CERVICAL DISEASE

Integration of the HPV test into cervical screening adds complexity but clarifies optimal management in many cases

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Advances in cervical cancer screening continue apace. We are fortunate that these advances are based on a substantial amount of high-quality prospective evidence. Many of these advances are designed to target the women who have clinically relevant disease while minimizing harm and anxiety caused by unnecessary procedures related to cervical screening test abnormalities that have little clinical relevance.

With clinicians being regularly judged on performance and outcomes, adoption of advances and new guidelines should be considered relatively quickly by women's health providers.

In this article, I focus on two significant advances of the past (and coming) year:

- recent application and unanimous approval by a Food and Drug Administration (FDA) expert panel for the use of the cobas human papillomavirus (HPV) DNA test as a primary cervical cancer screen
- the latest update of guidelines on the management of abnormal cervical screening tests from the American Society for Colposcopy and Cervical Pathology (ASCCP).

IN THIS ARTICLE

cobas HPV test is poised for FDA approval as a primary screen for cervical cancer

Wright TC Jr, Stoler MH, Behrens CM, Apple R, Derion T, Wright TL. The ATHENA human papillomavirus study: design, methods, and baseline results. Am J Obstet Gynecol. 2012;206(1):46.e1–e11.

An FDA expert panel unanimously approved the cobas (Roche Molecular Diagnostics; Pleasanton, California) HPV DNA test on March 12, 2014. The FDA will decide on potential approval within the coming months. Although the FDA sometimes reaches a different decision from one of its advisory committees when it comes to a final vote on a product or device, most often the FDA concurs with the committee's judgment. Therefore, approval of the cobas HPV test as a primary screen is likely.

The cobas HPV test yields a pooled result for 12 high-risk HPV types (hrHPV 31,

33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), as well as individual results for types 16 and 18; it also has an internal control for specimen adequacy. HPV 16 and 18 account for roughly 70% of all cases of cervical cancer, and infection with both types are known to place women at high risk for having clinically relevant disease—more so than the other hrHPV types.

Committee reviewed data from ATHENA in voting for approval

In considering the cobas HPV test, the advisory committee reviewed data from the Addressing the Need for Advanced HPV Diagnostics (ATHENA) trial, a prospective, multicenter, US-based study of 47,208 women aged 21 and older. These women were recruited at the time of undergoing routine screening for cervical cancer; only 2.6% had been vaccinated against HPV. All were screened by liquid-based cytology and an HPV test. Those who had abnormal cytology or a positive test for a high-risk HPV type underwent colposcopy, as did a randomly selected group of women aged 25 or older who tested negative on both tests.

The prevalence of abnormal findings was:

- 7.1% for liquid-based cytology
- 12.6% for pooled high-risk HPV
- 2.8% for HPV 16
- 1.0% for HPV 18.

As expected, cytologic abnormalities and infection with high-risk HPV types declined with increasing age. The adjusted prevalence of cervical intraepithelial neoplasia (CIN) grade 2 or higher in women aged 25 to 34 years was 2.3%; it declined to 1.5% among women older than age 34. Of note, approximately 500,000 US women are given a diagnosis of CIN 2 or CIN 3 each year in the United States.

Why ATHENA is important

This US-based trial was designed to assess the medical utility of pooled high-risk HPV DNA in addition to genotyping for HPV 16 and 18 in three populations:

- women aged 21 and older with a cytologic finding of atypical squamous cells of undetermined significance (ASC-US)
- women aged 30 and older with normal cytology
- women aged 25 and older in the overall screening population with any cytologic finding.

Investigators were particularly interested in the use of the HPV test as:

- a triage for women with abnormal cytologic findings
- an adjunct to guide clinical management of women with negative cytology results
- a potential front-line test in the screening of women aged 25 and older.

The participants of the ATHENA trial were representative of women undergoing screening for cervical cancer in the United States—both in terms of demographics and in the distribution of cytologic findings. For example, recent US census data indicate that the female population is 79% white, 13% black, and 16% Hispanic or Latino—figures comparable to the breakdown of race/ethnicity in the ATHENA trial.

The trial was conducted in a baseline phase (published in 2012) and a 3-year follow-up phase (not yet published). The 3-year data were reviewed by the FDA advisory committee during its consideration of the cobas HPV test as a primary screen.

Despite probable approval, incremental change is likely

Although a move to the HPV test as the primary screen is a definite paradigm shift for what has been cytology-based screening since the initiation of cervical cancer screening, the changeover from primary cytology to primary HPV testing likely will be slow. It will require education of clinicians as well as patients, and a shift in many internal procedures for pathology laboratories.

The ATHENA trial also leaves some intriguing questions unanswered:

- **How do we transition women into the new screening strategy?** Many women today still undergo cytology screening with

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HPV 16 and 18 account for approximately 70% of all cervical cancer cases

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reflex HPV testing, as appropriate, and an increasing number of women aged 30 and older undergo cotesting with both cytology and HPV testing. When should they begin screening in a primary HPV testing setting? And what screening intervals will be recommended? If a woman already has been screened with cytology, how should she transition into and at what interval should she begin primary HPV screening?

- **How should we manage women's care after the first round of primary HPV testing?** The ATHENA trial so far only has outcomes data after one round of HPV testing. While some data are available from Europe, we do not know what happens after two or three rounds of screening with primary HPV testing in a large US-based cohort. We clearly will be identifying and treating many women with preinvasive disease from screening after one round of testing, at a rate likely higher than with cytology alone—a good thing. We also likely will be reducing the number of unnecessary colposcopies for cytology that are not related to hrHPV.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Screening women using the cobas HPV test as a primary screen will require considerable education of providers and patients to explain how this change will affect how a woman will be managed after being screened for cervical cancer. Though much remains to be determined about this new cervical cancer screening paradigm (eg, logistics, timing, use of secondary tests), it should reduce the number of screening tests and colposcopies necessary to detect clinically relevant disease.

Updated ASCCP guidelines emphasize equal management for equal risk

Massad LS, Einstein MH, Huh WK, et al; 2012 ASCCP Consensus Guidelines Conference. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis. 2013;17(5 Suppl 1):S1–S27.

In formulating this latest set of guidelines for the management of abnormal cervical cancer screening tests and cancer precursors, the ASCCP led a conference consisting of scientific stakeholders to perform a comprehensive review of the literature. Also, with study investigators at Kaiser Permanente Northern California (KPNC) and the National Cancer Institute, the guidelines panel also modeled and assessed data on risk after abnormal tests from almost 1.4 million women followed over 8 years in the KPNC Medical Care Plan—this cohort has provided us with "big data."

The sheer size of the Kaiser Permanente population made it possible for the ASCCP-led panel to validate its previous guidelines or to modify them, where needed. It also made risk-based stratification possible for even rare abnormalities and clinical outcomes.

Although findings from the KPNC population may not be fully generalizable to the US population as a whole, they enhance our understanding of the optimal management of abnormal cervical cancer screening tests and cancer precursors. More widely dispersed study cohorts on a similar scale in the United States are unlikely in the near future.

Several significant modifications

Although the ASCCP reaffirmed most elements of its 2006 consensus management guidelines, it did make a number of changes:

- Women who have ASC-US cytology but

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Women who have ASC-US cytology with a negative HPV test should be followed with cotesting at 3 years rather than 5 years before returning to regular screening

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Management of cervical abnormalities by 5-year risk of CIN 3+

Column 3 orders risks from all cytologies and column 6 orders risks for each cotest. Column 7 gives the current ASCCP management guideline. Managing cotest results by these benchmarked implicit risk thresholds ensures equal management for equal risks.

Cytology result			Cotesting result			Current management based on cytology only (7)
Cytologic finding (1)	Frequency (2)	5-year risk of CIN 3+ (3)	HPV/Cytology (4)	Frequency (5)	5-year risk of CIN 3+ (6)	
SCC	0.01%	83%	HPV+/HSIL	0.20%	50%	Immediate colposcopy
HSIL	0.20%	48%	HPV+/AGC	0.05%	34%	
			HPV–/HSIL	0.01%	29%	
			HPV+/ASC-H	0.12%	25%	
ASC-H	0.17%	18%	HPV–/ASC-H	0.05%	3.8%	
AGC	0.21%	8.7%	HPV–/AGC	0.16%	1.1%	
LSIL	0.92%	5.3%	HPV+/ASC-US	1.10%	6.8%	
			HPV+/LSIL	0.77%	6.2%	
ASC-US	2.70%	2.6%	HPV+/Pap–	3.50%	4.5%	Return in 1 year
			HPV–/LSIL	0.18%	2.1%	
Pap–	95.80%	0.26%	HPV–/ASC-US	1.80%	0.45%	Return in 3 years
N/A	N/A	N/A	HPV–/Pap–	92.1%	0.08%	Return in 5 years

Source: Katki HA, et al. Benchmarking CIN 3+ risk as the basis for incorporating HPV and Pap cotesting into cervical screening and management guidelines. J Low Genit Tract Dis. 2013;17(5 Suppl 1):S28–S35.

AGC = atypical glandular cells; ASC-H = atypical squamous cells with a likelihood of high-grade cytology; ASC-US = atypical squamous cells of undetermined significance; CIN 3+ = cervical intraepithelial neoplasia grade 3 or higher; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion; N/A = not applicable; Pap– = negative Pap test; SCC = squamous cell carcinoma.

test HPV-negative now should be followed with cotesting at 3 years rather than 5 years before they return to routine screening.

- Women near age 65 who have a negative finding on ASC-US cytology and HPV testing should not exit screening.
- Women who have ASC-US cytology and test HPV-positive should go to immediate colposcopy, regardless of hrHPV results, including genotyping.
- Women who test positive for HPV 16 or 18 but have negative cytology should undergo immediate colposcopy.
- Women aged 21 to 24 years should be managed as conservatively and minimally invasively as possible, especially when an abnormality is minor.
- Endocervical curettage reported as CIN 1 should be managed as CIN 1, not as a positive endocervical curettage.
- When a cytologic sample is unsatisfactory, sampling usually should be repeated, even when HPV cotesting results are known. However, negative cytology that lacks sufficient endocervical cells or a transformation zone component usually can be managed without frequent follow-up.

Equal management should be performed for abnormal tests that indicate equal risk

The ASCCP-led management panel unanimously agreed to several basic assumptions

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

The updated ASCCP guidelines are inherently complex, but their complexity arises from a large body of high-quality prospective data from a large population of women. Equal risk should result in equal management of cervical screening test abnormalities. Practitioners need not feel obligated to memorize the guidelines, owing to the availability of algorithms for specific findings in specific populations at the ASCCP Web site (www.asccp.org/consensus2012). Apps also are available for the iPhone, iPad, and Android.

in formulating the updated guidelines. For example, they concurred that achieving zero risk for cancer is impossible and that attempts to achieve zero risk (which typically means more frequent testing) may cause harm. They also cited the 2011 American Cancer Society/ASCCP/American Society for Clinical Pathology consensus screening document, which stated: "Optimal prevention strategies should identify those HPV-related abnormalities likely to progress to invasive cancers while avoiding destructive treatment of abnormalities not destined to become cancerous."[1]

The panel also agreed that CIN 3+ is a "reasonable proxy for cancer risk." When calculating risk, the KPNC data were modeled for all combinations of cytology and HPV testing, using CIN 3+ for many of the outcomes, and when outcomes were rare, using CIN 2+. The theme of equal management for equal risk was the rationale behind the management approaches detailed in the **TABLE** on page 56. Risks were deemed to be low and return to normal screening was recommended when the risks were similar to the rate of CIN 3+ 3 years after negative cytology or 5 years after negative cotesting. However, immediate colposcopy was recommended when the 5-year risk of CIN 3+ for the combination of cytology and hrHPV testing, when indicated, exceeded 5%. A 6-month to 12-month return

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(intermediate risk) is indicated with a risk of CIN3+ of 2% to 5%.

An emphasis on avoiding harms

Abnormal findings at the time of cervical cancer screening can lead to a number of harms for the patient, including anxiety and emotional distress, particularly when colposcopy is necessary, as well as time lost from home and work life. For this reason, the guidelines panel emphasized that colposcopy and other interventions should be avoided when the risk of CIN 3+ is low and when the cervical screening abnormalities are likely to resolve without treatment.

However, women who experience postcoital bleeding, unexplained abnormal vaginal bleeding, pelvic pain, abnormal discharge, or a visible lesion should be managed promptly on an individualized basis.

Long-term effects of HPV vaccination are unknown

Among the areas that remain to be addressed are the unknown effects of widespread prophylactic HPV vaccination over the long term. We also lack full understanding of whether and how HPV vaccination will alter the incidence and management of cytologic and histologic abnormalities. Given the low rates of vaccination against HPV in the United States at present, this will need to be re-evaluated in the future.

Reference

1. Saslow D, Solomon D, Lawson HW, et al;ACS-ASCCP-ASCP Cervical Cancer Guideline Committee. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. CA Cancer J Clin. 2012;62(3):147–172.