The ASCCP Cervical Cancer Screening Task Force Endorsement and Opinion on the American Cancer Society Updated Cervical Cancer Screening Guidelines

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Abstract: The American Cancer Society (ACS) released updated cervical cancer screening guidelines in 2020 that endorse a shift in practice to primary human papillomavirus (HPV) screening in people with a cervix, beginning at ages of 25–65 years. When access to US Food and Drug Administration–approved primary HPV testing is not available, the ACS offers cotesting or cytology as acceptable alternative strategies but suggests that these testing modalities may be excluded from future iterations of the guidelines. The ASCCP recognizes the benefits and risks of primary HPV cervical cancer screening while acknowledging the barriers to widespread adoption, including implementation issues, the impact of limited HPV vaccination in the United States, and inclusion of populations who may not be well represented on primary HPV screening trials, such as underrepresented minorities. The ASCCP endorses the 2018 US Preventive Services Task Force Recommendation Statement and supports the ACS cervical cancer screening guidelines. Most importantly, the ASCCP endorses any cervical cancer screening for secondary prevention of cervical cancer and recommends interventions that improve screening for those who are underserved or unscreened.

Key Words: cervical cancer screening, cervical cancer, ASCCP

In 2012, the American Cancer Society (ACS), ASCCP, and American Society for Clinical Pathology published updated screening guidelines that were most notable for extending the screening interval to 3 or 5 years and including high-risk human papillomavirus (hrHPV) testing and genotyping with cytology as a cotest.1 The US Preventive Services Task Force (USPSTF) published its cervical cancer screening recommendations (see Table 1) in 2018. Although similar to the 2012 screening guidelines, these recommendations included the option to screen with HPV testing alone with reflex to cytology where appropriate (primary HPV testing) and reiterated the benefits of longer screening intervals in low-risk individuals.2 The biggest driver of the high positive and negative predictive values of cotesting is the HPV test; although cytology alone provides the current snapshot for disease, HPV testing predicts not only the current disease but also the future disease. Cotesting has also had broader clinical adoption, as the workflow is similar to reflex HPV testing for atypical squamous cells of undetermined significance cytology.

Current data support the efficacy and efficiency of primary HPV testing alone as a cancer screening strategy—while recognizing the implementation challenges—as well as management guidelines that recommend reflex to cytology after a positive non-HPV 16/18 hrHPV result.3,4 There are currently 2 HPV tests approved by the Food and Drug Administration (FDA) for use in primary HPV screening—as a sole test, without cytology. However, uptake of this screening strategy has been slow in the United States since the first approval in 2014 (see Table 2).5

The ACS guidelines published in 2020 (see Table 1) offer the same 3 options but with a strong recommendation to screen with primary HPV testing. The ACS recommends beginning screening in people with a cervix at average risk at age of 25 years and offers continued cotesting as an acceptable strategy where primary HPV testing is not available, while suggesting cotesting and cytology alone may be excluded in future guidelines.6 The ASCCP recognizes the need to transition to primary HPV screening and acknowledges that logistical considerations surrounding implementation, the impact of limited HPV vaccination in the United States, and inclusion of populations who may be marginalized are necessary and must be prioritized. Recent pushes for self-sampling of HPV might increase such access, if found to be comparatively effective in the United States and approved by the FDA. This article discusses the ASCCP position and response to these guidelines.

ISSUES WITH IMMEDIATE ADOPTION OF PRIMARY HPV SCREENING

Practical Issues

Implementation of a nationwide transition to primary HPV testing presents a variety of practical concerns. As with any new screening modality, the ASCCP expects that there will be barriers to overcome to achieve full access to primary HPV testing.1 Private and public laboratories need to adapt workflows and acquire new equipment, which requires allocating funds for both capital expenses and human resources to operationalize the new screening strategy. In addition, health care systems, private offices, and community-based health centers must coordinate with laboratories and payers to implement HPV primary screening with correct new codes for using cytology as a reflex test and billing with potential payment restrictions in some settings. Possibly the most challenging is the reluctance of providers and patients to quickly adapt to screening with primary HPV testing. Thus, a transition period with an overlap of acceptable screening methods needs to be in place until screening with primary HPV testing is seamlessly covered by both commercial and governmental payers, embraced nationally by providers and patients, and does not exclude institutions unable to make a rapid change in their workflow and operations.

While the ACS guidelines recommend implementation of primary HPV screening, they also acknowledge the time required for the transition.7 The 2012 guidelines included HPV cotesting and increased the testing interval based on the presence or absence of HPV results.8 While this was a change in practice from prior iterations of screening guidelines, the 2012 algorithms still included a combination of cytology and HPV testing, unlike the current suggested shift in practice to HPV as a standalone screening test. Despite utilization of the same tests (cytology and HPV testing) in the 9 years since release of the 2012 screening guidelines, health care providers and patients have demonstrated reluctance...
to accept an increase in the screening interval to 5 years with cotesting. Other aspects of these recommendations for screening have also been slowly and imperfectly adopted, despite expanded educational efforts and outreach.\textsuperscript{4,11} In 2017, a supplemental survey of the American College of Pathologists PAP Education Program queried laboratory participants about the use of primary HPV testing and found that 59.4% did not offer testing, despite FDA approval 3 years prior.\textsuperscript{12}

In addition to implementation issues, the unprecedented global pandemic has exposed financial challenges to health care at this time and rendered health care systems financially devastated.\textsuperscript{13} The cost and personnel burdens of transitioning to primary HPV screening on hospitals/medical centers, public health agencies, and independent laboratories are considerable and timely, and implementation may not be feasible because of the financial state and focus of the medical health system in the wake of COVID-19.\textsuperscript{13} The transition to primary HPV testing is expected to be a slow process, allowing health systems the opportunity to make the appropriate changes to convert to primary HPV testing for cervical cancer.\textsuperscript{2}

**Impact of HPV Vaccination**

Since the mid-20th century, secondary prevention has yielded remarkable reductions in cervical cancer cases and deaths in the United States by screening, detecting, and treating cervical cancer precursors. By the dawn of the 21st century, the etiologic role of hrHPV in the natural history of cervical cancer and its precursors was established, allowing primary prevention of cervical and other HPV-related cancers to supplement and eventually supersede the benefit of secondary prevention efforts. However, despite availability of HPV vaccination in the United States since 2006, most adults have not been vaccinated. In 2018, 39.9% of adults in the United States (53.6% of women) had received 1 or more doses of HPV vaccine, and only 21.5% (35.3% of women) received the recommended number of doses.\textsuperscript{14,15}

Studies looking at the real-world, population-level impact of immunization demonstrate significant reduction in rates of cervical intraepithelial neoplasia grade 2 (CIN 2+)\textsuperscript{16} and countries with the highest rates of immunization enjoy the greatest direct benefit of vaccination as well as some evidence of herd immunity and cross-protection against HPV types not included in the vaccine.\textsuperscript{16,22} As HPV vaccine coverage improves and immunized cohorts mature to screening age, we anticipate that cervical cancer and its precursors will become increasingly rare such that any HPV infection identified during screening will be significant. Until then, we are moving through a time of transition as decreasing prevalence of cervical disease continues to cause false-positive screening tests and make the risks associated with poor positive predictive value of identifying CIN 2+ more likely.\textsuperscript{23,24}

As the US population gains primary protection against cervical cancer, new data will emerge to inform decisions about when to initiate screening, and we expect adjustments that favor a screening debut at older ages, as is recommended in the ACS guidelines. To integrate primary and secondary prevention, several countries with high immunization coverage have fully transitioned to primary HPV screening programs\textsuperscript{25} and report significantly higher detection rates for CIN 2+ in individuals screened with primary HPV testing (1%) than in those screened with cytology beginning at age of 21 years (0.1%).\textsuperscript{24} In addition, with subsequent screening rounds of primary HPV screening, the efficiency in identifying clinically relevant disease, as defined as the number of colposcopies to pick up 1 case of CIN 2+, has improved. The ASCCP endorses the continued acceptability of screening with cytology as per the USPSTF guidelines. As the HPV immunized population increases, there will be diminished benefits and increasing harms of screening with cytology.

**TABLE 1. Current Cervical Cancer Screening Strategies From the USPSTF and ACS**

<table>
<thead>
<tr>
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<tr>
<td>&lt;21 y old</td>
<td>No screening</td>
<td>No screening</td>
</tr>
<tr>
<td>21–25 y old</td>
<td>Cytology alone every 3 y</td>
<td>Preferred:</td>
</tr>
<tr>
<td>25–29 y old</td>
<td>• Cytology alone every 3 y</td>
<td>• Primary HPV\textsuperscript{a} test every 5 y</td>
</tr>
<tr>
<td>30–65 y old</td>
<td>• Cytology alone every 3 y</td>
<td>Acceptable:</td>
</tr>
<tr>
<td></td>
<td>• Cotesting\textsuperscript{b} every 5 y</td>
<td>• Cotesting\textsuperscript{b} every 5 y</td>
</tr>
<tr>
<td></td>
<td>• Primary HPV\textsuperscript{c} test every 5 y</td>
<td>• Cytology alone every 3 y</td>
</tr>
<tr>
<td>&gt;65 y old</td>
<td>No screening necessary after adequate negative prior screening\textsuperscript{d}</td>
<td>No screening necessary in those without a history of CIN 2+ or a more severe diagnosis in the past 25 y or cervical cancer ever</td>
</tr>
<tr>
<td>Prior total hysterecomy</td>
<td>No screening necessary in those without a history of high-grade cervical dysplasia or cervical cancer</td>
<td></td>
</tr>
<tr>
<td>Prior HPV vaccination</td>
<td>Follow age-specific recommendations</td>
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\textsuperscript{a}Food and Drug Administration–approved test.

\textsuperscript{b}Cotesting is cytology and hrHPV testing.

\textsuperscript{c}Acceptable where access to primary HPV testing is not available.

\textsuperscript{d}Adequate negative prior screening is defined as 2 consecutive negative primary HPV tests, 2 negative cotests, or 3 negative cytology tests within the last 10 years, and the most recent in the past 3–5 years.

**TABLE 2. Primary HPV Available Testing Platforms**

<table>
<thead>
<tr>
<th>Primary HPV test</th>
<th>Year FDA approved</th>
<th>Individual genotypes reported</th>
<th>Pooled genotypes reported</th>
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<tbody>
<tr>
<td>cobas HPV</td>
<td>2014</td>
<td>16, 18</td>
<td>31, 33, 35, 45, 51, 52, 56, 58, 59, 66, 68</td>
</tr>
<tr>
<td>BD Onclarity HPV</td>
<td>2018</td>
<td>16, 18, 31, 45, 51, 52</td>
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In addition, the ASCCP is concerned about subsets of people with a cervix in the United States who are less likely to be fully vaccinated when compared with the broader US population. Interestingly, there is a “reverse disparity” in HPV vaccine initiation, with data showing higher initiation rates within racial minority groups and those who have public insurance. Importantly, this reverse disparity does not extend to all historically underserved populations, e.g., those living in rural areas. Reasons for the reverse disparity where it exists are not entirely clear but may be attributable in part to more directive counseling by health care providers who care for underserved populations, as historically, these populations have less access to cervical cancer screening and a higher prevalence of cervical cancer, thus increasing the perceived risk of undetected HPV persistence and subsequent cancer. Federally funded initiatives, such as the Vaccines for Children program, may play a role in increasing vaccination among underserved populations, as they have expanded access to the expensive HPV vaccine for Medicaid recipients. However, the impact on the reverse disparity is mitigated by the fact that the Affordable Care Act requires vaccination coverage for individuals with private insurance. The reverse disparity may also reflect a more generalized refusal of all childhood vaccines among parents who are White, college-educated, and of higher economic status. Whatever the causes, although these populations have higher HPV vaccine initiation rates, vaccine series completion rates unfortunately lag, highlighting the work that is still needed to ensure that these vulnerable populations receive adequate protection against HPV. It will be important that patients from racial minority groups and rural areas, who have lower rates of vaccine completion and lower access to screening in general, be screened with HPV-based testing by cotesting until primary HPV testing is more widely available.

**Health Equity**

In 2017, there were 12,152 new cases of cervical cancer in the United States, with Hispanic/Latinx and Black patients having the highest rates of cancer deaths (2.6 per 100,000 people and 3.4 per 100,000 people, respectively) compared with their White counterparts (2.1 per 100,000). The racial and ethnic differences in cervical cancer incidence, morbidity, and mortality continue despite HPV vaccination, multiple screening modalities, and programs such as the Centers for Disease Control and Prevention-sponsored National Breast and Cervical Cancer Early Detection Program aimed at reducing cervical cancer in uninsured and underserved individuals. There are concerns from minority community advocates about primary HPV testing as the preferred screening modality for the prevention of cervical cancer in the new ACS guidelines, because of concerns about varied HPV subtypes detected in minority populations and protection conferred from the current HPV vaccines. Non-Hispanic Black and Latinx/Hispanic people have certain HPV genotypes not covered by the recommended/available nonavalent HPV vaccine. However, current HPV tests approved for primary HPV screening include these subtypes, and therefore, primary HPV testing should identify those at risk for cervical cancer who are screened.

The primary concern is to ensure that all populations have equitable access to screening and appropriate diagnosis and treatment of cervical precancer or cancer in a timely fashion. Randomized clinical trials have demonstrated the benefits of primary HPV testing for all people with a cervix as long as the recommended screening intervals are followed and subsequent management, should there be a need, is closely adhered to—especially in at-risk populations. In Black patients, lack of follow-up, inequities in treatment, and differences in cancer type are contributing factors for higher incidence and mortality from cervical cancer. Recent data suggest that when accounting for hysterectomy adjusted rates of cervical cancer over the age of 65 years, there seem to be significant disparities that show non-White populations continue to be at increased risk for cervical cancer. As more data become available, they should be considered when drafting future recommendations regarding the age to exit screening. Efforts to reduce the burden of cervical cancer in racial/ethnic minority groups should focus on providing equitable access to care that assures not only screening but also timely diagnosis and equal evidence-based treatment.

Cervical cancer “exit screening” guidelines stated by several organizations (the ASCCP, ACS, and American Society for Clinical Pathology) require 3 consecutive negative cervical cytology results or 2 consecutive cotesting results 10 years before cessation of screening with the last test having been performed within 5 years (the USPSTF). The 2019 ASCCP Risk-Based Management Consensus Guidelines recommend that patients with spontaneous regression or prior treatment of high-grade precancerous lesions be followed for at least 25 years, even if this extends beyond 65 years of age, the upper limit for screening. However, 13% of patients aged 65 years have not been properly screened; this number increases to 37.1% in women without a regular primary care provider. A Kaiser study revealed that most cases of invasive cervical cancer cases in patients older than 65 years were in those who did not meet criteria for exiting cervical cancer screening. Focusing policies and programs on efforts to ensure that patients meet appropriate criteria before they exit screening represents a concrete step toward reducing the burden of cervical cancer in racial/ethnic minority populations and others who are underserved.

**Additional Clinical Considerations**

In addition to the importance of appropriate exiting from screening (as detailed previously), there are a few clinical considerations that further stress the need for screening and application of sound clinical judgment. Cervical adenocarcinomas have been on the rise and historically are not detected as well by cytology alone as their squamous counterparts. As more providers focus on the shift to HPV-based screening is its superior ability to detect adenocarcinomas and their precursor lesions, adenocarcinoma in situ. As adenocarcinomas are often within the endocervical canal, the quality of the colposcopy for all who screen positive by HPV testing is of critical importance including the need for endocervical curettages when the squamocolumnar junction or the lesion is not fully visualized on colposcopy. We must also stress that patients with signs or symptoms suspicious for cervical cancer (abnormal uterine bleeding, postcoital bleeding, pelvic pain, etc), even with negative screening tests, should have a diagnostic evaluation as recommended by the ASCCP and The American College of Obstetricians and Gynecologists. Sound and conservative clinical judgment should always be used when applying a guideline to an individual patient for safety, as it is not possible to develop guidelines that will apply to all clinical situations.

**RECOMMENDATIONS AND CONCLUSIONS**

- The ASCCP endorses current cervical cancer screening guidelines for secondary prevention of cervical cancer and recommends that improving screening, including expanding access to those who are underscreened or unscreened, is the top priority for decreasing cervical cancer incidence, morbidity, and mortality in the United States.
- The ASCCP Cervical Cancer Screening Task Force endorses the USPSTF cervical cancer screening recommendations and supports the ACS cervical cancer screening guidelines.

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*Per the ASCCP Guideline Review Policy, clinical documents endorsed by ASCCP are considered official ASCCP clinical guidance. Additionally, ASCCP endorses the April 2021 ACOG Practice Advisory: Updated Cervical Cancer Screening Guidelines.

**Per the ASCCP Guideline Review Policy clinical documents supported by ASCCP denotes that ASCCP deems the document to be of educational value to its members, although ASCCP may not agree with every recommendation or statement in the document.
• The USPSTF recommendations include all screening modalities, providing flexibility that may benefit those who are marginalized, underinsured, or experiencing inequity and health disparities.

• The ASCCP recognizes the need to move toward primary HPV-based cervical cancer screening and acknowledges that it will take time to transition clinical and laboratory workflow and operations.

• The ASCCP no longer endorses its 2012 cervical cancer screening guidelines that do not include primary HPV screening.

• The combination of abnormal results that occur from either guidance should be managed using the 2019 ASCCP Risk-Based Management Consensus Guidelines.

• Patients with signs or symptoms suspicious for cervical cancer (abnormal uterine bleeding, postcoital bleeding, pelvic pain, etc.) should have a diagnostic evaluation even if screening tests are negative.

• Adequate prior cervical cancer screening with 10 years of negative results (3 consecutive negative cervical cytology results or 2 consecutive cotesting results) is required to exit from screening.

• Patients with spontaneous regression or prior treatment of high-grade precancerous lesions should be followed for at least 25 years even if this extends beyond 65 years of age—the upper limit for screening—as they are in active management.

REFERENCES


