsor about determination of disease status.

The FDA approval of the Roche application does not alter the screening guidelines of the American Cancer Society and other stakeholder groups. An interim clinical guidance document with input from several professional societies is in draft form and publication is expected within the next several months. There is concern about additional colposcopy procedures in women ages 25–29 and whether this will lead to patient harm; while this age group accounted for a significant proportion of the CIN2+ cases, this age group also has higher CIN regression rates. The Cytopathology Education and Technology Consortium, of which the CAP is a member, submitted a draft statement to the FDA listing several concerns, including the possibility of HPV-negative invasive cancers, quality control, and specimen adequacy when this testing is performed in practice outside of clinical trials. This statement stressed that HPV testing should be performed in CLIA-approved laboratories that perform proficiency testing and use only HPV testing methods approved by the FDA for a primary screening indication with internal validation.

1. U.S. Food and Drug Administration. 2014 meeting materials of the Microbiology Devices Panel, March 12, 2014: meeting materials FDA generated. Available at: www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/MicrobiologyDevicesPanel/ucm388531.htm. Accessed June 12, 2014.
2. FDA approves first papillomavirus test for primary cervical cancer screening, April 24, 2014. Available at: www.fda.gov/newsevents/newsroom/pressannouncements/ucm394773.htm. Accessed June 12, 2014.
3. Simon K, Kondratovich M. FDA presentation March 12, 2014, Microbiology Devices Advisory Committee meeting. Available at: www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/MicrobiologyDevicesPanel/ucm388531.htm. Accessed June 12, 2014.
4. Wright TC, Stoler MH, Sharma A, et al. Evaluation of HPV-16 and HPV-18 genotyping for the triage of women with high-risk HPV+ cytology-negative results. *Am J Clin Pathol*. 2011;136:578–586.

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