

Current choices in cervical cancer screening

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The Papanicolaou (Pap) smear test came into widespread use in the 1950s and is considered to be the most successful screening test in modern medicine.¹ For more than 5 decades, cervical cytology was the only way to detect precancer or early invasive cancer. The discovery of the causative role of human papillomavirus (HPV) in the 1970s has laid the foundation for new ways to screen for, and potentially eradicate, this largely preventable disease.² Over the past decade, data have strongly suggested that primary HPV nucleic acid screening will eventually supplant cytology-based technology.³ This evolution toward primary HPV testing for optimal cervical cancer screening will require considerable provider support, patient education, and updated laboratory technology and procedures before existing cytology-based screening options (cytology alone and cotesting) can be phased out.

The prevention of cervical cancer can be primary or secondary. Cytology and HPV screening provide secondary prevention as they detect asymptomatic precancer and early cancers. Primary prevention focuses on the avoidance of genital HPV infection and its consequences by the use of HPV vaccination and behavioral steps such as condom use and smoking cessation. We should do everything we can to support primary prevention efforts, particularly through HPV vaccination as recommended by current guidelines.⁴

At least half of the approximately 14,000 cervical cancers diagnosed annually in the United States will be in unscreened or underscreened (not screened in the previous 5 years) women.^{5,6} Cervical cancer disproportionately affects racial minority, rural, and uninsured populations.^{7,8} It is essential to expand access to all available, effective cervical cancer screening options for the most vulnerable populations. The

targeted use of any particular screening modality in higher-risk populations is not supported by evidence-based guidelines; any effective screening is the priority.

Current screening components

CYTOLOGY: Cervical cytology can be collected as a conventional slide (“smear”); cells are taken directly from the cervix using a broom device or spatula (with or without an endocervical brush) and spread on a glass slide with immediate spraying with or immersion in a fixative. Liquid-based cytology calls for the similarly collected cells to be transferred directly into a liquid fixation and transport medium, a Pap “test.” Conventional slide and liquid-based cytology have equivalent performance in the detection of cervical cancer and its significant precursors.^{9,10} Liquid-based cytology now accounts for nearly all cervical cytology testing in the United



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Table 1. Comparison of Current Screening Options^{3,14,15}

	Advantages	Disadvantages
Cytology with reflex HPV testing	<ul style="list-style-type: none"> • Proven efficacy • Familiar to patients and providers 	<ul style="list-style-type: none"> • Less sensitive than HPV testing • Requires repeat every 3 years to compensate for limited sensitivity
Cotesting	<ul style="list-style-type: none"> • Increased sensitivity • Repeat at 5-year intervals • May be more sensitive for adenocarcinomas 	<ul style="list-style-type: none"> • Double the number of tests compared with primary HPV testing with little gain in sensitivity • Less familiar to patients and providers
Primary HPV testing	<ul style="list-style-type: none"> • Increased sensitivity • Repeat at 5-year intervals • May be more sensitive for adenocarcinomas 	<ul style="list-style-type: none"> • Unfamiliar to patients and providers

HPV, human papillomavirus

States, as automated slide preparation and preliminary review are possible, and the remaining transport medium can be used for HPV and other testing.

HPV TESTING: By convention, HPV testing refers to clinical testing only for either 13 or 14 high-risk HPV types. Cells are collected from the cervix using the same collection devices, technique, and transport media as those recommended for cytology sampling. These HPV types account for nearly all cervical cancers.^{11,12} Some HPV tests provide “genotyping.” This refers to testing that specifically identifies HPVs 16 and 18, whereas the other high-risk HPVs are detected within a pooled group. HPVs 16 and 18 are considerably more oncogenic than the others and their detection may influence management.¹³

At this time, 5 clinical HPV tests are available in the United States that are US Food and Drug Administration approved. Only 2 of these are currently approved for primary HPV testing in individuals aged 25 years and older (cobas 4800 HPV Test, Roche Diagnostics; and BD Onclarity HPV Assay, Becton, Dickinson and Company).

It is widely accepted that testing for low-risk HPV types (types 6 and 11)

has no role in clinical practice and it is strongly discouraged; the presence of these types does not increase the risk of developing anogenital cancers. Also, HPV testing should not be used to screen for sexually transmitted infections, as it detects only a specific group of genital HPV types at levels indicative of an elevated risk of cervical intraepithelial neoplasia 3 or cancer (CIN 3+). Therefore, a negative test does not mean that HPV is not present.

Current screening options

Three effective screening options are supported by clinical guidelines: cytology, cotesting, and primary HPV testing (**Table 1**).^{3,14,15} They can be selected based on patient and provider preference (shared decision-making optimal), financial considerations (patient and/or health care system resources), and familiarity with the triage of results.¹⁶ Few labs are set up for primary HPV screening, but this option is expected to become more widely available in the near future.

CERVICAL CYTOLOGY: Cervical cytology screening can be ordered as cytology alone but is most commonly ordered with reflex HPV testing. Reflex HPV

testing is arranged in advance with the clinical laboratory with established parameters for when an HPV test should be performed once the cytology results have been obtained. Its main use is to stratify the risk of CIN 3+ of an atypical squamous cell of undetermined significance cytology, which is the most common and lowest-risk Pap abnormality. Cytology, usually with reflex HPV testing, remains a mainstay of cervical cancer prevention and is highly cost-effective.¹⁷ It is repeated at shorter intervals (3 years) than cotesting or primary HPV testing to compensate for its lower sensitivity and less durable reassurance that CIN 3+ will not develop.¹⁸

COTESTING: Cotesting is cytology with a concurrent HPV test. The HPV test is carried out regardless of the Pap result, even if that was negative. Concurrent HPV negativity offers stronger reassurance that CIN 3+ is not present and will not develop over the next several years than cytology alone; this reassurance allows for screening intervals to be extended safely to 5 years.¹⁸⁻²² Cotesting was deemed the preferred screening modality (over cytology) in 2012 by 2 of 3 major gynecologic institutions^{23,24},

however, this is not the case for the latest guidelines.^{3,14} Disadvantages of cotesting include complex results to manage appropriately and more expense (doubles the number of tests), and it is less specific than cytology alone. Cotesting also results in more colposcopy referrals, which can lead to more treatment of transient HPV infections and lesions that may have regressed over time without intervention.^{3,25}

PRIMARY HPV TESTING: Primary HPV testing reverses the traditional cytology-based screening paradigm by obtaining the results of the HPV test first and calling for a reflex cytology result only if the specimen is HPV positive. The rationale for this strategy is that the presence of high-risk HPV infection is necessary to develop CIN 3+ and therefore there is no need for a cytology test if the HPV test is negative. The HPV positivity rate in the general population varies between studies. The results of 1 large US study using the cobas test found HPV positivity rates were higher (10.5%) than the baseline abnormal cytology rates (6.4%).²⁵ For now, the collection of cells is the same as for cytology or cotesting. Contact with the cervix, particularly the squamocolumnar junction, is not as critical for HPV testing as for cytology, and therefore self-collection by vaginal swab may become an option in the foreseeable future to determine who needs further evaluation.²⁶ Current guidelines call for the triage of positive primary HPV results by reflex cytology testing; the paired results inform management decisions.²⁷⁻²⁹ Reflex testing with more precise technology for predicting the presence of CIN 3+ risk may replace cytology triage using candidates such as p16/Ki67 dual staining.³⁰⁻³²

HPV: Evidence behind the evolution

Findings from numerous large, randomized, controlled trials have established that HPV-based testing improves screening sensitivity compared with cytology, increasing the detection of CIN 3+ in the first round of screening by a factor of 2 to 3.³³ The absence of high-risk HPV is associated with lower risks of developing CIN 3+ over longer intervals than is negative cytology screening.^{18,19,34-36} A large, randomized US trial compared the 3 current screening strategies in women 25 years and older. The sensitivities for the detection of CIN 3+ were cytology, 48%; cytology changing to cotesting at age 30, 62%; and primary HPV testing, 76%.²⁵ This increased sensitivity of HPV-based testing comes at the cost of decreased specificity and increased referrals for colposcopy. Also, over-referral can lead to treatment of mild and moderate severity lesions that may regress spontaneously. It is important to manage abnormal results according to risk-based management guidelines that seek to avoid overtreatment.²⁸

Another argument in support of HPV-based testing is the relative and absolute increase in cervical adenocarcinoma incidence in the United States and elsewhere over recent decades, despite cervical cancer screening.^{37,38} Adenocarcinomas now make up 20% to 30% of cervical cancers.⁵ This implies that cytology screening identifies squamous lesions vs glandular ones with greater sensitivity and perhaps that identification of squamous precursors is more effective in cancer prevention than the identification of adenocarcinomas in situ. It is hoped that HPV-based screening will be more sensitive than cytology for identifying cervical adenocarcinoma in situ and adenocarcinomas.

Although evidence shows that HPV-based testing offers advantages over cytology-based screening, there is debate as to whether cotesting is preferable to primary HPV testing; the basis of debate is over sensitivity.³⁹ The concept of cervical cancer screening without cytology can be unfamiliar and unsettling to patients and providers alike. However, the incidence of HPV-negative but cytology-abnormal

Table 2. Current Guideline Recommendations¹⁵

	Begin screening	Age-specific screening	Screening modality and frequency
USPSTF ¹⁴	21 years	21-29 years ≥30 years	Cytology every 3 years 1. Primary HPV testing every 5 years 2. Cotesting every 5 years 3. Cytology every 3 years
American Cancer Society ³	25 years	≥25 years	1. Primary HPV testing every 5 years* 2. Cotesting every 5 years 3. Cytology every 3 years

*Preferred screening modality
HPV, human papillomavirus; USPSTF, United States Preventive Services Task Force.

tests preceding cervical precancer and cancer is a relatively rare event; it is estimated the cytology component of cotesting would prevent 5 cervical cancers per 1 million women per year.⁴⁰ This small gain comes at a considerable cost, doubling the number of tests performed and adding considerable expense and resource utilization, not to mention leading to the diagnosis and overtreatment of lesser lesions. No screening program is expected to diagnose or prevent every case of the target disease, and attempting to do so, particularly in the case of cervical cancer, would be cost prohibitive and misguided.⁴¹

It should be remembered that HPV vaccination will continue to decrease the prevalence of vaccine-type oncogenic HPVs in the general population over time. As precursor lesions and cervical cancers become rarer, false-positive cytologic abnormalities will become more common and cytology screening will become even less efficient.

Current guidelines

The most recent cervical cancer screening guidelines come from the United States Preventive Services Task Force (USPSTF)¹⁴ and the American Cancer Society (ACS).³ The American College of Obstetricians and Gynecologists, on behalf of other stakeholder organizations, has issued a statement endorsing the USPSTF guidelines (Table 2).¹⁵

Both major guidelines endorse all 3 screening options (cytology, cotesting, and primary HPV testing) for individuals 30 years and older. There are 2 major differences between them, however. First, the USPSTF continues to recommend that screening start at age 21, whereas the ACS now recommends delaying the initiation of screening to



- Current guidelines recognize 3 highly effective ways to screen for cervical cancer: cytology, cotesting, and primary human papillomavirus (HPV) testing.
- Clinical HPV testing detects the presence of high-risk HPVs that account for nearly all cervical cancers.
- HPV-based screening is more sensitive than cytology and allows for longer intervals between screenings.
- Cotesting offers little advantage over primary HPV testing and comes at greater cost.
- Disparities in cervical cancer incidence can be countered by screening using any guideline-supported modality with evidence-based management of abnormal results.

age 25, because of the rarity of cervical cancer below this age and the potential for overtreatment of lesions destined to spontaneously regress.

Second, the USPSTF recommends that individuals aged 21 to 29 years be screened with cytology every 3 years because of the higher rate of HPV positivity in this age group; thereafter, any of the 3 screening modalities can be used, with shared decision-making encouraged. The ACS recommends primary HPV testing every 5 years as the preferred screening modality from age 25 on; if primary HPV testing is not yet clinically available, screening with cotesting every 5 years or cytology every 3 years is acceptable. The ACS recommends phasing out cytology and cotesting as soon as primary HPV testing can be implemented. The rationale for primary HPV testing supplanting cytology is its greater sensitivity for detecting current CIN 3+ and superior reassurance that CIN 3+ will not develop over the next 5 years compared with a negative cytology. The ACS acknowledges that very few settings are ready for this transition in terms of laboratory infrastructure.

Conclusion

Preventing cervical cancer is a process. Primary prevention with HPV

vaccination and secondary prevention with effective screening remain the priorities. As vaccine uptake increases, cytology screening is expected to become less efficient. Cervical cancer screening will continue to evolve along with our understanding of HPV biology and technological advances. Ultimately, a highly accurate and cost-effective test with streamlined triage and management of abnormal results will translate into the best outcomes for the most individuals. Clinical guidelines are shifting from cytology to HPV-based testing, with primary HPV testing presenting the most advantageous balance between sensitivity, specificity, and cost. During this time of transition, it should be remembered that the best strategy is to screen as many women as possible using any of the 3 strategies approved by current clinical guidelines. ■

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