New Guidance on Cervical Cancer Screening

Three Medical Societies Recommend HPV Primary Testing

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Since the Food and Drug Administration's (FDA) April 2014 approval of the Roche Molecular Systems cobas HPV test, clinicians and laboratorians have been waiting for guidance on how to use the assay, which detects DNA from 14 high-risk types of human papilloma virus (HPV) that together cause 90% of cervical cancers. In January 2015, the American Society for Colposcopy and Cervical Pathology (ASCCP), and the Society of Gynecologic Oncology (SGO) issued interim guidance that newly suggests HPV primary (HPVpr) testing as a possible screening strategy, in addition to cytology and use of both tests, also known as co-testing.

The interim guidance recommends that clinicians consider HPVpr testing for women starting at age 25. Those with negative results should not be retested again for at least 3 years, while women who test positive for HPV 16 and 18 should have colposcopy. Women positive for the 12 other high-risk HPV genotypes should have refl ex cytology (Obster Gynecol 2015; 125: 330-7).

Among HPVpr's advantages over cytology and co-testing is a single FDA-approved algorithm for handling abnormal results, the interim guidance notes. HPVpr also offers better sensitivity and negative-predictive value (NPV) for cervical intraepithelial neoplasia grade 3 (CIN3) or higher, as demonstrated by recently published fi nal data from the ATHENA (Addressing THE Need for Advanced HPV Diagnostics) trial (Gynecol Oncol 2015; doi:10.1016/j. ygyno.2014.11.076). However, HPVpr's increased sensitivity results in more colposcopies than co-testing or cytology, although the number of colposcopies needed to detect a single case of CIN3 after HPVpr is roughly equal, the study says.

"The new guidelines support the well-researched premise that HPV causes cervical dysplasia and malignancies," said interim guidance fi rst author Warner K. Huh, MD, associate professor of gynecologic oncology and associate scientist at the University of Alabama Comprehensive Cancer Center in Birmingham. "When women get negative HPV results, there's an extraordinarily low risk of their developing cancer. You don't get the same reassurance with the Pap."

Authors of the interim guidance and others in the fi eld have expressed concern about the increased use of colposcopies that will occur with HPVpr, while others have urged continued caution about its use in women ages 25 to 29. But experts agree: clinician education about HPV, the interim guidance, and relevant data is crucial.

Recommendations and Data

In developing the interim guidance, its authors reviewed 11 studies, including ATHENA. This trial followed 47,000 women ages 21 or older for 3 years to compare cytology, co-testing, and HPVpr for detecting high-grade lesions. For women who had HPVpr screening, researchers handled abnormal results according to the FDA-approved algorithm also recommended in the interim guidance.

For women in all age groups, HPVpr had the highest sensitivity for CIN3, 76.1%, versus 47.8% for cytology and 61.7% for co-testing. The specificity for CIN3+ was 97.1%, 94.6%, and 93.5% for cytology, cotesting, and HPVpr, respectively.

Women ages 30-39 had the highest rate of CIN3, 40.3%, compared to women 25-29 (34.3%), and 40 or older (25.3%). Among the young women who had co-testing, more than half of CIN3 detected by HPV tests were not found by cytology, the researchers noted.

Among young women, HPVpr testing had both the highest sensitivity for CIN3, 76.1%, and NPV, 99.7%, while its specifi city was 93.5% and its positive-predictive value (PPV) was 12.9%. In contrast, co-testing's sensitivity for CIN3 was 61.7%, specifi city was slightly higher at 94.6%, and PPV and NPV were slightly lower at 12.6% and 99.5%, respectively. Both HPVpr testing and co-testing outperformed cytology, which for CIN3 had a sensitivity of 47.8%, specifi city of 97.1%, PPV of 17%, and NPV of 99.3%.

Among women age 30 or older, HPVpr also had the highest sensitivity and NPV for CIN3, at 72.3% and 99.7%, respectively. HPVpr had specifi city of 94.9% and PPV of 12.1%. Meanwhile, for CIN3, co-testing had sensitivity of 69.3%, specifi city of 94.7%, PPV of 11.4%, and the same NPV, 99.7%. In this age group, for CIN3, cytology had a sensitivity of48%, specificity of 97.7%, as well as PPV and NPV of 16.7% and 99.5%, respectively.

The downside of primary screening is a signifi cant increase in the number of colposcopies compared to either cytology or co-testing, the researchers wrote. Compared to cytology, HPV primary screening almost doubled the number of colposcopies among women age 25 or older. Among the cytology group, there were 1,934 colposcopies, versus 3,769 in the HPVpr group. However, the number of colposcopies required to detect a single case of CIN3 was almost the same for HPVpr and cotesting— 12.9 and 12.8, respectively.

Concerns About Young Women

Prior to release of the interim guidance, using HPVpr in women ages 25–29 had been a topic of debate. Some, including Attila Lorincz, PhD, worried about overuse of colposcopy in these younger women, whose infections might regress. Lorincz developed the fi rst HPV test and is professor of molecular epidemiology at the Wolfson Institute of Preventive Medicine at Queen Mary University of London.

Lorincz supports the interim guidance recommendations for HPVpr screening in women age 30 or older and in women ages 25–29, with carefully considered triage. However, he is still concerned about HPVpr in younger women and urges clinicians to study the interim guidance in detail so they can clearly explain both risks and benefi ts. "The authors say these relatively common lesions in young women are important to detect and treat immediately, yet in the paper they state that up to 60% of CIN2 in young women regress," said Lorincz. He pointed to a recent analysis that found more than 1% of women who have cervical treatment suffer serious obstetrical complications such as miscarriage and ectopic pregnancy (BMJ 2014;349:g6192).

An ATHENA researcher defends the recommendation for HPVpr screening in younger women. "Screening is not about fi nding cancer, but about preventing it. After age 30, the cancer incidence goes up. So age 25 to 29 is the sweet spot for finding pre-cancer, and HPV primary screening in these women is a reasonable choice," said Mark H. Stoler, MD, professor emeritus of pathology, cytology, and gynecology and associate director of surgical pathology and cytopathology at the University of Virginia School of Medicine in Charlottesville and past president of the American Society for Clinical Pathology.

"The absolute numbers of colposcopy [in the ATHENA data] look big, but not bigger than with co-testing. More colposcopy is what we have to contend with in order to fi nd more disease," Huh added.

More Study Needed

Noting a dearth of direct cost comparisons of HPVpr, co-testing, and cytology, the interim guidance calls for more such research. A study by Huh compared costs of HPVpr with HPV 16 and 18 genotyping over 40 years and used preliminary ATHENA sensitivity and specifi city data. Huh found that the strategy reduced overall screening costs compared with cytology and co-testing, but it included only women ages 30 or older (Appl Health Econ Health Policy 2015;13:95–107). This analysis preceded Roche's FDA application for primary screening, noted Huh, who hypothesized that the added colposcopies expected in younger women would likely make HPVpr less cost-effective.

While interim guidance directs clinicians to retest HPVpr-negative women no sooner than 3 years later, without specifying an optimum interval, it also calls for data to help determine one. Studies conducted outside of the U.S. are poised to deliver that triage data. Lorincz is collaborating with Mexican researchers on FRIDA (Forwarding Research for Improved Detection and Access for Cervical Cancer Screening), which involves 100,000 women, but no HPV testing for those younger than 30. Other triage studies are ongoing at Vrije Universiteit Medical Center in the Netherlands, and in Canada, where researchers are fi nishing the HPV Testing for Cervical Cancer Screening (HPV FOCAL) study.

Educating Clinicians

In addition to the interim guidance, multiple screening guidelinessubject to more rigorous development processes still exist, notes Frederick Nolte, PhD, professor of pathology and laboratory medicine, vice chair of laboratory medicine, and director of clinical laboratories at the Medical University of South Carolina in Charleston. He urged laboratorians to help clinicians sort out the various recommendations.

Because the interim guidance considers cobas the only appropriate HPVpr test until FDA approves others, "there has to be dialogue between labs and clinicians about what HPV test the lab offers," he added. Labs that do not use cobas should refer clinicians seeking

HPVpr screening to labs that do. Nolte also urged labs to determine if clinicians are ordering HPV assays for primary screening, cotesting, or as refl ex tests.

Before discussing the most appropriate HPV test, some laboratorians may fi rst need to dispel many clinicians' insistence on annual cytology, despite various guidelines' recommendation for cytology screening every 3 years, said Lee Shulman, MD, chief of the Division of Obstetrics and Gynecology–Clinical Genetics and professor in obstetrics and gynecology and clinical genetics at Northwestern University in Chicago.

Shulman urged laboratorians to remind clinicians that although cytology is a powerful detector of cervical cancer, it is not very effective at detecting changes that lead to cancer, which is the real goal of screening. Many clinicians forget that cervical surveillance is the main purpose of the annual gynecology visit, he added. Clinicians may cling to cytology screening because they fear patients won't return for annual visits without it. Meanwhile, some clinicians have resisted use of HPV tests because insurance companies have balked at paying for them. "That's changing now," Shulman said.

As the state of knowledge about cervical cancer screening and practice evolves, laboratorians and clinicians should prepare for a future in which they will do more HPVpr tests and follow- up of HPV 16/18 positive results, and more young people receive HPV vaccinations, which could eventually alter the effectiveness of screening tests (see sidebar). "Labs will need to keep on their toes due to the rapidly changing landscape in HPV testing, which is going to become an even bigger and more important test over the next fi ve to ten years," Lorincz said. "Keep your eyes on the many changes to come."

A New HPV Vaccine

Shortly before three medical societies released interim guidance on use of a human papilloma virus (HPV) test for primary screening, the Food and Drug Administration in December 2014 announced approval of a new vaccine that has the potential to protect against approximately 90% of cervical, vulvar, vaginal, and anal cancers.

Gardasil 9, manufactured by Merck and approved for females ages 9 through 26 and males ages 9 through 15, protects against fi ve HPV types not covered by other HPV vaccines on the market. These types—31, 33, 45, 52, and 58—cause 20% of cervical cancers. As other FDA-approved HPV vaccines do, Gardasil 9 also protects HPV types 16 and 18, which cause 70% of cervical cancers, as well as types 6 and 11, which cause genital warts.

Increased use of the vaccine will eventually lead to changes in cervical cancer screening, Stoler said , who helped develop Gardasil 9. "Screening only works when there's a certain prevalence. As vaccination increases and HPV prevalence drops, we will need more sensitive tests to fi nd residual disease in the population."

In Australia, an 80% vaccination rate among young people led the nation's Medical Services Advisory Committee to recommend that in 2016, cytology be phased out and replaced with HPV primary testing beginning at age 25, with a 5-year screening interval, Stoler noted.

Even with a relatively low vaccination rate of 30% to 40% among young people in the United States, incidence of HPV infection among U.S. teens is decreasing, Huh noted. A study by researchers at the Centers for Disease Control and Prevention shows that compared to the 4 year period prior to vaccine availability, infections with four HPV types targeted by the vaccine decreased by 56% among girls ages 14 to 19 in the 4 years after its introduction (J Infect Dis2013;208:385–93).

Disclosures: Dr. Huh is on the Scientific Advisory Board at Merck, which manufactures Gardasil. Dr. Stoler is a consultant and speaker for Roche Molecular Systems and helped develop the Gardasil 9 vaccine. Dr. Shulman is a speaker for Roche and has received honorarium from Qiagen. Dr. Nolte is a member of the Gen-Probe scientific advisory board and has received grants from the company. His lab was a clinical trial site for the Hologic Cervista HPV assay.

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