Assessing the impact of new cervical cancer screening guidelines

By Ed Baker, MD, FACOG, February 2013

With more than 12,000 women diagnosed with invasive cervical cancer annually in the United States, the importance of screening certain patient populations for human papillomavirus (HPV)—the main cause of cervical cancer—has become a key topic of discussion in women’s health. Approximately two-thirds of all cervical cancer cases are caused by the two highest-risk HPV genotypes, HPV 16 and HPV 18. Yet, women who should receive screening for high-risk HPV in addition to Pap cytology to assess their risk for cervical cancer often do not. While the global impact of Pap cytology screening in women’s health cannot be overstated, up to one-third of cervical cancers occur in appropriately screened women with normal Pap cytology results.¹,²

Recent clinical studies have further highlighted the critical role HPV testing can play in assessing cervical cancer risk. The ATHENA trial, for example, which involved more than 47,000 women, demonstrated that one in 10 women positive for HPV 16 and/or 18 had high-grade cervical disease that was missed by cytology.³ It has become clear that normal cytology does not always mean cancer-free and that there are multiple limitations to using cytology alone.

In March 2012, a multidisciplinary partnership between the American Cancer Society (ACS), the American Society for Colposcopy and Cervical Pathology (ASCCP), and the American Society for Clinical Pathology (ASCP) released updated cervical cancer screening guidelines. The recommendations state that high-risk HPV co-testing provides increased sensitivity for detecting cervical abnormalities and changes, and is preferred to using Pap cytology alone for women ages 30 to 65.

In November 2012, the nation’s largest OB-GYN organization, the American College of Obstetricians and Gynecologists (ACOG), separately published guidelines for cervical cancer screening that aligned with the recommendations of the partnership groups.

The updated guidelines also provide new screening intervals for women ages 30 to 65 who have Pap and HPV co-testing, recommending an interval of every five years if neither test shows new abnormalities.

From a broad perspective, there are several notable developments in the guidelines that could significantly affect the way clinicians manage cervical cancer screening and the way labs support clinicians in that area of patient management.

Preference for co-testing Reflexive high-risk HPV testing has been commonly used for triage of ASC-US (Atypical Squamous Cells of Undetermined Significance) cytology, but Pap and HPV co-testing in women ages 30 to 65, while considered an acceptable option, has certainly not been uniform practice. For the first time, the guidelines now state that this is the preferred screening method for this population. In the past the two alternatives were considered equally valid; now the guidelines affirm that HPV testing has a lot to offer above and beyond cytology.

Uniform recommendations In the past, the bodies that established screening guidelines had different recommendations, and if clinicians followed one group’s recommendations they would likely be violating someone else’s. So there were obvious reasons for the lack of uniformity in practice. This time, ACS, ASCCP, and ASCP solicited input from other key stakeholders, such as ACOG, and the result is that there are now fairly uniform guidelines across all of the groups. Clinicians, then, no longer have to wonder whose guidelines to follow, which should make the recommendations easier to adopt and lead to more uniformity of practice.
**Recommendation against annual Pap test** For several decades, there has been ample evidence that there is no clinical benefit to having a Pap test every year as opposed to every two to three years. Previous guidelines emphasized this point but stopped short of making a recommendation against an annual test. Now the guidelines include an explicit recommendation against yearly testing, specifically stating that an annual Pap test should not be done except in certain situations. So now physicians have to be willing to go against guidelines in order to do an annual Pap for most of their patients. This may be a difficult change for OB-GYNs to adopt if they have the perception that the Pap test is the primary reason patients come in for their annual exam. On the other hand, it may prompt a valuable conversation about how advances in medicine are enabling better care with less frequent testing and about how the annual exam is important as a comprehensive review of a woman’s health.

**HPV testing and genotypes 16/18 in patient management** The guidelines include extensive discussion about which HPV genotypes should be considered to test and how HPV test results should be used for preferential patient management. One of the most significant findings, based on the ATHENA study and others, was that an HPV negative result was so reliable in predicting a very low risk that an ASC-US cytology result could more or less be ignored; in effect, the findings indicated that the HPV test trumped the cytology test and the patient could be treated the same as women in the normal screening pool—that is, cytology negative.

For the inverse type of discordant results—HPV positive and cytology negative—the guidelines indicate two options: repeat co-testing in a year; perform an HPV genotyping test. For the latter option, HPV 16 or 16/18 positive results are the only ones shown to represent a significant enough differential risk to warrant separate patient management protocols, specifically immediate colposcopy.

**Expectations for clinical adoption and testing protocols** It is difficult to predict the level and rate of adoption of the new guidelines among physicians, in part because ACOG—the most influential body for OB-GYNs—just issued its guidelines in November 2012.

There are likely many OB/GYNs who agree, in principle, that co-testing has something to offer over the Pap test and will adopt it as standard screening practice for women from 30 to 65. There will also be Pap loyalists who may not see the value in co-testing and, notwithstanding pressure from payers, will stick with cytology alone, which is still considered acceptable according to the new guidelines. However, many in both camps will probably struggle with the longer screening intervals that have been recommended. A likely scenario is that a significant number of clinicians will adopt co-testing but not move very quickly to the five-year recommended testing interval.

Assuming that more clinicians do begin to adopt the preferred option in the new guidelines, there is obviously potential for HPV testing to increase significantly. If the paradigm moves from only doing HPV testing for ASC-US cytology, which might represent 10% of the 30- to 65 year-old patient population, to doing co-testing for everyone in that age group, that represents a tremendous volume increase, even if some clinicians adopt the longer testing intervals. And it’s unlikely the latter will happen on a widespread basis, at least in the near future.

The recommendations in the guidelines about discordant results may also impact the specific types of HPV tests that are ordered. As mentioned earlier, for women who have a negative cytology test and a positive HPV test, clinicians can either do a repeat co-test in 12 months or do a genotype test for HPV 16 or 16/18. This kind of discordant result will occur with some degree of frequency, and either option will contribute to a higher volume of HPV testing. For the genotyping option, there are FDA-approved HPV tests that provide individual 16/18 genotype results as a reflex test to a positive pooled high-risk result or that provide individual 16/18 results and the pooled result at the same time from one test.
Providing support for clinicians

There are several areas in which labs can provide support to clinicians regarding the new screening guidelines. One is educating them on the specific types of tests they offer and when to use them, especially when there is a wholesale change in the lab’s offering. In that case there is an opportunity for the lab, especially the pathologist, to approach the clinician proactively to offer some education to understand various differences.

This is particularly important when there are multiple options, including lab-developed tests, per the following guidelines commentary from Saslow et al:

The guidelines cannot be expected to perform as designed (i.e., to balance benefits and harms) when using HPV tests with different performance characteristics. Laboratory-developed tests (LDTs), which are currently exempt from regulatory oversight by the FDA, rarely have undergone the necessary evaluation using clinical endpoints of CIN3+ and CIN2+ in properly designed studies. Therefore, we recommend against the use of LDTs for cervical cancer screening.4

In light of this position, it’s important for labs to adopt an FDA-approved test and make sure clinicians know they are using an FDA-approved test that performs according to the characteristics that have been described in the guidelines. Clinicians typically assume, when they order a co-test, that it is FDA-approved and complies with the standards that are going to be used. If that is not the case, it’s incumbent upon the lab to point it out and explain the process that has been followed to validate the test and ensure that it performs according to the characteristics in the guidelines.

Another area in which labs can provide support for clinicians is in clarifying the distinction between high-risk and low-risk HPV types and their association with cervical cancer risk. These two categories both commonly appear in lab sheets, but many OB-GYNs do not understand what they mean in terms of patient management. Per Saslow, testing for low-risk HPV types has no clinical role in cervical cancer screening for the evaluation of women with abnormal cytology.4 By clarifying distinctions like this and explaining their specific test offering, labs can play a key role in helping clinicians make screening choices that are consistent with the new guidelines and support effective patient management.

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References