From the President’s Desk: With time, greater clarity on HPV screening, 6/14

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June 2014—The Food and Drug Administration on April 24 approved use of the Cobas HPV test manufactured by Roche Molecular Systems as a primary standalone screen for cervical cancer in women 25 years and older. There was a lot of chatter in the general interest press about cervical cytology, not all of it well informed.

The current screening guidelines, published in 2012, resulted from a consensus effort organized by the American Cancer Society, the American Society for Colposcopy and Cervical Pathology (ASCCP), and the American Society for Clinical Pathology. In fall 2013, a task force convened by the ASCCP and the Society of Gynecologic Oncology began work on interim guidance for standalone primary screening for cervical cancer in the United States. Pathologists from the American Society of Cytopathology, the ASCP, and the CAP are members of this task force.

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The ASCP, CAP, and American Society of Cytopathology are longstanding members of the Cytopathology Education and Technology Consortium (CETC), which also includes the American Society for Cytotechnology, International Academy of Cytology, and Papanicolaou Society of Cytopathology. It was the CETC that drafted and presented a statement to the FDA advisory panel in March.

We are in debt to the cytopathologists who are keeping us current on this complex topic. Shortly after the FDA ruling, ASC president Ritu Nayar, MD, who co-chairs the CETC, wrote a president’s message (ascpresidentsmessage.wordpress.com) that sets out context and concerns. Two additional CAP experts have shared educational insights for this column: Diane Davey, MD, a member of the Society of Gynecologic Oncology/ASCCP task force and the CAP Cytopathology Committee, and Barbara Crothers, DO, who chairs the CAP Cytopathology Committee.

Interest in this topic appears to be high across the CAP membership as well as clinical colleagues and the greater community. This month, I have just a few comments about what we do and do not know, and what we can expect next.

- This approval applies only to HPV screening with the Roche Cobas HPV test, using the ThinPrep Pap test PreservCyt Solution, and endocervical brush/spatula.
- Cobas is a qualitative in vitro test for detection of human papillomavirus in patient specimens that uses amplification of target DNA by PCR and nucleic acid hybridization techniques for detection of 14 high-risk HPV types in a single analysis. It specifically identifies types HPV 16 and HPV 18 (which account for 70 percent of cervical cancers) while concurrently detecting an additional 12 high-risk types.
- The FDA approval does not change current medical practice guidelines for cervical cancer screening. Primary screening with HPV alone is not covered in the current consensus guidelines.
- Laboratories accepting these specimens will need to perform verification/validation and continue to monitor quality assurance, as warranted, for HPV testing.
- The provisional proposal for followup of HPV positive screens, presented to the FDA by Roche, is complex; implementation may be difficult.
- If the professional societies agree to add this new option to future guidelines, they will probably include recommendations for followup on specific results and cotesting via specific combinations of cytology and HPV testing.
- Although final results of the ATHENA study have not yet been published, FDA approval was based on a controlled trial with ensured followup and likely central review of specimens.
- We do not know how well the controlled trial will replicate in practice because we have little experience with a cervical cancer screening paradigm of this kind in the United States, where followup is opportunistic.
- We currently have no comparative studies of HPV-only testing and cotesting with cytology and HPV.
- There is particular concern about provisions for standalone HPV screening of women 25 to 29 years old and the associated stipulation that women in this age group who screen positive for HPV 16 and HPV 18 go directly to colposcopy.
- False-positive HPV tests that lead to overtreatment may increase overall patient harm.
- Evidence that older women (especially those who have cervical cancer)

have more false-negative HPV results and younger women have higher—and likely transient—positive results argues for cotesting in these age groups.

- While HPV-negative cervical cancers are rare, they occur in almost all morphologic subtypes of cervical cancer.
- Early adopters should become knowledgeable about the nature of HPV infection and its role in cervical cancer.

Less than three weeks after the FDA ruling, a paper published in Cancer (ncbi.nlm.nih.gov/pubmed/24821088) reported that calculations used to produce national cervical cancer incidence rates employed in guideline development had failed to take into account the high prevalence of hysterectomy in the United States. After adjusting for hysterectomy, cervical cancer rates were highest among women ages 65 to 69. Current guidelines indicate that certain women with an appropriate screening history can exit screening at ages 60 to 65; in view of these data, this provision may need to be reconsidered or additional emphasis placed on verifying a woman's screening history.

The *Cancer* paper examined cervical cancer rates by age and race among all women in the United States whose cervix was intact. The corrected data set showed higher age-specific cervical cancer incidence rates, a shift in peak incidence to the 65- to 69-year-old age group, and an increased disparity in cervical cancer incidence between black and white women. Data set correction had the largest impact on older black women due to their high prevalence of hysterectomy, the authors said. The rate of cervical cancer among white women ages 65 to 69 was less than half what it was for black women in their age group.

It sometimes seems to me that we have a cultural inclination to accept statistics at face value. As pathologists, we have many opportunities to interact with data sets and interpret their content for colleagues, but the conversation shouldn't stop there. This is a good time to remind everyone involved that a number is just a number without clinical correlation.

We should have something from the SGO/ASCCP task force later this summer. The specialty societies will continue to monitor accumulating evidence and consider potential changes to the 2012 screening guidelines. Properly deployed, the Cobas test could become an effective screening tool, but there's no compelling reason to get ahead of the evidence. As experience accumulates, greater clarity will emerge.

Most women who die of cervical cancer have never been screened or have not been screened effectively. Whatever noise there might be in the greater environment, our first goal is to promote the public health value of screening for cervical cancer.

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Dr. Herbek welcomes communication from CAP members. Write to him at president@cap.org.