Abstract

Adoption of new cervical cancer screening guidelines by the American Cancer Society and others in 2012 required new guidelines for the management of abnormal screening and follow-up tests. The American Society for Colposcopy and Cervical Pathology led a consensus conference including 26 professional organizations and agencies that developed new management guidelines. These guidelines are risk-based and derive from analysis of approximately 1.4 million women screened by the Kaiser Permanente Northern California medical group, with risk assessment in collaboration with NCI. New guidelines provide guidance for the conservative management of young women, for women with unsatisfactory Papanicolaou (Pap) tests and tests with limited transformation zone component, for women with discordant Pap and human papillomavirus (HPV) cotesting results, and for the incorporation of HPV 16/18 genotyping results into management decisions. The increasing number of available tests and the increasingly nuanced understanding of risk mean that clinicians will need to offset the complexity of diagnostic and treatment algorithms with technology and specialization. (J Natl Compr Canc Netw 2014;12:349–353)

In cervical cancer prevention, as with modern oncology, new technology is increasing the complexity of management decisions. The core paradigm for cervical cancer prevention has not changed over the past 65 years: diagnose and destroy cancer precursors and early cancer before metastasis can result in morbidity and mortality.¹,² Destructive techniques have changed little since cone biopsy was developed as fertility-sparing treatment for carcinoma in situ, with cryotherapy, laser ablation, and loop excision merely variations in technique for destruction of the metaplastic cervical transformation zone.

What has changed, and what has increased the complexity of cervical cancer prevention algorithms, is the increasing sophistication of diagnostics designed to improve the sensitivity of precancer detection. The Papanicolaou (Pap) test is more than 70 years old,¹ but in 1988 the Bethesda System introduced new categories of abnormality, such as atypical squamous cells of undetermined significance (ASC-US) and low-grade squamous intraepithelial lesion (LSIL), that usually are not associated with precancer yet are common enough to account for most precancers diagnosed in screened populations.³,⁴ Accurate tests for human papillomavirus (HPV), the viral cause of cervical cancer, allow even earlier identification of cervical disease, although with an even less frequent association with precancer.⁵

Increasing sensitivity has resulted in diminished specificity. Epidemiologic and natural history studies led to the realization that HPV infections are nearly ubiquitous in sexually active humans,⁶ yet usually regress after immune recognition.⁷,⁸ Destructive cervical therapies may increase the risk for preterm delivery.⁹ Minimizing harm from overdiagnosis of self-limited cervical HPV disease that is not fated to become cancer requires balancing of the sensitivity and specificity of cervical diagnostics.

Colposcopy was developed in the 1920s and has since been the triage test used to improve diagnostic specificity after abnormal screening cytology. However, colposcopy is relatively invasive and costly and can be painful, and recent research has shown that the sen-
sitivity of colposcopy is limited.10,11 Other tests are available or in development to improve specificity, including tests for HPV types 16 and 18.3

Given the paucity of comparative trials that might allow clinicians to select among screening and triage options, the complexity of management algorithms must increase to allow for various choices. Cytology alone, cotesting with cytology and HPV testing, and, in the future, HPV testing alone can identify women with different levels of precancer risk and each require distinct algorithms for management. Cytology reporting includes a spectrum of grades of abnormality, each with different risk. Adding HPV testing doubles the risk, and optional HPV typing further increases the complexity of management. For some abnormalities, colposcopy or observation with serial cytology or cotesting are reasonable options, and in some cases treatment or observation are similarly reasonable, depending on patient characteristics and values. As new molecular diagnostics gain approval, including new HPV tests, proliferation markers, and differentiation markers, the complexity of management strategies promises to increase.

Traditional processes for guidelines development are inadequate to meet the challenge of increasing complexity in cervical cancer prevention. Federally funded prospective comparative trials, such as the ASCUS/LSIL Triage Study (ALTS), are unlikely in the current fiscal environment. In the absence of these trials, expert opinion is insufficient to distinguish among potential management paths.

Instead, the counterweight to the proliferation of screening and triage options in cervical cancer prevention is the development of risk-based guidelines using “big data.” In the United States, clinicians with the Kaiser Permanente Northern California (KPNC) medical group have screened more than a million women with Pap and HPV cotesting since 2004. Almost 400,000 young women have been screened with Pap tests alone. Follow-up results, including diagnoses of cervical intraepithelial neoplasia (CIN) and cancer, have been downloaded to a de-identified database. Computer analysis of this database has allowedstatisticians at the NCI to determine risks across time for disease end points such as CIN2 or worse (CIN2+), CIN3 or worse (CIN3+), and cancer after various screening and follow-up findings.12

Translating observed risks to management guidelines requires determination of the acceptable threshold for intervention, which in turn depends on the risk of cervical disease after various tests and test combinations. Preventing all cervical cancer is not possible. Most cancers in women younger than 25 years and some cancers that fail to exfoliate or that originate in the endocervix are not preventable through screening.13 Determining the threshold for intervention has evolved from historical precedent and expert opinion. In 2012, screening guidelines from the US Preventive Services Task Force and from the American Cancer Society and others advised screening for cervical cancer using Pap tests at 3-year intervals.14,15 At 5 years, the risk for CIN3+ after a negative Pap and HPV cotest is actually lower than the 3-year risk after a negative Pap. This led to recommendations for a 5-year screening interval for women undergoing cotesting between the ages of 30 and 65 years.

Similar concepts govern the assignment of benchmarks for triage and surveillance tests. For example, in the United States, colposcopy has been accepted as the standard management for women with Pap test results indicating LSIL, whereas women with ASC-US are usually triaged to colposcopy or surveillance based on HPV test results. The risk of CIN3+ in women with an HPV-positive ASC-US result is similar to that in women with LSIL. Using the principle of “similar management for similar risks,” women with HPV-positive ASC-US should undergo colposcopy. This strategy was validated by ALTS and incorporated into guidelines for cervical cancer screening and the management of CIN and adenocarcinoma in situ, developed under the leadership of the American Society for Colposcopy and Cervical Pathology (ASCCP) in 2001 and 2006.16,17 By extension, women with similar risk for CIN3+ based on other screening or triage tests also should undergo colposcopy.

The KPNC database does not include newer diagnostic and treatment tests, such as HPV genotyping. However, it does allow calculation of cervical disease risk among various age groups after Pap and HPV tests, and after colposcopy and surveillance testing. Combining these results with published findings from validation studies for newer tests allows risk estimations for currently available cervical cancer prevention tests.

In September 2012, ASCCP convened a conference of representatives from 26 professional societies, governmental institutes and agencies, and
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nonprofit organizations. Before the meeting, representatives convened on conference calls and online to consider evidence from an analysis of the KPNC database by NCI staff. Results were considered in the context of published literature, which was also used to guide the incorporation of HPV genotyping into resulting guidelines. The result is the first risk-based set of cancer prevention guidelines. These guidelines should serve as an example for future risk-based guidelines for other cancers.

With the increasing use of HPV testing to assess cervical cancer risk in screening populations, consensus conference participants emphasized the importance of validation for HPV assays. Evidence from studies using one assay may not translate when other assays with different sensitivity and specificity cut points are used. Test validity should have been documented by FDA licensing and approval or publication in peer-reviewed scientific literature. Only testing for high-risk types is acceptable for patient management, and testing for low-risk types has no role in cervical cancer prevention strategies.

In the United States, assay approval is the province of the FDA. In developing guidelines, participants at the ASCCP guidelines conference sought to provide management pathways for clinicians who elect to use particular assays. No endorsement is intended.

The current ASCCP guidelines contain several changes from previous versions. ASCCP had released guidelines on how to manage Pap test results that are unsatisfactory or limited by an absent or insufficient transformation zone component, most recently in 2008. However, these guidelines were developed before the adoption of cotesting in screening. In addition, as the product of ASCCP’s Pathology Committee, they were based on evidence review but had not been subjected to a consensus development process. New guidelines indicate that Pap test results that are unsatisfactory require repeating even if they are HPV-negative. This guideline was adopted because current HPV tests lack confirmatory tests for squamous cellularity, and clinicians may not be confident that sufficient cervical cells have been sampled to ensure that the HPV test is a true-negative. However, women with Pap tests reported as satisfactory and negative but lacking a transformation zone component can be managed without an early repeat, because the risk for CIN3⁺ in these women is not increased compared with women whose results showed endocervical cells.

Screening with Pap and HPV cotesting has doubled the number of possible test results requiring individualized management. Across all Pap test results, women with high-risk HPV are at a higher risk for CIN3⁺ than those with negative HPV test results; however, risk is only sometimes sufficiently altered by HPV test results to change management. Because the risk for CIN3⁺ decreases with age, older women with HPV-negative LSIL may be managed the same as those with HPV-negative ASC-US. However, treatment or colposcopy is indicated for all women with high-grade squamous lesions, regardless of HPV result.

In 2012, an ASCCP consensus conference on cervical cancer screening, co-sponsored with the American Cancer Society and the American Society of Clinical Pathologists, recommended 5-year follow-up for women with positive ASC-US Pap tests with negative HPV results. This was based on a finding that risk of precancer in the KPNC cohort approximated that of women with negative Pap/HPV cotesting results. However, updated KPNC cohort results with a larger sample presented at the management conference indicated that risk after an HPV-negative ASC-US result was higher than that after negative cotesting. Follow-up with cotesting at 3 years rather than 5 is now recommended.

Results from ALTS showed that women with ASC-US could be managed with colposcopy, HPV triage with colposcopy for those testing HPV-positive, or 2 Pap tests 6 and 12 months after the ASC-US result. The KPNC results showed that current risk for CIN3⁺ after an ASC-US Pap is below the agreed threshold for colposcopy. Women with ASC-US should be managed with HPV triage, although when HPV testing is not available, a repeat Pap test in a year is acceptable.

Genotype tests to distinguish HPV types 16 and 18 from other high-risk HPV types that convey a lower risk for CIN3⁺ over time are now available. Participants at the ASCCP consensus conference found that the presence of HPV 16 or 18 in women with negative Pap tests increases their risk for CIN3⁺ sufficiently to merit colposcopy. Among women with Pap tests read as ASC-US or worse, risk for CIN3⁺ is lower in those with non-HPV 16/18 high-risk types than for those with HPV 16/18, but is still sufficient
to justify colposcopy. Because results do not alter management, the consensus conference agreed that HPV 16/18 genotyping should not be used to further assess women with ASC-US Pap test results.

HPV-negative ASC-US results are also not sufficiently reassuring to allow women to stop undergoing screening at age 65 years. KPNC data show that although dysplasia risk is low after HPV-negative ASC-US results in that group, cancer risk is disproportionately high. Women who reach 65 years of age with an HPV-negative ASC-US result should be retested in 3 years and should continue surveillance until they have 2 consecutive negative cotests or 3 consecutive negative Pap tests.

In 2006, ASCCP developed conservative management guidelines for adolescents with abnormal Pap test results and CIN. These guidelines became obsolete when more recent screening guidelines recommended deferring initiation of screening until age 21 years. However, similar principles led to the development of similar guidelines for women 21 to 24 years of age. Risk for cervical cancer in that age group is low, many women with high-grade abnormalities will have transient lesions destined to regress in response to host immune recognition of HPV, and treatment increases risk for preterm delivery in future pregnancies.

Cotesting for screening is recommended only for women 30 to 65 years of age. For younger women, many ASCCP management guidelines recommend strategies that use Pap testing alone, without HPV testing, to determine risk during follow-up. Cotesting was incorporated into follow-up strategies in some algorithms for women 25 to 29 years of age to minimize complexity, because cancer risk begins to increase in this age group.

For women 30 to 65 years of age, current guidelines minimize Pap-only pathways after colposcopy, on the principle that HPV testing is available to most US practices that offer colposcopy. Cotesting reduces the frequency of subsequent follow-up visits. Although risk is low for women with HPV-negative ASC-US in follow-up schemes, consensus conference participants voted to avoid making algorithms even more complex and recommended colposcopy if either component is abnormal for most cotest surveillance strategies.

Current guidelines have some limitations. Women contributing to the KPNC database may not be representative of all US populations, and sites that have documented a higher or lower 5-year CIN3+ risk for various Pap grades may use more- or less-stringent management. However, perceived “high risk” may not be sufficient to justify deviation from national consensus guidelines. The KPNC database covers only an 8-year span, and the long-term risks are unclear. This includes uncertainty about whether high-risk women, such as those treated for CIN3, can ever return to routine screening with 3-year Pap testing or 5-year cotesting. The ASCCP guidelines allow return to routine screening after 3 negative cotests at 12, 24, and 60 months, but this is a CIII recommendation, based on expert opinion. Potential harms are not quantified in the KPNC database and were not analyzed for consideration during guidelines development. Cervical disease risk after some uncommon events, such as 3 consecutive HPV-negative ASC-US results, cannot be calculated even from a database including 1.4 million women. How to incorporate tests not included in the KPNC database, such as genotyping tests and tests still in development, depends on expert interpretation of trial results in smaller groups and may be controversial. Thresholds for intervention are based on assumptions of harm, such as the risk of preterm delivery after cervical disease treatment, and these harms are not well quantified and may be negligible in US women commonly treated with shallow excisions.

The NCCN Cervical Cancer Screening Panel has endorsed the ASCCP management guidelines. Links to guidelines and algorithms are available on the NCCN Web site at NCCN.org. Also see the NCCN Guidelines Insights for Cervical Cancer Screening, in this issue.

The new ASCCP guidelines have been criticized for their complexity, but information technology is enabling clinicians in many fields to manage complexity. Algorithms are available to guide clinicians through decision steps in managing women in various age groups with varying combinations of initial and follow-up test results. These algorithms have been downloaded almost 19,000 times during the first 10 months after release. Future iterations of the guidelines promise to be even more complex as management options grow more diverse. In cervical cancer prevention, as in all oncology, clinicians will need to increasingly embrace information technology to manage complex management options.
References


