Put It on the Board

Third cervical cancer screening paradigm may be on the way

April 2014—Clinical trial data and a Food and Drug Administration panel's full-throated endorsement stand to reshape cervical cancer screening practice recommendations in the U.S.

The FDA's Microbiology Devices Advisory Committee in March voted 13-0 in favor of a new indication for Roche's Cobas human papillomavirus test that would allow the assay to be used as a primary screen for cervical cancer in women 25 and older. At this article's deadline, the FDA had not yet acted on the panel's advice but the agency usually heeds its advisory committees' recommendations. The Roche test—approved in 2011—uses amplification of target DNA by polymerase chain reaction and nucleic acid hybridization to detect 14 types of high-risk HPV and specifically identify genotypes 16 and 18.

Dr. Nayar

The FDA committee said women who test negative with the Cobas HPV test "should be followed up in accordance with the physician's assessment of screening and medical history, other risk factors, and professional guidelines." Women who test positive for 16 or 18 would be referred for colposcopy, while women who test negative for those two but positive for one of the other 12 high-risk HPV types would be evaluated by cervical cytology to determine whether referral for colposcopy is needed.

The panel's advice was based on the results of a Roche-funded prospective clinical trial that enrolled more than 47,000 American women. The study, dubbed ATHENA, found that the Cobas HPV test had a sensitivity of 58.26 percent in detecting cervical intraepithelial neoplasia, grade three or higher, compared with 43.63 percent sensitivity achieved by cervical cytology. Meanwhile, Pap testing had a false-positive rate of 6.04 percent for CIN 3 or greater, compared with 4.28 percent for the Cobas HPV test.

Roche's assay "detects more women with disease and requires fewer women without disease to go to colposcopy than cytology alone," said an executive summary prepared for the FDA panel. That document and other meeting materials are available at http://j.mp/hpvmeet.

In 2012, the American Cancer Society, American Society for Colposcopy and Cervical Pathology, American Society for Clinical Pathology, American College of Obstetricians and Gynecologists, and the U.S. Preventive Services Task Force agreed that women ages 21 to 29 should be screened every three years with cervical cytology. Women 30 to 65 years old should be cotested with Pap and HPV testing every five years, or screened every three years with cervical cytology alone, the organizations said (Schiffman M, et al. *N Engl J Med.* 2013; 369:2324–2331).

Moving away from cytology's first-line role in cervical cancer screening would help clinicians and laboratorians, says Thomas C. Wright Jr., MD. He helped design the ATHENA trial and is former director of the Division of Gynecologic, Obstetric, and Cytologic Pathology at Columbia University Medical Center. Roche has paid Dr. Wright for his consulting work and he receives honoraria from the company for speaking engagements, he says.

"From a clinical perspective, having a cytology in HPV-negative women really gives you minimal demonstrable benefit," Dr. Wright tells CAP TODAY. "But it does add complications. You end up with a whole group of cytological abnormalities in women who are HPV-negative, and you have to follow up many of them."

For labs, using the Cobas HPV test as a first-line screen would reduce medical liability risk related to gynecologic cytology, Dr. Wright predicts. “Those lawsuits can be very expensive,” he says.

The ASCCP and the Society of Gynecologic Oncology have appointed a panel to develop interim guidance on cervical cancer screening based on the ATHENA trial data. The panel—which includes two voting members representing the American Society of Cytopathology (ASC), the ASCP, and the CAP—will issue its advice by this summer, says Warner K. Huh, MD. He is a professor of gynecologic oncology at the University of Alabama at Birmingham and chair of the interim guidance panel.

“We’re not asking for the death of cytology,” Dr. Huh says. “We are saying it should be used differently than the way we’re using it now. . . . We’re not suggesting that primary HPV testing replace current screening paradigms. We’re saying this is a third paradigm that should be considered and that outperforms cytology.”

Dr. Huh and several other experts say there are no data to determine conclusively whether HPV testing alone outperforms cotesting in cervical cancer screening. The ATHENA trial did not put those two screening approaches head to head.

“We just don’t have enough information to say whether primary HPV testing trumps cotesting,” Dr. Huh says. “That will be the more debatable issue in the months and years to come.”

The proliferation of cervical cancer screening options is part of what concerns ob-gyns, says David Chelmow, MD, who spoke at the FDA panel meeting on behalf of ACOG. He chairs the Department of Obstetrics and Gynecology at Virginia Commonwealth University Medical Center.

“There is already significant confusion about the revised guidelines, and many women are not being screened in accordance with the recommendations. Introducing a third screening alternative will likely further increase confusion, and the risk to women of getting either over- or underscreened,” Dr. Chelmow said in his testimony.

A coalition of professional organizations dealing with diagnostic cytopathology—the Cytopathology Education and Technology Consortium, or CETC—has raised other concerns about shifting to the Cobas HPV test as a primary screen. The biggest fear is missing cases of cancer. The U.S. cancer registry study has found that 12.6 percent of cervical cancers are either HPV-negative or contain rare HPV subtypes, notes a Feb. 27 CETC statement to the FDA panel. Members of the CETC are the ASC, the ASCP, the American Society for Cytotechnology, the CAP, the International Academy of Cytology, and the Papanicolau Society of Cytopathology.

“Due to the documentation of HPV-negative squamous cell carcinoma and adenocarcinoma, women should have a morphological examination (Pap test) in their screening history and should not be screened solely with HPV tests,” the CETC letter says. The consortium emphasizes that “as with any laboratory test, the sensitivity of HPV testing is not 100 percent.” The CETC cautions that clinicians are likely to equate all HPV assays, even those that are laboratory-developed tests or that have not been FDA-approved for the specific indication of primary cervical cancer screening.

Another worry is adequate quality control for the Cobas HPV test, says Ritu Nayar, MD, co-chair of the CETC, president of the ASC, member of the CAP’s Cytopathology Committee, and professor of pathology at Northwestern University Feinberg School of Medicine. The beta-globin gene internal control used in the test is not specific for cervical epithelial cells. Thus, it is possible that specimens could wrongly be deemed adequate when they contain only inflammatory cells and no epithelial cells.

Dr. Nayar says the trial data do appear to support the notion of screening first with the more sensitive HPV test and then, if that is positive, following with more specific testing such as the Pap. But she adds a note of caution.

“As real-world testing offers challenges not seen in controlled clinical trials, the application of this testing algorithm to the general U.S. population will be far more complex.”

If the FDA approves Roche’s assay as a primary screening option, Dr. Nayar says, U.S. clinicians will have three

first-line screening options that have varying testing intervals and downstream triage algorithms.

“We know from prior guidelines that it takes substantial time and effort to develop evidence-based algorithms and provide education for providers and patients,” she adds. “Practice patterns don’t change overnight. It takes time—sometimes years—before new tests and guidelines receive acceptance and significant penetration in everyday practice.”

For more with Dr. Nayar, go to captodayonline.com.

An ‘opt-out’ update

The American College of Medical Genetics and Genomics has changed its recommendations for the return of results from genome-scale sequencing. It now recommends that the option to opt out of the analysis of medically actionable genes be offered to patients who are considered candidates for such testing. This moves the opt-out discussion to the point at which the sample is sent rather than when the ordering physician receives the results, as it recommended originally.

Saying in a statement that the positions of ACMG members on the initial recommendations were assessed in multiple ways, ACMG president Gail Herman, MD, PhD, added, “It was our understanding from the beginning… that they would evolve over time.”

Leica, QualityStar team up

Leica Biosystems has partnered with QualityStar, an external quality assurance service provider, to deliver a metrics-based anatomic pathology QA program using Leica’s Aperio ePathology solutions. QualityStar is an independent QA consortium and subscription service.

FDA clears HSV 1 & 2 Direct

Focus Diagnostics received expedited FDA 510(k) clearance and CLIA moderate complexity categorization for its Simplexa HSV 1 & 2 Direct molecular test on the 3M Integrated Cycler. It is the first molecular test to be cleared by the FDA for the qualitative detection and differentiation of herpes simplex virus 1 and 2 in cerebrospinal fluid from patients suspected to have HSV central nervous system infection, including encephalitis.

Illumigene Pertussis has FDA OK

Meridian Bioscience received FDA clearance for its molecular diagnostic test for Bordetella pertussis, its fifth assay on the Illumigene platform. This test is the first FDA-cleared molecular standalone assay for *B. pertussis*.