CYTOPATHOLOGY EDUCATION AND TECHNOLOGY CONSORTIUM

_____2025

TO: United States Preventive Service Task Force

FROM: Cytopathology Education and Technology Consortium (CETC)*

**The CETC is an independent consortium of professional organizations involved in diagnostic cytopathology. The member organizations are the American Society of Cytopathology (ASC), the American Society for Clinical Pathology (ASCP), the American Society for Cytotechnology (ASCT), the College of American Pathologists (CAP), the International Academy of Cytology (IAC) and the Papanicolaou Society of Cytopathology (PSC). The representatives from each of the organizations are nationally recognized members of the cytopathology community.*

RE: Response to the 2024 USPSTF Draft Guidelines for Cervical Cancer Screening

We are writing to comment about the major Task Force recommendations below:

"The USPSTF recommends screening for cervical cancer every 3 years with cervical cytology alone in women ages 21 to 29 years and then every 5 years with clinician- or patient-collected high-risk human papillomavirus (HPV) primary screening in women ages 30 to 65 years. As an alternative to HPV primary screening for women ages 30 to 65 years, the USPSTF recommends continued screening every 3 years with cervical cytology alone or screening every 5 years with high-risk HPV testing in combination with cytology (cotesting)."

We are concerned that patient-collected Human papillomavirus (HPV) primary screening is considered equivalent to clinician-collected. The CETC believes there is insufficient long-term evidence to promote a 5-year screening interval for self-collected specimens. There is also insufficient language stressing the importance of utilizing platforms approved or cleared by the FDA for the specific indications of primary HPV screening and testing of patient self-collected specimens. The remaining Task Force recommendations for patients with a cervix younger than age 21, older than age 65, and patients who have had a hysterectomy are worded appropriately and are consistent with consensus guidelines published by other major organizations.

The Cytopathology Education and Technology Consortium (CETC) recommends that:

1. **Primary HPV screening of clinician and self-collected specimens should be performed only with testing platform(s) that are FDA-approved or cleared for those specific specimens. The draft recommendations should make this statement prominently, so this requirement is made clear to all ordering clinicians and testing laboratories.**
2. **The primary HPV patient (self) collection strategy should be recommended every 3 years until more long-term data are available. In addition, self-collection should only be used in average-**

risk individuals with a cervix who are asymptomatic (without vaginal bleeding or discharge). For individuals in the surveillance setting with an abnormal result on prior screening or biopsy, self-collected HPV specimens should not be considered equivalent to clinician-collected specimens.

3. **We commend the Task Force for including co-testing and cervical cytology alone as Grade A recommended screening strategies along with primary HPV screening. It is important to allow provider and individual choice, while also recognizing the continued need for a transition period. Several more years will be needed for some practices and laboratories to transition to offer primary HPV testing, as testing platforms not currently FDA-approved for primary HPV screening (of both clinician- and self-collected specimens) are commonly used in the U.S.**

Additional justifications for our recommendations are summarized below along with selected, pertinent references:

1. Utilization of FDA-approved HPV testing methodologies

The draft guidelines do not adequately (and prominently) specify that HPV testing platforms utilized for primary screening of clinician- and patient-collected specimens should be FDA-approved/cleared for those specific specimens.

2. Screening for self-collected samples should occur every 3 years and be restricted to people who are asymptomatic without heavy bleeding or discharge

We appreciate that the primary HPV self-collection testing strategy may help improve screening in underserved populations, by reducing potential barriers to screening in selected population groups. However, the draft guidelines make no distinction between clinician- and self-collected HPV specimens. There are limited long-term data on the efficacy of self-collected specimens in U.S. populations, where opportunistic screening remains the norm. Primary HPV screening specimens lack a microscopic assessment for the presence of adequate cervical/vaginal squamous epithelial cells. Specimens from people with heavy discharge or bleeding may theoretically contain sufficient human DNA and thus not be detected as unsatisfactory. In contrast, clinicians will be aware of sampling limitations while performing an examination and specimen collection. Similarly, there are insufficient long-term data to conclude that self-collected HPV specimens are equivalent to those clinicians collect for surveillance of people with a history of abnormal screening tests and/or treatment. The draft recommendation excludes people with previously treated high-grade precancers and cancers, but there are many people under surveillance for other types of abnormal screening results who would benefit from regular office visits and examinations.

3. Multiple screening strategies should be maintained as Grade A recommendations

3a. Co-testing and cytology screening are still in widespread use.

A transition period of several years is necessary to move from co-testing or primary cytology screening to primary HPV testing. Several groups are addressing an orderly transition by providing a wide array of educational resources for clinicians, patients, and cytopathology laboratory medical directors and staff. The American Cancer Society (ACS) initiated the Primary HPV Screening Initiative (PHSI) in 2020, nested under the ACS National Roundtable on Cervical Cancer (1,2). The College of American Pathologists (CAP) and other laboratory groups are addressing laboratory accreditation and quality control/assurance issues related to primary HPV testing. Laboratories must have clear guidance on how to properly implement primary HPV testing, including self-collected specimens. If a sufficiently long transition period is not provided, testing methods and patient test reporting may suffer in quality.

3b. New technologies to optimize screening and triage methods will help to minimize false negative screening results.

The prevalence of high-risk (HR)-HPV types varies with demographic populations. The current U.S. population is very diverse, and no test is perfect: HPV testing, cytology, and colposcopy all have limitations. A subset of carcinomas, both squamous and glandular, as well as other tumor types, may not be detected by primary HPV testing. With the use of HPV vaccination, the relative incidence of cervical adenocarcinoma has increased significantly, and these tumors have a higher rate of testing HPV-negative. *A number of studies performed in the U.S. and other countries have found that 9-10% of invasive cancers will test negative for HPV by commercially available tests, as will a similar percentage of high-grade precancers (3-10).* The use of co-testing may help detect cancers missed by primary HPV testing, especially in patients who are infrequently screened. The added sensitivity of co-testing may also help mitigate the negative impact of the COVID pandemic on cancer screening rates (11). Several new FDA-approved tests including the dual stain, extended HPV genotyping, and artificial intelligence-assisted (AI) liquid cervical cytology interpretation have entered clinical practice. Some of these testing platforms may allow for more effective, risk-based triage of positive HPV screening tests, while AI-assisted platforms may augment the sensitivity, specificity, and reproducibility of cytology screening (12). As noted with primary HPV testing, use of an FDA approved/cleared testing platform is paramount.

Thank you for your consideration.

Sincerely,

Diane D. Davey, MD
Co-Chairs, On behalf of The Cytopathology Educational and Technology Consortium

Jenna LeBlanc, MS, CT(ASCP), CT (IAC)

Kristen Atkins, MD
President, American Society of Cytopathology

Gregory Sossaman, MD
President, American Society for Clinical Pathology

Catherine Bammert, PhD, CT, MB(ASCP), CT(IAC)
President, American Society for Cytotechnology

Donald Karcher, MD
President, College of American Pathologists

Aziza Nassar, MD, MPH
President, Papanicolaou Society of Cytopathology

Selected References:

1. Downs LS, Nayar RN, Gerndt J, Saslow D. for the American Cancer Society Primary HPV Screening Initiative. Implementation in action: Collaborating on the transition to primary HPV screening for cervical cancer in the United States. CA Cancer Journal for Clinicians. https://doi.org/10.3322/caac.21786.
2. Nayar R. Cervical cancer prevention in the United States—where we've been and where we're going: The American Cancer Society Primary HPV Screening Initiative. Cancer Cytopathol 2023;131:747-750.
3. Ashman D, Zhang H, Li J, et al. HPV detection rates and histopathologic follow-up of patients with HSIL cytology in a large academic women's hospital laboratory. J Am Soc Cytopathol 2020;9:550-555.
4. Hopenhayn C, Christian A, Christian WJ, et al. Prevalence of human papillomavirus types in invasive cervical cancers from 7 US cancer registries before vaccine introduction. J Low Genit Tract Dis. 2014;18:182e189.
5. Ge Y, Mody FF, Olsen RJ, et al. HPV status in women with high-grade dysplasia on cervical biopsy and preceding negative HPV tests. J Am Soc Cytopathol 2019;8:149-156
6. Karaaslan S, Dilcher TL, Abdelsayed M, Goyal A. Significant outcomes associated with high-risk human papillomavirus negative Papanicolaou tests. J Am Soc Cytopathol 2023;12: 189-196.
7. Kinney W, Wright TC, Dinkelspiel HE, DeFrancesco M, Thomas Cox J, Huh W. Increased cervical cancer risk associated with screening at longer intervals. Obstet Gynecol. 2015;125:311e315.
8. Pirog EC, Loveras B, Moljin A, et al, for the RIS HPV TT Study Group. HPV relevance and genotypes in different histologic subtypes of cervical adenocarcinoma, a worldwide analysis of 780 cases. Mod Pathol. 2014;27:1559e1567.
9. Zhao C, Li Z, Nayar R, et al. Prior High-risk human papillomavirus testing and Papanicolaou test results of 70 invasive cervical carcinomas diagnosed in 2012: results of a retrospective multicenter study. Arch Pathol Lab Med. 2015;139:184e188.
10. Zheng B, Li Z, Griffith CC, Yan S, Chen C, Ding X, Liang X, Yang H, Zhao C. Prior high-risk HPV testing and Pap test results for 427 invasive cervical cancers in China's largest CAP-certified laboratory. Cancer Cytopathol. 2015;123:428–34.
11. Miller MJ, Xu L, Qin J, et al. Impact of COVID-19 on cervical cancer screening rates among women Aged 21–65 Years in a large integrated health care system — Southern California, January 1–September 30, 2019, and January 1–September 30, 2020. Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report. 2021; 70 (No. 4, Jan. 29):109-113.
12. Harinth L, Elishaev E, Ye Y, et al. Analysis of the sensitivity of high-grade squamous intraepithelial lesion Pap diagnosis and interobserver variability with the Hologic Genius Digital Diagnostics System. Cancer Cytopathol. 2024 Nov 5. doi: 10.1002/cncy.22918. Online ahead of print.