

Current approaches and challenges to cervical cancer prevention in the United States

A digest of cervical cancer screening options and new tools and innovations that may help reduce cervical cancer rates—along with equitable preventive care and increased HPV vaccination rates

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CASE Intervention approaches for decreasing the risk of cervical cancer

A 25-year-old woman presents to your practice for routine examination. She has never undergone cervical cancer screening or received the human papillomavirus (HPV) vaccine series. The patient has had 3 lifetime sexual partners and currently uses condoms as contraception. What interventions are appropriate to offer this patient to decrease her risk of cervical cancer? Choose as many that may apply:

1. cervical cytology with reflex HPV testing
2. cervical cytology with HPV cotesting
3. primary HPV testing
4. HPV vaccine series (3 doses)
5. all of the above

The answer is number 5, all of the above. Choices 1, 2, and 3 are acceptable methods of cervical cancer screening for this patient. Catch-up HPV vaccination should be offered as well.

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Equitable preventive care is needed

Cervical cancer is a unique cancer because it has a known preventative strategy. HPV vaccination, paired with cervical screening and management of abnormal results, has contributed to decreased rates of cervical cancer in the United States, from 13,914 cases in 1999 to 12,795 cases in 2019.¹ In less-developed countries, however, cervical cancer continues to be a leading cause of mortality, with 90% of cervical cancer deaths in 2020 occurring in low- and middle-income countries.²

Disparate outcomes in cervical cancer are often a reflection of disparities in health access. Within the United States, Black women have a higher incidence of cervical cancer, advanced-stage disease, and mortality from cervical cancer than White women.^{3,4} Furthermore, the incidence of cervical cancer

Disclaimer: We acknowledge that while we use “women” and “she/her” in this article to describe patients as reported by study investigators, all persons with female reproductive organs should undergo cervical cancer screening regardless of their gender identity.



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increased among American Indian and Alaska Native people between 2000 and 2019.⁵ The rate for patients who are overdue for cervical cancer screening is higher among Asian and Hispanic patients compared with non-Hispanic White patients (31.4% vs 20.1%; $P=.01$) and among patients who identify as LGBTQ+ compared with patients who identify as heterosexual (32.0% vs 22.2%; $P<.001$).⁶ Younger patients have a significantly higher rate for overdue screening compared with their older counterparts (29.1% vs 21.1%; $P<.001$), as do uninsured patients compared with those who are privately insured (41.7% vs 18.1%; $P<.001$). Overall, the proportion of women without up-to-date screening increased significantly from 2005 to 2019 (14.4% vs 23.0%; $P<.001$).⁶

Unfortunately, despite a known strategy to eliminate cervical cancer, we are not accomplishing equitable preventative care. Barriers to care can include patient-centered issues, such as fear of cancer or of painful evaluations, lack of trust in the health care system, and inadequate understanding of the benefits of cancer prevention, in addition to systemic and structural barriers. As we assess new technologies, one of our most important goals is to consider how such innovations can increase health access—whether through increasing ease

and acceptability of testing or by creating more effective screening tests.

Updates to cervical screening guidance

In 2020, the American Cancer Society (ACS) updated its cervical screening guidelines to start screening at age 25 years with the “preferred” strategy of HPV primary testing every 5 years.⁷ By contrast, the US Preventive Services Task Force (USPSTF) continues to recommend 1 of 3 methods: cytology alone every 3 years; cytology alone every 3 years between ages 21 and 29 followed by cytology and HPV cotesting every 5 years at age 30 or older; or high-risk HPV testing alone every 5 years (TABLE).⁸

To successfully prevent cervical cancer, abnormal results are managed by performing either colposcopy with biopsy, immediate treatment, or close surveillance based on the risk of developing cervical intraepithelial neoplasia (CIN) 3 or worse. A patient’s risk is determined based on both current and prior test results. The ASCCP (American Society for Colposcopy and Cervical Pathology) transitioned to risk-based management guidelines in 2019 and has both an app and a web-based risk assessment tool available for clinicians (<https://www.asccp.org>).⁹

TABLE Cervical cancer screening guidelines of the ACS and USPSTF^{7,8}

	Ages 21–24	Ages 25–29	Ages 30–65
American Cancer Society (2020 guidelines)	No screening	Preferred: Primary HPV test every 5 years Acceptable: HPV and Pap cotest every 5 years OR Pap test alone every 3 years	Preferred: Primary HPV test every 5 years Acceptable: HPV and Pap cotest every 5 years OR Pap test alone every 3 years
US Preventive Services Task Force (2018 guidelines)	Pap test alone every 3 years	Pap test alone every 3 years	Primary HPV test every 5 years OR HPV and Pap cotest every 5 years OR Pap test alone every 3 years

Abbreviations: ACS, American Cancer Society; HPV, human papillomavirus; USPSTF, US Preventive Services Task Force.

All organizations recommend stopping screening after age 65 provided there has been a history of adequate screening in the prior 10 years (defined as 2 normal cotests or 3 normal cytology tests, with the most recent test within 5 years) and no history of CIN 2 or worse within the prior 25 years.^{10,11} Recent studies that examined the rate of cervical cancer diagnosed in patients older than 65 years have questioned whether patients should continue screening beyond 65.¹⁰ In the United States, 20% of cervical cancer still occurs in women older than age 65.¹¹ One reason may be that many women have not met the requirement for adequate and normal prior screening and may still need ongoing testing.¹²

Primary HPV screening

Primary HPV testing means that an HPV test is performed first, and if it is positive for high-risk HPV, further testing is performed to determine next steps. This contrasts with the currently used method of obtaining cytology (Pap) first with either concurrent HPV testing or reflex HPV testing. The first HPV primary screening test was approved by the US Food and Drug Administration (FDA) in 2014.¹³

Multiple randomized controlled trials in Europe have demonstrated the accuracy of HPV-based screening compared with cytology in the detection of cervical cancer and its precursors.¹⁴⁻¹⁷ The HPV FOCAL trial demonstrated increased efficacy of primary HPV screening in the detection of CIN 2+ lesions.¹⁸ This trial recruited a total of 19,000 women, ages 25 to 65, in Canada and randomly assigned them to receive primary HPV testing or liquid-based cytology. If primary HPV testing was negative, participants would return in 48 months for cytology and HPV cotesting. If primary liquid-based cytology testing was negative, participants would return at 24 months for cytology testing alone and at 48 months for cytology and HPV cotesting. Both groups had similar incidences of CIN 2+ over the study period. HPV testing was shown to detect CIN 2+ at higher rates at the time of initial screen (risk ratio [RR], 1.61;



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95% confidence interval [CI], 1.24–2.09) and then significantly lower rates at the time of exit screening at 48 months (RR, 0.36; 95% CI, 0.24–0.54).¹⁸ These results demonstrated that primary HPV testing detects CIN 2+ earlier than cytology alone. In follow-up analyses, primary HPV screening missed fewer CIN 2+ diagnoses than cytology screening.¹⁹

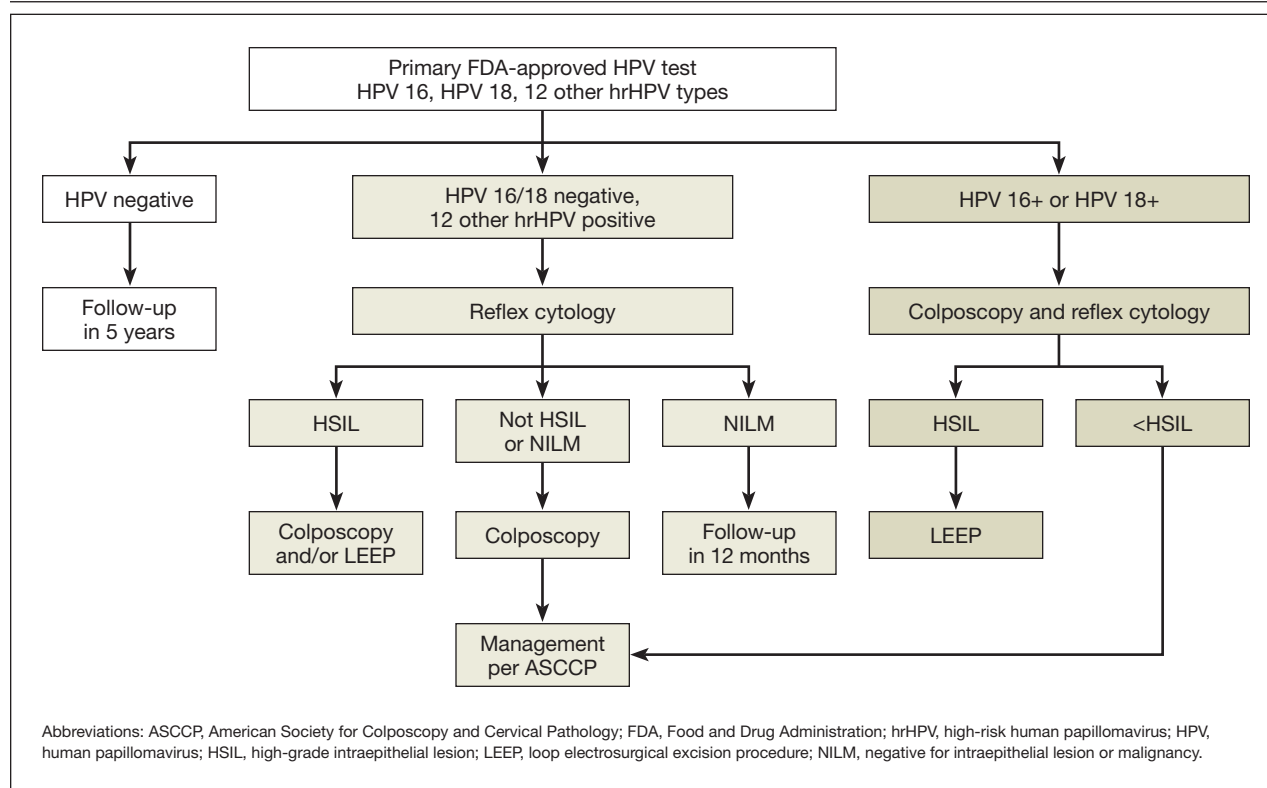
While not as many studies have compared primary HPV testing to cytology with an HPV cotest, the current most common practice in the United States, one study performed in the United States found that a negative cytology result did not further decrease the risk of CIN 3 for HPV-negative patients (risk of CIN 3+ at 5 years: 0.16% vs 0.17%; $P=0.8$) and concluded that a negative HPV test was enough reassurance for a low risk of CIN 3+.²⁰

Another study, the ATHENA trial, evaluated more than 42,000 women who were 25 years and older over a 3-year period.²¹ Patients underwent either primary HPV testing or combination cytology and reflex HPV (if ages 25–29) or HPV cotesting (if age 30 or older). Primary HPV testing was found to have a sensitivity and specificity of 76.1% and 93.5%, respectively, compared with 61.7% and 94.6% for cytology with HPV cotesting,

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FIGURE Management after primary HPV testing performed for screening^{9,22,36}



This flow diagram is adapted from the interim clinical guidance of the use of primary HPV testing for cervical cancer screening²² and the risk-based management guidelines from ASCCP.⁹

but it also increased the total number of colposcopies performed.²¹

Subsequent management of a primary HPV-positive result can be triaged using genotyping, cytology, or a combination of both. FDA-approved HPV screening tests provide genotyping and current management guidelines use genotyping to triage positive HPV results into HPV 16, 18, or 1 of 12 other high-risk HPV genotypes.

In the ATHENA trial, the 3-year incidence of CIN 3+ for HPV 16/18-positive results was 21.16% (95% CI, 18.39%–24.01%) compared with 5.4% (95% CI, 4.5%–6.4%) among patients with an HPV test positive for 1 of the other HPV genotypes.²¹ While a patient with an HPV result positive for HPV 16/18 should directly undergo colposcopy, clinical guidance for an HPV-positive result for one of the other genotypes suggests using reflex cytology to triage patients. The ASCCP

recommended management of primary HPV testing is included in the **FIGURE**.²²

Many barriers remain to transitioning to primary HPV testing, including laboratory test availability as well as patient and provider acceptance. At present, 2 FDA-approved primary HPV screening tests are available: the Cobas HPV test (Roche Molecular Systems, Inc) and the BD Onclarity HPV assay (Becton, Dickinson and Company). Changes to screening recommendations need to be accompanied by patient and provider outreach and education.

In a survey of more than 500 US women in 2015 after guidelines allowed for increased screening intervals after negative results, a majority of women (55.6%; 95% CI, 51.4%–59.8%) were aware that screening recommendations had changed; however, 74.1% (95% CI, 70.3%–77.7%) still believed that women should be screened annually.²³ By contrast,

participants in the HPV FOCAL trial, who were able to learn more about HPV-based screening, were surveyed about their willingness to undergo primary HPV testing rather than Pap testing at the conclusion of the trial.²⁴ Of the participants, 63% were comfortable with primary HPV testing, and 54% were accepting of an extended screening interval of 4 to 5 years.²⁴

p16/Ki-67 dual-stain cytology

An additional tool for triaging HPV-positive patients is the p16/Ki-67 dual stain test (CINtec Plus Cytology; Roche), which was FDA approved in March 2020. A tumor suppressor protein, p16 is found to be overexpressed by HPV oncogenic activity, and Ki-67 is a marker of cellular proliferation. Coexpression of p16 and Ki-67 indicates a loss of cell cycle regulation and is a hallmark of neoplastic transformation. When positive, this test is supportive of active HPV infection and of a high-grade lesion. While the dual stain test is not yet formally incorporated into triage algorithms by national guidelines, it has demonstrated efficacy in detecting CIN 3+

In the IMPACT trial, nearly 5,000 HPV-positive patients underwent p16/Ki-67 dual stain testing compared with cytology and HPV genotyping.²⁵ The sensitivity of dual stain for CIN 3+ was 91.9% (95% CI, 86.1%–95.4%) in HPV 16/18–positive and 86.0% (95% CI, 77.5%–91.6%) in the 12 other genotypes. Using dual stain testing alone to triage HPV-positive results showed significantly higher sensitivity but lower specificity than using cytology alone to triage HPV-positive results. Importantly, triage with dual stain testing alone would have referred significantly fewer women to colposcopy than HPV 16/18 genotyping with cytology triage for the 12 other genotypes (48.6% vs 56.0%; $P < .0001$).

Self-sampling methods: An approach for potentially improving access to screening

One technology that may help bridge gaps in access to cervical cancer screening is self-collected HPV testing, which would preclude

the need for a clinician-performed pelvic exam. At present, no self-sampling method is approved by the FDA. However, many studies have examined the efficacy and safety of various self-sampling kits.²⁶

One randomized controlled trial in the Netherlands compared sensitivity and specificity of CIN 2+ detection in patient-collected versus clinician-collected swabs.²⁷ After a median follow-up of 20 months, the sensitivity and specificity of HPV testing did not differ between the patient-collected and the clinician-collected groups (specificity 100%; 95% CI, 0.91–1.08; sensitivity 96%; 95% CI, 0.90–1.03).²⁷ This analysis did not include patients who did not return their self-collected sample, which leaves the question of whether self-sampling may exacerbate issues with patients who are lost to follow-up.

In a study performed in the United States, 16,590 patients who were overdue for cervical cancer screening were randomly assigned to usual care reminders (annual mailed reminders and phone calls from clinics) or to the addition of a mailed HPV self-sampling test kit.²⁸ While the study did not demonstrate significant difference in the detection of overall CIN 2+ between the 2 groups, screening uptake was higher in the self-sampling kit group than in the usual care reminders group (RR, 1.51; 95% CI, 1.43–1.60), and the number of abnormal screens that warranted colposcopy referral was similar between the 2 groups (36.4% vs 36.8%).²⁸ In qualitative interviews of the participants of this trial, patients who were sent at-home self-sampling kits found that the convenience of at-home testing lowered barriers to scheduling an in-office appointment.²⁹ The hope is that self-sampling methods will expand access of cervical cancer screening to vulnerable populations that face significant barriers to having an in-office pelvic exam.

It is important to note that self-collection and self-sample testing requires multidisciplinary systems for processing results and assuring necessary patient follow-up. Implementing and disseminating such a program has been well tested only in developed countries^{27,30} with universal health care

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The p16/Ki-67 dual stain test, which was FDA approved in 2020, is an additional tool for triaging HPV-positive patients



Overall HPV vaccination rates in the United States continue to improve, with 58.6%³⁴ of US adolescents having completed vaccination in 2020. However, these rates still are significantly lower than those in many other developed countries.

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Our path to increasing primary prevention of cervical cancer is clear: We must increase rates of HPV vaccination

systems or within an integrated care delivery system. Bringing such technology broadly to the United States and less developed countries will require continued commitment to increasing laboratory capacity, a central electronic health record or system for monitoring results, educational materials for clinicians and patients, and expanding insurance reimbursement for such testing.

HPV vaccination rates must increase

While we continue to investigate which screening methods will most improve our secondary prevention of cervical cancer, our path to increasing primary prevention of cervical cancer is clear: We must increase rates of HPV vaccination. The 9-valent HPV vaccine is FDA approved for use in all patients aged 9 to 45 years.

The American College of Obstetricians and Gynecologists and other organizations

recommend HPV vaccination between the ages of 9 and 13, and a “catch-up period” from ages 13 to 26 in which patients previously not vaccinated should receive the vaccine.³¹ Initiation of the vaccine course earlier (ages 9–10) compared with later (ages 11–12) is correlated with higher overall completion rates by age 15 and has been suggested to be associated with a stronger immune response.³²

A study from Sweden found that HPV vaccination before age 17 was most strongly correlated with the lowest rates of cervical cancer, although vaccination between ages 17 and 30 still significantly decreased the risk of cervical cancer compared with those who were unvaccinated.³³

Overall HPV vaccination rates in the United States continue to improve, with 58.6%³⁴ of US adolescents having completed vaccination in 2020. However, these rates still are significantly lower than those in many other developed countries, including Australia, which had a complete vaccination rate of 80.5% in 2020.³⁵ Continued disparities in vaccination rates could be contributing to the rise in cervical cancer among certain groups, such as American Indian and Alaska Native populations.⁵

Work—and innovations—must continue

In conclusion, the incidence of cervical cancer in the United States continues to decrease, although at disparate rates among marginalized populations. To ensure that we are working toward eliminating cervical cancer for all patients, we must continue efforts to eliminate disparities in health access. Continued innovations, including primary HPV testing and self-collection samples, may contribute to lowering barriers to all patients being able to access the preventative care they need. ●

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