Human papillomavirus (HPV), the most common sexually transmitted virus, is the etiologic agent responsible for more than 99% of all cervical cancers. Of the more than 100 HPV genotypes, only 14 are considered high risk for progression of cervical disease. Of these 14 HPV genotypes, types 16, 18, and 45 are associated with approximately 80% of all invasive cervical cancers. These three types are found in 75% of all squamous carcinoma cases, with type 16 being the most common. These three types also are found in 80%-94% of all adenocarcinoma cases, with types 18 and 45 being the most common. In women infected with HPV types 16 and/or 18, compared with those infected with other high-risk types, the cumulative risk of developing cervical cancer is 10 times higher.\(^1,2\)

HPV co-testing as an adjunct to cervical cytology

The goal of cervical cancer screening is to identify and treat high-grade cancer precursors, avoid potentially harmful diagnostic testing and treatment, and minimize healthcare costs. The ideal screening strategy would provide a level of sensitivity to minimize missing disease as well as a level of specificity to minimize false positives.\(^3,4\)

Cervical cytology (i.e., the Pap test) is used to examine a sample of cervical cells to determine whether any abnormalities exist that could signal the presence of cancer precursors. Screening with the Pap test has been very successful in lowering cervical cancer morbidity and mortality in countries where this test is readily accessible. Although the Pap test identifies women with cancer precursors, it does not identify women at risk for developing these precursors. HPV tests use molecular technology to detect the presence of high-risk HPV (hrHPV) types that can cause pre-cancerous abnormalities in cervical cells and that, when persistent, can lead to progression of cervical disease. In 2003, the \textit{digene} HPV Test (manufactured by Qiagen), the first hrHPV test, was approved by the FDA for co-testing with cervical cytology and for triage of mild cytologic abnormalities. Today, several FDA-approved HPV tests are available (e.g., Cervista™ HPV HR and Genfind™ DNA Extraction Kit, Cervista™ HPV 16/18, cobas HPV Test, APTIMA® HPV Assay), with more in the pipeline.

In 2012, the American Cancer Society (ACS), the American Society of Colposcopy and Cervical Pathology (ASCCP), and the American Society for Clinical Pathology (ASCP) published updated cervical cancer screening guidelines to include revised recommendations for the use of co-testing with cytology and hrHPV testing.\(^4\) Co-testing is recommended every 5 years for women aged 30-65 years. For women aged 21-29 years, the recommendation is for screening every 3 years with cytology alone.\(^4\)

Table 1 shows the 2012 guideline recommendations for management of women with abnormal cytology and/or HPV test results when using co-testing.\(^4\) Table 2 lists management recommendations after the subgroup of women with cytology-negative, HPV-positive results undergo 12-month repeat co-testing.\(^5\)

HPV testing as primary screening for cervical cancer

During the 2012 guideline update process, there was discussion of the potential utility of HPV testing alone as primary screening for cervical cancer—to be used as an alternative to primary screening with cytology or co-testing with cytology and HPV testing. Although HPV testing alone as a primary screening approach was not recommended at the time of the 2012 updates,\(^4,6\) the body of evidence to support primary screening with hrHPV testing has grown since that time.

Findings from the Addressing the Need for Advanced HPV Diagnostics (ATHENA) study (2008-2012) have provided substantial support for the safety and effectiveness of HPV testing when used as a primary screening tool for cervical cancer.\(^3,7\) In 2014, the FDA approved the first HPV test for an additional indication as a primary screen for cervical cancer for women aged 25 years or older.\(^8\) The approved test (cobas® HPV test) detects 12
The ATHENA study was a 3-year prospective investigation designed to compare nine cervical cancer screening strategies with the screening standard of cytology with HPV triage of atypical cells of undetermined significance for the detection of high-grade cervical disease. Between 2008 and 2009, 47,208 women aged 21 years or older presenting for routine cervical cancer screening were enrolled. In the baseline phase of the study, participants had both cytology and HPV testing. Women who had a positive Pap test result or whose cervical cells screened positive for hrHPV, as well as a subset of women whose Pap test and HPV test results were both negative, underwent a colposcopy and cervical tissue biopsy. All biopsy results were compared with the Pap test and the HPV test results.

Participants who had biopsy-confirmed cervical intraepithelial neoplasia (CIN) 2 or a more severe result in the baseline phase exited the study. The remaining 41,955 participants aged 25 years or older were assigned to a 3-year follow-up phase that concluded in December 2012. The lower limit of 25 years of age was used for the follow-up phase because current U.S. guidelines recommend against HPV testing for any reason below this age.

The 3-year follow-up phase of the ATHENA study provided findings on several parameters evaluating the effectiveness and safety of hrHPV testing as a primary screening method for cervical cancer. These parameters included comparisons of cumulative risk, cumulative incidence rates, sensitivity, specificity, and negative predictive value.

Women who were hrHPV negative at baseline had a lower 3-year cumulative risk of CIN3+ than did women with negative baseline cytology. Over the 3-year follow-up, CIN3+ was identified in 34 women with negative hrHPV at baseline, as compared with 164 women with baseline-negative cytology.

HPV genotype status at baseline was predictive for CIN3+ during the course of the follow-up (cumulative incidence rate). In the baseline portion of the study, CIN3+ was identified in 17.8% of HPV 16-positive women. At 3 years, 25.2% of women who were HPV 16 positive at baseline had CIN3+ identified. In women with hrHPV genotypes other than 16/18 at baseline, the 3-year cumulative incidence rate for CIN3+ was 5.4%. Women who were HPV type 18 positive at baseline had a 3-year cumulative incidence rate that was in between those with HPV 16 and those with the 12 other high-risk genotypes. In the 3 years of follow-up, the cumulative

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**Table 1. Management of women with negative or abnormal co-testing results**

<table>
<thead>
<tr>
<th>Cytology result</th>
<th>HPV test result</th>
<th>Recommended management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Routine co-testing in 5 years</td>
</tr>
</tbody>
</table>
| Negative        | Positive        | Option 1: Repeat co-test in 12 months  
Option 2: Reflex testing for HPV genotypes 16/18. If positive, colposcopy. If negative, co-test in 12 months. |
| ASC-US          | Negative        | Routine co-testing in 5 years |
| ASC-US          | Positive        | Colposcopy |
| LSIL            | Negative        | Repeat co-testing in 12 months (preferred)  
Colposcopy acceptable |
| LSIL            | Positive        | Colposcopy |
| HSIL            | Negative or positive | Colposcopy or immediate LEEP |

ASC-US: atypical squamous cells of undetermined significance; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LEEP, loop electrosurgical excision procedure; LSIL, low-grade squamous intraepithelial lesion.
incidence rate of CIN3+ in women who were cytology negative at baseline was more than twice that of women who were hrHPV negative at baseline.

Over 3 years, hrHPV primary testing had a higher sensitivity for detection of CIN3+ than did either cytology or co-testing; adjusted sensitivities were 76.1%, 47.8%, and 61.7%, respectively.7 Cytology alone had the highest specificity (97.1%) and hrHPV primary testing had the lowest specificity (93.5%). High-risk HPV primary testing had a significantly higher negative predictive value (probability that a person with a negative test result truly does not have the condition) than did cytology.

The ATHENA study results confirmed findings of other prospective, randomized screening studies conducted primarily in Europe. HPV primary screening increases sensitivity. Cytology and co-testing do not significantly increase protection against development of CIN2+ or CIN3+ compared with HPV primary screening.7

As a consequence of the findings from the ATHENA study and the FDA approval of an existing HPV test for primary screening, a panel of 13 experts, including representatives from the ASCCP, the ACS, the ASCP, the Society of Gynecologic Oncology (SGO), and the American Congress of Obstetricians and Gynecologists (ACOG), convened to consider interim guidance for primary screening using hrHPV testing.6 The panel reviewed the data from the ATHENA study, along with data from the other European randomized controlled screening trials, and concluded that high-risk HPV primary screening was at least as effective as, and possibly superior to, cytology at the same screening intervals in currently accepted screening recommendations in the U.S. A consensus was reached that hrHPV screening can be considered as an alternative to current U.S. cytology-based cervical cancer screening methods. Cytology alone and co-testing remain the screening options specifically recommended in major guidelines.

In January 2015, the SGO and the ASCCP issued the Interim Guidance Report for the use of primary hrHPV testing for cervical cancer screening.6 The interim guidance document aims to provide information for healthcare providers who are interested in primary hrHPV testing and an overview of the potential advantages and disadvantages of this strategy, as well as to highlight areas in need of further investigation. Major recommendations in the interim guidance include age to begin use of primary hrHPV testing, screening interval, and management of positive hrHPV test results.

Primary hrHPV screening should not be initiated in women younger than 25 years old because, in this age group, progression to cancer from HPV infection is uncommon.6 Harms associated with colposcopy and related tests and treatments outweigh benefits. The interim guidelines apply to women aged 25-65 years.

The screening interval using hrHPV testing as the primary screen should be no sooner than every 3 years.6 (Few data are available to indicate the optimal screening interval for primary hrHPV screening.) Follow-up data in the ATHENA trial were restricted to 3 years among women with negative baseline screening results. The panel determined that insufficient prospective U.S. data exist to recommend screening intervals beyond 3 years.

Women who have a positive primary hrHPV screen should be triaged using a combination of genotyping specific for HPV 16 and 18 along with the 12 other

<table>
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<tr>
<th>Table 2. Management recommendations after the subgroup of women with cytology-negative, HPV-positive results undergo 12-month repeat co-testing5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cytology result</strong></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Negative</td>
</tr>
<tr>
<td>Negative</td>
</tr>
<tr>
<td>ASC-US or worse</td>
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ASC-US, atypical squamous cells of unknown significance; HPV, human papillomavirus.
hrHPV genotypes combined. Women who test positive for HPV 16 or 18 should be followed with colposcopy evaluation. Women who test negative for HPV 16 and 18 but positive for the combined 12 other hrHPV genotypes should be followed with a reflex cytology. The Figure depicts the recommended primary HPV screening algorithm.

Implications for nurse practitioners
The authors of the interim guidelines provide words of caution as we move forward. Regardless of the screening test we use, careful specimen collection technique and laboratory controls remain important, and false-negative results will continue to occur. In addition, no matter how good a test is, it will not benefit women who, for whatever reason, remain unscreened, underscreened, or lost to follow-up.

Comparative effectiveness studies are needed to evaluate projected number of lifetime screenings, colposcopies, and follow-up visits, with direct cost comparisons of screening strategies. Prospective studies are needed to understand the most appropriate screening intervals that will result in the lowest cancer risks.

Our leading organizations that have provided us with our current cervical cancer screening recommendations are continuously reviewing evidence. We will likely see updates in the near future.

References