










# Cervical Cancer Screening for Individuals at Average Risk: 2020 Guideline Update from the American Cancer Society

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Additional supporting information may be found online in the Supporting Information section at the end of the article.

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**Abstract:** The American Cancer Society (ACS) recommends that individuals with a cervix initiate cervical cancer screening at age 25 years and undergo primary human papillomavirus (HPV) testing every 5 years through age 65 years (preferred); if primary HPV testing is not available, then individuals aged 25 to 65 years should be screened with cotesting (HPV testing in combination with cytology) every 5 years or cytology alone every 3 years (acceptable) (*strong recommendation*). The ACS recommends that individuals aged >65 years who have no history of cervical intraepithelial neoplasia grade 2 or more severe disease within the past 25 years, and who have documented adequate negative prior screening in the prior 10 years, discontinue all cervical cancer screening (*qualified recommendation*). These new screening recommendations differ in 4 important respects compared with the 2012 recommendations: 1) The preferred screening strategy is primary HPV testing every 5 years, with cotesting and cytology alone acceptable where access to US Food and Drug Administration-approved primary HPV testing is not yet available; 2) the recommended age to start screening is 25 years rather than 21 years; 3) primary HPV testing, as well as cotesting or cytology alone when primary testing is not available, is recommended starting at age 25 years rather than age 30 years; and 4) the guideline is transitional, ie, options for screening with cotesting or cytology alone are provided but should be phased out once full access to primary HPV testing for cervical cancer screening is available without barriers. Evidence related to other relevant issues was reviewed, and no changes were made to recommendations for screening intervals, age or criteria for screening cessation, screening based on vaccination status, or screening after hysterectomy. Follow-up for individuals who screen positive for HPV and/or cytology should be in accordance with the 2019 American Society for Colposcopy and Cervical Pathology risk-based management consensus guidelines for abnormal cervical cancer screening tests and cancer precursors. *CA Cancer J Clin* 2020;0:1-26. © 2020 American Cancer Society.

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## Introduction

The incidence of and mortality from cervical cancer have declined markedly in the United States since the mid-20th century, largely because of widespread screening practices that were initiated in the 1950s. Nevertheless, in the US, an estimated 13,800 cases of invasive cervical cancer will be diagnosed, an estimated 4290 deaths from cervical cancer will occur in 2020, and disparities by race/ethnicity and socioeconomic status persist.<sup>1</sup> These disparities, as well as the stabilization of incidence rates of squamous cell cervical cancer in non-Hispanic whites and increasing rates of advanced cervical cancer in some age groups of

non-Hispanic whites,<sup>2</sup> underscore the need for increased access and adherence to recommended screening practices for both primary and secondary prevention.<sup>3,4</sup>

Recommendations for cervical cancer screening have evolved over the years, influenced by greater understanding of the natural history of the disease, the causal role of infection with high-risk human papillomavirus (hrHPV) types, and changing screening test technology. Major changes have included an older age to begin screening, discarding reference to first vaginal intercourse as a factor in beginning screening early, lengthening the screening interval, and the inclusion of HPV testing in screening protocols. The most recent update of the American Cancer Society (ACS) guideline took place in 2012 and was a joint guideline among the ACS, the American Society for Colposcopy and Cervical Pathology (ASCCP), and the American Society for Clinical Pathology.<sup>5</sup>

In this update of the ACS guideline for cervical cancer screening, we recommend that cervical cancer screening should begin in average-risk individuals with a cervix at age 25 years and cease at age 65 years and that the preferred strategy for regular screening is primary HPV testing every 5 years (Table 1). We emphasize that the United States is in a transition period from cytology testing to HPV testing, and, in the near term, cytology testing, either alone or as part of cotesting, will continue to have a role as practice patterns evolve and access to primary HPV testing can be assured. Here, we discuss those challenges at length as well as quality-assurance issues, enduring disparities, the need to significantly improve documented adherence to screening in older individuals to enable the cessation of screening, and future trends, such as the anticipated influence of HPV vaccination on disease trends and the potential role of self-sampling HPV testing in screening (Table 1).

## Background

### Screening for the Prevention and Control of Cervical Cancer

For more than a half century, cervical cytologic testing, first with the Papanicolaou (Pap) test and more recently with liquid-based cytology, has been the foundation for screening for cervical cancer and has been highly effective in substantially reducing the burden of this disease in the United States as well as globally. Persistent infection with hrHPV, principally HPV types 16 (HPV16) and HPV18, is the cause of almost all cervical cancers.<sup>6</sup> The long period between HPV infection and the development of cervical cancer has made it possible for cervical cancer screening to be effective in reducing both incidence and mortality from cervical cancer. Although HPV infections are common in healthy adults,<sup>7</sup> only a small proportion of infections persist and progress to precancerous cells in the cervix.<sup>6,8,9</sup> This progression to a precancerous state occurs over many years, and significant rates of regression and lack of progression have been observed, especially in younger individuals.<sup>10</sup> Thus, although HPV infections and cervical intraepithelial neoplasia (CIN) are common, they only rarely lead to cervical cancer.<sup>6,11</sup>

The primary goal of cervical cancer screening is to detect treatable abnormalities and precancers (CIN grade 2 [CIN2], CIN3, and adenocarcinoma in situ [AIS]) that are likely to progress to invasive cancer, thus reducing cervical cancer incidence, mortality, and treatment-related morbidity.<sup>6</sup> A secondary but important goal is the detection of earlier stage invasive cervical cancer, which also contributes to reduced mortality and decreased treatment-related morbidity. Ideally, a screening strategy should maximize the benefits of screening by detecting precursor abnormalities that are likely to progress to cervical cancer as well as early stage cancers, while avoiding the detection of transient HPV

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**TABLE 1. American Cancer Society Recommendations for Cervical Cancer Screening, 2020**

The recommendations apply to all asymptomatic individuals with a cervix, regardless of their sexual history or human papillomavirus (HPV) vaccination status, including those who have undergone supracervical hysterectomy and transgender men who retain their cervix.

These recommendations represent guidance from the American Cancer Society (ACS) for persons who are initiating cervical cancer screening or have had all normal cervical cancer screening results in the past, or have been returned to routine cervical cancer screening based on follow-up recommendations from the Risk-Based Management Consensus Guidelines. The recommendations do not apply to individuals at increased risk for cervical cancer due to solid organ or stem cell transplantation, human immunodeficiency virus infection or immunosuppression from other causes, or in utero exposure to diethylstilbestrol.

### Recommendations

The ACS recommends that individuals with a cervix initiate cervical cancer screening at age 25 y and undergo primary HPV testing every 5 y through age 65 y (preferred). If primary HPV testing is not available, individuals aged 25-65 y should be screened with cotesting (HPV testing in combination with cytology) every 5 y or cytology alone every 3 y (acceptable) (*strong recommendation*).<sup>a</sup>

*Cotesting or cytology testing alone are included as acceptable options for cervical cancer screening because access to primary HPV testing with a test approved by the FDA for primary screening may be limited in some settings. As the United States makes the transition to primary HPV testing, the use of cotesting or cytology alone for cervical cancer screening will be eliminated from future guidelines.*

The ACS recommends that individuals with a cervix who are older than age 65 y, who have no history of cervical intraepithelial neoplasia grade 2 or a more severe diagnosis within the past 25 y, and who have documented adequate negative prior screening in the 10-y period before age 65 y discontinue cervical cancer screening with any modality (*qualified recommendation*).<sup>a,b</sup>

- Adequate negative prior screening is currently defined as 2 consecutive negative HPV tests, or 2 consecutive negative cotests, or 3 consecutive negative cytology tests within the past 10 y, with the most recent test occurring within the recommended interval for the test used. These criteria do not apply to individuals who are currently under surveillance for abnormal screening results.
- Individuals older than age 65 y without conditions limiting life expectancy for whom sufficient documentation of prior screening is not available should be screened until criteria for screening cessation are met.
- Cervical cancer screening may be discontinued in individuals of any age with limited life expectancy.

Abbreviation: FDA, US Food and Drug Administration.

<sup>a</sup>A strong recommendation conveys the consensus that the benefits of adherence to that intervention outweigh the undesirable effects that may result from screening. Qualified recommendations indicate there is clear evidence of benefit of screening but less certainty about the balance of benefits and harms or about patients' values and preferences, which could lead to different decisions about screening.

<sup>b</sup>Older than age 65 years means that cervical cancer screening is not recommended for individuals aged 66 years and older.

infections and benign abnormalities that could lead to overtreatment and other harms associated with screening.

Understanding of HPV infection as the main causal factor for cervical cancer has provided a basis for the introduction of HPV testing for cervical cancer screening,<sup>5,12-14</sup> first for cotesting with cytology and subsequently as a stand-alone screening test.<sup>15-17</sup> The development of testing for oncogenic hrHPV types resulted in improved sensitivity for precancers and a new and more reliable element of prediction and stratification of future risk for cervical precancer and cancer based on current and past test results.<sup>11,18,19</sup>

### Evolution in Cervical Cancer Prevention and Early Detection

On the basis of emerging evidence and pending approval by the US Food and Drug Administration (FDA) of a molecular test for hrHPV types, the 2002 ACS guideline update included a preliminary recommendation for cervical cancer screening using cytology combined with an HPV test (cotesting) every 3 years.<sup>20</sup> Guidance was provided that combined testing should not take place more often than every 3 years and that there was a critical need for counseling and education related to HPV infection. In 2012, the ACS guideline recommended cotesting every 5 years as a preferred screening strategy or cytology alone for cervical cancer screening.<sup>5</sup> Table 2 provides a comparison of the 2012 ACS guideline<sup>5</sup> with the new guideline, including a reference to new guidance for the management of positive results and subsequent

surveillance from the ASCCP 2020 Risk-Based Management Consensus Guideline.<sup>21</sup> The previously established screening strategy of cytology alone was adopted as the benchmark from which reasonable risk was determined.<sup>5</sup> Cotesting was the preferred option for screening because of the increased detection of advanced precancers (and of adenocarcinoma and its precursors) and the lower risk conferred by a negative screening result. On the basis of accumulated evidence and assessment of the balance of benefits and harms, in 2018, the US Preventive Services Task Force (USPSTF) included stand-alone HPV testing (primary HPV testing) among the tests recommended for cervical cancer screening.<sup>15</sup>

Previously, the terms *hrHPV testing alone* (with *hr* designating high-risk) and *primary hrHPV testing* have been used to designate the stand-alone HPV screening test. Because tests that include low-risk types are rarely used, we have adopted the simpler designation of *primary HPV testing*. Currently, there are only 2 FDA-approved primary HPV tests available for cervical cancer screening,<sup>14,16,17</sup> and both are approved for primary HPV testing beginning at age 25 years (Table 3).<sup>14</sup> Five HPV tests are FDA-approved for cotesting.<sup>14,17</sup> Although it is too early to measure utilization of primary HPV testing for cervical cancer screening, utilization of cotesting has increased, whereas screening with cytology alone has declined.<sup>15,22-25</sup>

The introduction and uptake of HPV vaccination in 2007 and the entry of vaccinated cohorts, now in their 20s, into the screening-eligible age range are expected to have a substantial impact on cervical cancer screening strategies

TABLE 2. Comparison of Current and Previous American Cancer Society (ACS) Guidelines for Cervical Cancer Screening

RECOMMENDATIONS FOR CERVICAL CANCER SCREENING		
POPULATION	ACS 2020 <sup>a</sup>	ACS 2012 <sup>b</sup>
Aged <25 y	No screening	Cytology alone every 3 y starting at age 21 y
Aged 25-65 y	Starting at age 25 y, primary HPV test alone every 5 y (preferred) <i>Use an FDA-approved HPV test for primary screening</i>  Cotesting every 5 y or cytology alone every 3 y are acceptable options <sup>b</sup>  <i>Cotesting or cytology testing alone are acceptable where access to primary HPV testing is limited or not available; as the United States makes the transition to primary HPV testing, the use of cotesting or cytology alone for cervical cancer screening will not be included in future guidelines<sup>b</sup></i>  For management of positive results and subsequent surveillance, refer to ASCCP 2020 Risk-Based Management Consensus Guideline (Perkins, 2020 <sup>21</sup> )	Cytology alone every 3 y until age 29 y Aged 30-65 y, switch to cotesting (preferred), cytology alone every 3 y (acceptable) <sup>a</sup>  <i>Screening by primary HPV testing alone not recommended for most clinical settings</i>
Aged >65 y	Discontinue screening if adequate negative prior screening  Individuals aged >65 y without documentation of prior screening should continue screening until criteria for cessation are met  <i>Adequate negative prior screening is currently defined as 2 consecutive, negative primary HPV tests, or 2 negative cotests, or 3 negative cytology tests within the past 10 y, with the most recent test occurring within the past 3-5 y, depending on the test used</i>	No screening after adequate negative prior screening
After hysterectomy	Individuals without a cervix and without a history of CIN2 or a more severe diagnosis in the past 25 y or cervical cancer ever should not be screened	No screening after hysterectomy (with removal of the cervix) for reasons not related to cervical cancer and no history of cervical cancer or serious precancer
HPV vaccinated	Follow age-specific screening recommendations (same as unvaccinated individuals)	Follow age-specific screening recommendations

Abbreviations: ASCCP, American Society of Colposcopy and Cervical Pathology; CIN2, cervical intraepithelial neoplasia grade 2; FDA, US Food and Drug Administration; HPV, human papillomavirus.

<sup>a</sup>Cotesting is HPV testing in combination with cytology.

<sup>b</sup>Individuals should not be screened more frequently than at the recommended interval for the test used and should not be screened annually at any age by any method. Annual testing may be recommended as surveillance after abnormal screening results.

and outcomes in coming years.<sup>18,26-29</sup> The initial uptake of the HPV vaccine was slow in the United States after FDA approval in 2006, but current enhanced dissemination efforts have resulted in steadily increasing levels of vaccination and population coverage at the recommended ages of 11 to 12 years.<sup>30-32</sup> On the basis of the 2018 National Health Interview Survey, 39.9% of adults aged 18 to 26 years reported having received one or more doses of the HPV vaccine (53.6% of women).<sup>33</sup> The most recent report from the National Immunization Survey-Teen of adolescents aged 13 to 17 years showed that coverage with one or more doses of HPV vaccine in 2018 among females and males was 68.1%, and 51.1% were up to date based on HPV vaccine recommendations.<sup>32</sup>

Cytology-based screening is much less efficient in vaccinated populations, as abnormal cytology disproportionately identifies minor abnormalities resulting from HPV types that are associated with lower cancer risk.<sup>6,18</sup> Thus, in those who continue to be screened with cytology only, as the prevalence of high-grade cervical abnormalities and the incidence of cervical cancer decline, the proportion of

false-positive findings is expected to increase significantly. There is emerging evidence on screening outcomes from other countries with higher vaccine uptake,<sup>34-36</sup> and some preliminary data from the United States<sup>37-39</sup> that show significant declines in cervical abnormalities in vaccinated populations, and which point to the likelihood that future recommendations for cervical cancer screening will need to incorporate HPV vaccination status.

## Methods

The ACS cancer screening guideline development process has been described previously.<sup>40-42</sup> The ACS volunteer Guideline Development Group (GDG) is responsible for developing cancer screening guidelines following a protocol that is designed to maintain rigor, transparency, independence, and consistency. The GDG interprets the evidence from systematic evidence reviews, supplemental evidence where gaps exist, and modeling analyses; considers the overall balance of benefits and harms of the screening interventions, taking into account patient preferences; formulates, deliberates, and votes on the wording and strength of the



TABLE 3. Cervical Cancer Screening Tests

TEST	DEFINITION	FDA-APPROVED TEST	GENOTYPE
Cytology (also known as Pap test or Pap smear)	Examination of the cells in a sample taken from the cervix under a microscope to check for the presence of abnormal cells (abnormal cells may be precancerous or cancerous cells)		
Primary HPV test	A test to detect the DNA of oncogenic (high-risk) types of HPV in a sample taken from the cervix	cobas <sup>®</sup> HPV (approved 2014)	HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68
	HPV is the causal agents of almost all cervical cancers	Onclarity HPV (approved 2018)	HPV types 16, 18, 45, 11, 31, 33, 35, 39, 51, 52, 56, 58, 59, 66, and 68
Cotest (cytology and HPV test administered together)	A test that combines cytology to look at cells under a microscope and test for HPV DNA in the same sample taken from the cervix	Digene HC2 (approved 2003)	No
		Cervista HPV HR (approved 2009)	No
		Cervista HPV16/18 (approved 2009)	HPV types 16 and 18
		Aptima HPV (approved 2011)	No
		Aptima HPV16 and 18/45 (approved 2012)	HPV types 16 and 18/45

Abbreviations: Aptima HPV, human papillomavirus assay from Hologic, Inc; Cervista HPV HR, high-risk human papillomavirus test (Cervista; cobas HPV, human papillomavirus test (cobas; Digene HC2, hybrid capture 2 test (Digene; FDA, US Food and Drug Administration; Hologic, Inc); HPV, human papillomavirus; Onclarity HPV, human papillomavirus assay from Becton, Dickinson & Company; Pap, Papanicolaou; Qiagen; Roche Molecular Systems). Adapted from: US Food and Drug Administration. FDA Executive Summary: New Approaches in the Evaluation for High-Risk Human Papillomavirus Nucleic Acid Detection Devices. Prepared for the March 8, 2019 meeting of the Microbiology Devices Panel of the Medical Devices Advisory Committee (see FDA 2019<sup>14</sup>).

recommendations; provides explicit explanations of the logical relationships between the screening interventions and health outcomes; and prepares the guideline update for publication. The GDG was supported by a group of expert advisors with clinical and research expertise in the natural history of cervical cancer, risk, and the detection, diagnosis, and management of cervical abnormalities (see Supporting Materials). The expert advisory group, along with external stakeholder organizations (see Supporting Materials), served as external reviewers of the draft recommendation statements and the rationale before publication.

A critical element in the ACS guideline development protocol is a transparent disclosure and conflict management process that minimize biases and conflicts of interest. All participants (GDG members, ACS staff, expert advisors) were required to disclose financial and nonfinancial (personal, intellectual, practice-related) relationships and activities related to cervical cancer and screening that might be perceived as posing a conflict of interest. The disclosures from all participants were distributed to committee members, and the GDG chairpersons had the responsibility to ensure that all perspectives were considered in deliberations and decision making. In addition to the disclosures listed in the article, nonfinancial disclosures of the authors are reported in the Supporting Materials.

For the update of the cervical cancer screening guideline, the GDG chose to use 2 reports commissioned by the USPSTF for its 2018 cervical cancer screening update as

sources of evidence to inform recommendations: 1) a systematic evidence review on cervical screening conducted by the Kaiser Permanente Research Affiliates Evidence-Based Practice Center,<sup>4,43</sup> and 2) a decision analysis based on a mathematical disease-simulation model that was produced by researchers at the Center for Health Decision Science of the Harvard T.H. Chan School of Public Health.<sup>44,45</sup> The ACS staff conducted continued surveillance of the literature on cervical cancer screening outcomes and reviewed potentially relevant articles after the publication date of the evidence review report (August 2018).

The key questions for the systematic review by Melnikow and colleagues<sup>43</sup> focused on the effectiveness of primary HPV testing as a screening strategy, and the data analysis of included studies was restricted mostly to randomized controlled trials (RCTs) conducted in women aged 25 to 65 years, leaving several key questions identified by the GDG that were not fully addressed by the USPSTF. In 2012, the ACS recommended that cervical cancer screening should be initiated at age 21 years and that women aged >65 years who have a history of regular screening with negative results should discontinue screening.<sup>5</sup> The starting age of 21 years has been questioned based on understanding of the natural history of cervical cancer, the low disease burden at young ages, and the risk of adverse obstetric outcomes associated with over-treatment of precursor lesions. There also are questions

about the recommended age for cessation of screening and the incidence of cervical cancer and advanced disease in individuals aged >65 years, the potential of late HPV infection or re-emergence and progression of latent infection, and poor adherence to the criteria for exiting screening. Because these topics were not directly addressed in the systematic evidence review performed by Melnikow et al,<sup>43</sup> the GDG initiated a supplemental literature review of the evidence to address the performance of screening in younger and older women.

The GDG also commissioned the modeling group that provided the decision analysis for the USPSTF 2018 update to examine outcomes associated with different starting ages: one of the key questions identified by the GDG that was not fully addressed in the published report.<sup>44,45</sup> In the decision analysis, Kim et al<sup>44,45</sup> stressed the inherent limitations of evaluating new cervical cancer screening technologies with RCTs. Given widespread utilization of cervical cancer screening and its secondary prevention potential, it is infeasible to observe mortality endpoints, resulting in reliance on surrogate, or intermediate, outcomes predictive of invasive disease or mortality. Furthermore, as a practical matter, RCTs include only a limited number of screening rounds.<sup>44,45</sup> Decision analysis using mathematical models can complement RCT findings by simulating longer periods of screening, commonly over the lifetime of individuals, and a broader range of outcomes under numerous screening scenarios, far beyond what could ever be achieved by RCTs.

The decision model used as a source of evidence<sup>44,45</sup> for the cervical cancer screening recommendation is a microsimulation model, in which individual women born in 1996 enter the model at age 9 years, begin screening at age 21 years, and are followed over their lifetimes.<sup>44,45</sup> The model simulates the natural history of the disease (ie, HPV infection, grades of CIN, and stages of invasive squamous cell cervical cancer) and tracks health services (ie, the number of screening tests, screening test outcomes, diagnostic procedures) and health outcomes (ie, life-years gained, disease-specific incidence and mortality). Additional methodologic details have been published elsewhere.<sup>44,45</sup>

For this guideline update, the model was adapted to include a screening start age of 25 years with the screening strategies previously evaluated. The model generated 3 efficiency outcomes for comparing the tradeoff of harms and benefits associated with the different screening scenarios: 1) the incremental number of colposcopies per life-year gained, 2) the incremental number of screening tests per life-year gained, and 3) the incremental number of colposcopies per case of cervical cancer averted.<sup>44,45</sup> Strategies with a higher number of colposcopies and lower life-years than an alternative strategy were considered *inefficient* and

were eliminated from the calculation; all other strategies were considered *efficient*. Ranking the strategies by the number of colposcopies in ascending order and eliminating the inefficient strategies, the relative efficiency for a specific screening modality was evaluated using the incremental number of referrals to colposcopy per life-year gained, defined as the additional number of colposcopies divided by the additional life-years gained from this specific strategy compared with the strategy that had the next fewer number of colposcopies.

To examine the burden of disease overall and in age-specific subgroups, the GDG used analyses conducted by the ACS Surveillance and Health Services Research program based on cancer incidence data from the Surveillance, Epidemiology, and End Results program and the National Program of Cancer Registries programs as provided by the North American Association of Central Cancer Registries and mortality data from the National Center for Health Statistics.<sup>46-48</sup> The GDG examined a range of disease burden indicators, including age-specific incidence, mortality, and 10-year incidence-based mortality by age at diagnosis.

### Factors in Developing Recommendations

The GDG used the principles of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) evidence-to-decision framework for recommendation development.<sup>49</sup> The evaluation of evidence and deliberations were principally focused on judgments of the following criteria from both an individual patient and population perspective:

1. *The balance between desirable and undesirable effects.* The greater the difference between desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted; the narrower the difference, the higher the likelihood that a qualified recommendation is warranted;
2. *The quality of evidence.* The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted; where evidence is more limited, a qualified recommendation is warranted; and
3. *Values and preferences.* The greater the variability or uncertainty in patients' values and preferences, the higher the likelihood that a qualified recommendation is warranted.

The additional criteria in the GRADE evidence-to-decision framework considered are: *acceptability*, the acceptability of the screening strategy to key stakeholders; *feasibility*, consideration of the evidence that implementing the screening strategy in the current health care setting is feasible; *equity*, judgment on whether implementation of the screening strategy would have an effect on health inequities; and

*cost/resource allocation*, although the ACS does not formally apply cost and resource use as a criterion for formulating recommendations, it may evaluate potential patient burdens and individual decision-making considerations relevant to guideline recommendations.

### **Outcomes of screening and balancing benefits and harms**

As noted above, the aim of the systematic evidence review that served as the principal source of empirical evidence for this guideline update was to evaluate the benefits and harms of cervical cancer screening using primary HPV testing and cotesting.<sup>4,3</sup> The GDG prioritized a reduction in cervical cancer incidence through the identification and treatment of advanced cervical precursor abnormalities, in addition to mortality reduction, as the primary beneficial outcomes of screening. The incidence and mortality of cervical cancer in the United States are low<sup>1</sup>; therefore, few studies have been sufficiently powered to evaluate these outcomes. For this reason, the detection of prevalent CIN3 or more severe disease (CIN3+) commonly is used as the best surrogate measure of incident cervical cancer risk, although many studies use CIN2+ as the surrogate measure of risk. Although recognized as a benefit of screening, a lower weight was ascribed to the beneficial effect of reassurance against cancer from a negative screening test. The principal recognized harms of cervical cancer screening include (most importantly) potential treatment-related adverse obstetric outcomes (especially preterm birth)<sup>50</sup>; the diagnosis of, and corresponding clinical actions triggered by, CIN that would have regressed without treatment<sup>11</sup>; physical discomfort associated with testing and clinical procedures (ie, colposcopy, biopsy, and treatment)<sup>51</sup>; and the anxiety precipitated by false-positive findings.<sup>52</sup> Despite its limitations, the number of colposcopies is consistently used as the primary surrogate measure of harm because colposcopies commonly are prerequisite to more invasive treatments with greater short-term and long-term risks of harms, and the number of individuals undergoing colposcopy usually is reported in controlled studies.<sup>5,45</sup>

### **Patient preferences, acceptability, and adherence to screening**

Although cervical cancer screening with an annual Pap test has not been a recommended strategy for many years, adherence to longer intervals associated with currently recommended screening strategies has been uneven, in part because of established patterns of practice that prioritize continuity of regular care and perceived reluctance among individuals being screened to deviate from a test conducted more frequently that intuitively would appear to provide greater protection.<sup>53</sup> Screening more frequently than recommended will increase unnecessary burden and

exposure to the risk of harms. There is some indication that women's acceptance of longer cervical cancer screening intervals has increased.<sup>54</sup> Concerns have been raised, however, that longer intervals may result in delays beyond the recommended time frames, potentially leading to lower overall adherence to cervical cancer screening recommendations.<sup>55</sup> Nonadherence to regular screening as individuals approach the age for cessation of screening<sup>56</sup> is of particular importance and may reduce the benefits. Failure to initiate screening near the recommended starting age may similarly reduce screening benefits.<sup>57</sup>

### **Disparities and unscreened and under screened populations**

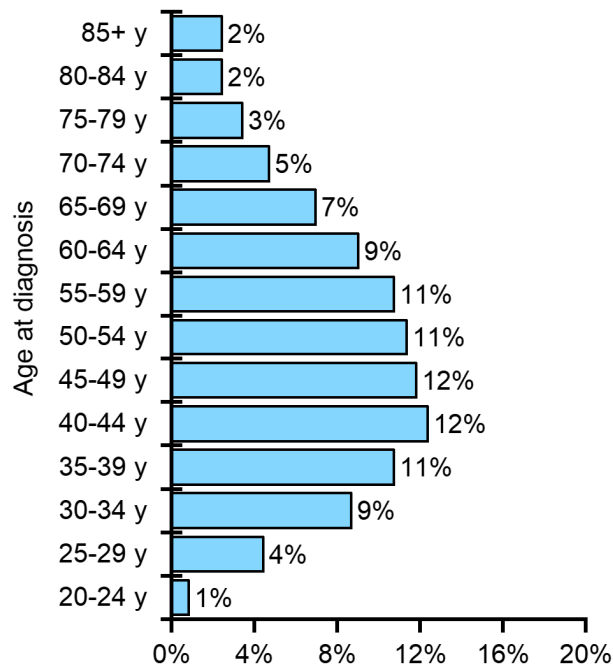
Cervical cancer incidence and mortality have sharply declined over time, but disparities still exist, with differences by state and rural/urban residence,<sup>58,59</sup> and with greater burden in racial/ethnic minorities, particularly after adjustment for hysterectomy status,<sup>2,60</sup> and in individuals of lower socioeconomic status.<sup>58,61</sup> In addition, those without insurance are more likely to be diagnosed with late-stage cervical cancer than those who are privately insured.<sup>62</sup> The contributors to these inequities include the differential participation and follow-up in cervical cancer screening programs, health-seeking behaviors, and screening and treatment access barriers.<sup>56,60,63</sup> An important predictor for developing cervical cancer at older ages, and also for being diagnosed with later stage disease, is inadequate screening at younger ages or stopping screening before criteria for screening cessation have been met.<sup>62,64,65</sup> There is concern that longer screening intervals may differentially affect adherence to screening in racial/ethnic minorities and in individuals with limited access to health care.<sup>55</sup>

## **Recommendations**

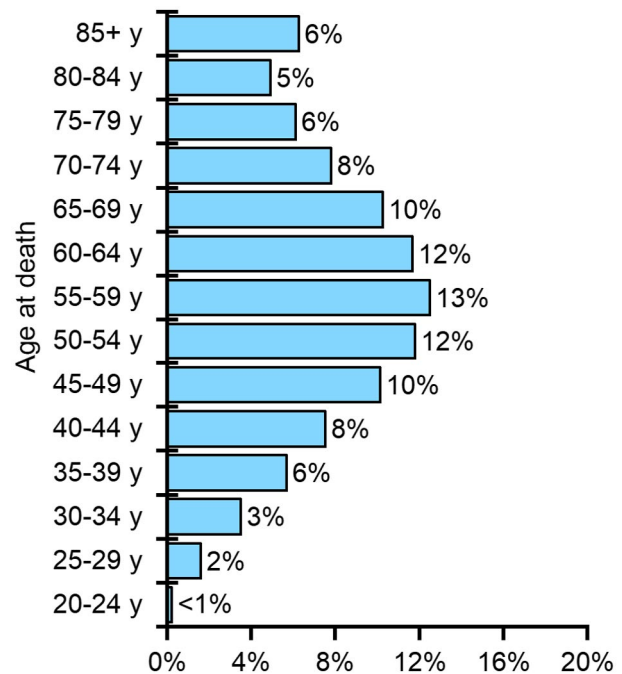
**The ACS recommends that individuals with a cervix initiate cervical cancer screening at age 25 years and undergo primary HPV testing every 5 years through age 65 years (preferred). If primary HPV testing is not available, individuals aged 25 to 65 years should be screened with cotesting (HPV testing in combination with cytology) every 5 years or cytology alone every 3 years (acceptable) (strong recommendation) (Table 1).**

*Cotesting or cytology-alone testing are acceptable options for cervical cancer screening because access to an FDA-approved primary HPV test may be limited in some settings. As the United States makes the transition to primary HPV testing, the use of both cotesting and cytology for cervical cancer screening will not be included in future guidelines.*

This recommendation for cervical cancer screening applies to asymptomatic individuals with a cervix, regardless of sexual history or HPV vaccination status. The recommendation is based on the GDG's judgment of the



**FIGURE 1.** Distribution of Cervical Cancer Cases by Age at Diagnosis, United States, 2012 to 2016. Data Source: North American Association of Central Cancer Registries Incidence Data-Cancer in North America Analytic File.<sup>46</sup>



**FIGURE 2.** Distribution of Cervical Cancer Deaths by Age at Death, United States, 2013 to 2017. Data Source: National Center for Health Statistics.<sup>47</sup>

preponderance of the benefits of cervical cancer screening over the harms and the evidence demonstrating the effectiveness of available tests on screening outcomes. On the basis of the consistent low cervical cancer incidence and mortality among women aged <25 years, the high incidence of transient infections, the risk of adverse obstetric outcomes of treatment, and the decision analysis demonstrating a favorable benefit-to-harm balance for beginning screening at age 25 years, cervical cancer screening is strongly recommended from age 25 years with primary HPV testing (preferred) or, as the United States makes the transition to primary HPV testing, with the previously recommended screening strategies of cotesting every 5 years or cytology alone every 3 years (acceptable). As in previous recommendations for cervical cancer screening, individuals should not be screened more frequently than at the recommended intervals for the test used.

### Age to Begin Cervical Cancer Screening

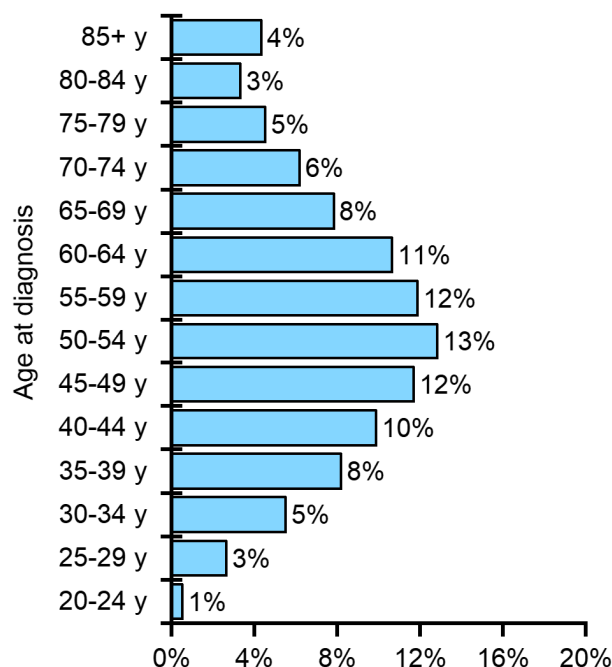
The recommended age to begin cervical cancer screening has evolved over the years with greater understanding of the natural history of the disease and the causal role of HPV. Early guidelines in the last century set the age to begin screening at age 20 years,<sup>66</sup> then age 18 years,<sup>67</sup> then age 21 years<sup>20</sup> for women who had not had vaginal intercourse, but earlier if the onset of sexual activity occurred before these ages. Since 2010, the ACS and other organizations<sup>68-70</sup> have recommended that cervical cancer

screening should begin at age 21 years (and no earlier), regardless of the age of first vaginal intercourse. In this update of the guideline for cervical cancer screening, the ACS now recommends that cervical cancer screening begin at age 25 years.

Neither the evidence review nor the decision analysis performed for the 2018 USPSTF update of recommendations for cervical cancer screening specifically addressed strategies with a starting age >21 years,<sup>4,44,45</sup> although the evidence review examined comparisons between the performance of primary HPV testing in populations younger or older than ages 30 to 35 years and the decision analysis compared strategies with different ages at which to switch from cytology to HPV screening.

With any guideline update, it is important to re-examine the foundation of past recommendations and determine whether they are still relevant based on a current assessment of the burden of disease (Figs. 1-3)<sup>46-48</sup> and evidence supporting estimates of the balance of benefits and harms. There are approximately 11 million women in the groups aged 20 to 24 and 25 to 29 years.<sup>71</sup> The overall burden of cervical cancer among women ages 20 to 24 years is relatively small, with 0.8% of all new cases diagnosed in this age group, compared with 4% among women aged 25 to 29 years (Fig. 1), and about 0.5% of cervical cancer deaths are attributable to a diagnosis at ages 20 to 24 years, compared with 3% attributable to a diagnosis among women ages 25 to 29 years (Fig. 3). It is not known how





**FIGURE 3.** Distribution of Cervical Cancer Deaths by Age at Diagnosis, United States, 2012 to 2016. Patients (N = 4116) were diagnosed during 2002 through 2016 and were followed for up to 10 years after diagnosis. Data Source: Surveillance, Epidemiology, and End Results (SEER) Program, SEER 18 registries.<sup>48</sup>

many cervical cancer cases attributable to a diagnosis in patients aged 20 to 24 years were among women who were at high risk (eg, immunosuppressed and/or HIV-positive individuals for whom different screening recommendations would apply).

Evidence on the prevalence of high-grade cervical abnormalities across age groups<sup>37,72</sup> and the natural history of HPV infection<sup>6,72</sup> was also considered. The prevalence of HPV infection is a function of both the incidence (soon after sexual initiation) and persistence of the infection.<sup>6</sup> The highest incidence and prevalence of infection with hrHPV types generally is observed in women aged <25 years and decreases with age.<sup>73,74</sup> In younger women, the HPV incidence rate is relatively high, rates of persistence and progression are low, and regression of precursor abnormalities is high compared with older age groups.<sup>75-77</sup> As previously discussed, the majority of infections do not persist or progress to precancer but appear to undergo natural regression in a relatively short period of time (<2 years).<sup>6,78</sup> Studies using large clinical data sets show near zero cancer risk, and the lowest detection of cervical precancerous abnormalities is observed in women aged <25 years.<sup>79-81</sup>

Observational studies have reported that screening women aged 21 to 24 years has little demonstrated benefit in reducing the incidence of invasive disease compared with screening women aged  $\geq 25$  years.<sup>82-87</sup> A significant fraction of treatable lesions are expected to regress,<sup>88</sup>

leading to a potentially high rate of overtreatment and associated harms (including potential adverse obstetric outcomes), with follow-up testing and treatment of cervical abnormalities detected in screen-positive women in this age group.<sup>86,89</sup>

In the supplemental modeling analysis (Table 4),<sup>44,45</sup> starting screening with primary HPV testing at age 25 years, compared with a screening strategy of cytology alone from age 21 years followed by switching to primary HPV testing at age 25 years, retained >99% of the life-years gained, (64,193 vs 64,195, respectively) with fewer colposcopies (1775 vs 1826). Also, compared with the strategy of cytology alone beginning at age 21 years and switching to cotesting at age 30 years, starting screening with primary HPV testing at age 25 years showed a 13% gain in cervical cancer cases prevented and a 7% gain in cervical cancer deaths prevented, with similar life-years gained (64,193 vs 64,194, respectively) and with only 9% more colposcopies but 45% fewer tests (HPV or cytology) required overall. Furthermore, it is expected that the colposcopy rate will decline as HPV vaccination coverage expands and a growing fraction of HPV-vaccinated women reach the age to begin screening.<sup>18</sup>

The primary evidence review source<sup>4,43</sup> did not formally address vaccination status but reported finding limited evidence on how vaccination against specific hrHPV types affected outcomes of screening.<sup>4</sup> The supplemental literature review identified several observational studies reporting reductions in the risk of CIN2+ and hrHPV among vaccinated compared with unvaccinated individuals,<sup>18,34-36</sup> particularly when vaccination occurs before age 15 years, and recent US reports also indicate declining trends in the detection of CIN2+ and hrHPV in young women during the period since introduction of HPV vaccination.<sup>37,38,90-94</sup> These population-based data are promising and support the conclusions from vaccine RCTs<sup>95,96</sup> showing a protective effect in those who received the HPV vaccine. It is uncertain what level of vaccine uptake in the general population will achieve the level of individual protection and herd immunity that would warrant changes in screening protocols for all women or for those with documented vaccination history.

In initial deliberations, the GDG considered that there would likely be some benefit, although small, from continued screening of individuals in the group aged 21 to 24 years who have not been vaccinated against HPV at the recommended age. However, the small potential benefit of continued screening of individuals in this age group was judged not to outweigh the potential harms, especially as vaccination uptake in the United States continues to increase. As of 2018, 39.9% of adults aged 18 to 26 years (53.6% of women) reported having received at least one

**TABLE 4. Model-Estimated Benefits and Burdens of Cervical Cancer Screening Starting at Age 21 Versus 25 Years, per 1000 Screened Over a Lifetime**

SCREENING STRATEGY <sup>a</sup>	PER 1000 WOMEN					
	TOTAL NO. OF TESTS <sup>b</sup>	NO. OF COLPOS	CIN2,CIN3 DETECTED	CANCER CASES	CANCER DEATHS	LYG
1. No screening	0	0	0	18.86	8.34	63,921.34
2. Cyto every 3 y from age 21 y/cotest every 5 y ages 30-65 y	19,806	1630	201	1.08	0.30	64,192.97
3. Cyto every 4 y from age 21 y/HPV every 3 y ages 25-65 y	17,067	2209	217	0.75	0.23	64,195.53
4. Cyto every 4 y from age 21 y/HPV every 5 y ages 25-65 y	12,042	1826	209	0.81	0.25	64,195.35
5. Cyto every 4 y from age 21 y/cotest every 5 y ages 25-65 y	20,859	2029	213	0.82	0.26	64,195.26
6. Cyto every 3 y from age 25 y/HPV every 5 y ages 30-65 y	10,671	1303	175	1.46	0.40	64,188.10
7. Cyto every 3 y ages 25-65 y	13,313	564	142	2.60	0.86	64,176.12
8. HPV every 5 y ages 25-65 y	10,954	1775	195	0.94	0.28	64,193.52

Abbreviations CIN, cervical intraepithelial neoplasia; COLPOS, colposcopies; Cotest, cytology and human papillomavirus test; Cyto, cytology; HPV, human papillomavirus test; LYG, life-years gained.

<sup>a</sup>Scenarios 1 through 5 were reported previously (see Kim 2018<sup>44,45</sup>), whereas scenarios 6 through 8 were estimated as part of the supplementary modeling analysis.

<sup>b</sup>Values indicate the total number of tests, irrespective of primary, triage, or surveillance context.

dose of the HPV vaccine.<sup>33</sup> Serious consideration was given to the challenges of implementing a recommendation for individuals aged 21 to 24 years, depending on vaccination status, including major concerns about the variability in availability and access to vaccine registries and challenges in the transfer of patient records from pediatric to adult care. On the basis of the very small burden of disease in women at young ages, the potential obstetric harms associated with treatment of precursor lesions, and the implementation obstacles associated with determining vaccination status, the GDG chose to recommend that all individuals begin screening (with primary HPV testing preferred) at age 25 years.

### Screening Strategies for Cervical Cancer

Since the 2012 guideline, there has been an evolution in the evidence base for cervical cancer screening, an increase in the use of cotesting,<sup>22</sup> regulatory approval of primary HPV screening tests,<sup>14</sup> and the inclusion of primary HPV screening in the USPSTF 2018 recommendation statement.<sup>15</sup> On a foundation of the demonstrated benefits of incidence and mortality reduction attributable to cervical cancer screening, the systematic evidence review assessed the outcomes and performance of newer screening strategies (HPV testing, with or without cytology, vs cytology alone) in different age groups.<sup>43</sup> The evidence from RCTs<sup>75,76,97-99</sup> and other studies<sup>100,101</sup> showed that HPV-based cervical cancer screening has superior sensitivity and long-term negative predictive value compared with cytology-alone screening. Data from a

routine screening practice in a large US health system show that the risk of future CIN3+ and cervical cancer declines with an increasing number of negative cotests.<sup>100</sup> The low risk of subsequent cancer conferred by a negative HPV test result was similar to that for HPV alone and cotesting.<sup>100,101</sup>

The FDA indication for each of the 2 assays approved for primary HPV screening states that women who test negative for hrHPV types should be followed according to the physician's assessment of medical and screening history, other risk factors, and professional guidelines.<sup>14</sup> The clinical trials on which the FDA based its approval of tests for HPV primary screening had a follow-up time of only 3 years.<sup>74,102</sup> However, since 2012, cotesting has been recommended at a 5-year interval.<sup>5</sup> For primary HPV screening, with similar benefits and lower risk of harms, guidelines from leading organizations, including those from the ACS,<sup>5</sup> ASCCP,<sup>5</sup> the American Society for Clinical Pathology,<sup>5</sup> USPSTF,<sup>15</sup> and the American College of Obstetricians and Gynecologists<sup>103</sup> recommend a screening interval of 5 years based on evidence from a wider range of studies and the results of microsimulation modeling.

A recent trend analysis showed a continued increase in adenocarcinoma incidence rates.<sup>2</sup> Given the known limitations of cytology for adenocarcinoma detection,<sup>3</sup> several studies have suggested that screening with HPV testing could improve the detection of adenocarcinoma and its precursors,<sup>75,104-106</sup> although the systematic evidence review judged the evidence to be uncertain.<sup>4</sup>

The microsimulation modeling analysis conducted for the USPSTF suggests that, compared with no screening, screening with cytology alone every 3 years beginning at age 21 years, cotesting every 5 years after switching at age 30 years from cytology alone, and primary HPV testing every 5 years after switching at age 30 years from cytology alone, with screening ceasing at age 65 years under all strategies, can reduce the number of cervical cancer deaths from 8.34 (no screening) to 0.76, 0.30, and 0.29 deaths per 1000 women, respectively.<sup>44,45</sup> Compared with cytology alone, the higher CIN detection associated with primary HPV testing is accompanied by an increased number of false-positives and likely more colposcopies. In contrast, cytology alone has lower sensitivity for precancer and cancer than primary HPV testing or cotesting.<sup>4</sup> In the decision analysis,<sup>44,45</sup> cytology alone resulted in the lowest benefit in terms of life-years gained and cancer cases prevented and the lowest number of CIN2 or CIN3 and CIN 3+ cases detected.<sup>44,45</sup> Because of the higher number of total tests, cotesting was not efficient across any of the screening measures. For these reasons, the USPSTF concluded that cotesting was an alternative to the preferred strategies of primary HPV testing every 5 years and cytology alone every 3 years.<sup>15</sup> The evidence indicates that primary HPV testing is more effective compared with cytology alone and is more efficient than cotesting.

### HPV-Based Testing in Individuals Younger Than 30 Years

The ACS 2012 recommendation for cotesting as the preferred test was limited to women aged  $\geq 30$  years. In the new recommendation, primary HPV testing is preferred, and both cotesting and cytology alone are included as acceptable transitional screening strategies from age 25 years for all individuals. The inclusion of an HPV test improves sensitivity over cytology alone; however, as noted above, the increased number of tests associated with cotesting will likely increase the harms associated with screening in individuals aged 25 to 29 years, hence the importance of a rapid transition to primary HPV testing.

Recent guidelines have recommended the use of HPV-based testing for cervical cancer screening, either with cotesting beginning at age 30 years<sup>5,15</sup> or with stand-alone primary HPV testing beginning either at age 25 years<sup>16</sup> or at age 30 years.<sup>15</sup> There is clear evidence of superior sensitivity of HPV-based testing compared with cytology across all age groups.<sup>3</sup>

In the RCTs of the effectiveness of primary HPV testing, women were eligible to start screening at age 25 years. The evidence report<sup>4,43</sup> cited Ronco et al, concluding that there were substantially higher rates of HPV positivity among women younger than 30 to 35 years (13.1%) compared with

women aged  $>35$  years (5.8%)<sup>76</sup>; consequently, colposcopy rates, which were equivalent to the positive HPV test rates, were higher in younger women. By comparison, although they were slightly higher in women aged  $<35$  years, the rates of positive cytology tests were similar across age groups (4% vs 3.1%, respectively).<sup>4,43,76</sup>

In a prospective US screening study (Evaluation of the cobas<sup>®</sup> 4800 HPV Test of High-Grade Cervical Disease in Women Undergoing Routine Cervical Cancer Screening [ATHENA]; clinicaltrials.gov identifier, NCT00709891) evaluating the performance of primary HPV screening in women aged  $\geq 25$  years, HPV testing was significantly more sensitive for the detection of CIN3+ than cytology alone.<sup>102</sup> Both HPV16/HPV18 positivity and cytologic abnormalities were highest in women aged 25 to 29 years, and more than one-half of the women in this age group who had CIN2+ (or CIN3+) identified on colposcopy had a negative cytology result.<sup>102</sup>

The results of the decision analysis performed for the USPSTF showed that a cluster of screening strategies, starting with cytology at age 21 years and switching to primary HPV testing at age 25, 27, or 30 years, were efficient or near efficient.<sup>44,45</sup> Earlier switching to HPV testing resulted in more life-years saved, but with additional colposcopies, and harm-to-benefit ratios decreased (became more attractive) with a later age at switching.<sup>45</sup> The supplemental modeling analysis conducted for the ACS showed that starting primary HPV screening at age 25 years conferred a slightly higher benefit in terms of life-years gained and cervical cancer cases and deaths averted compared with starting screening with cytology at age 21 years and switching to HPV at age 30 years.

Given the increased prevalence of HPV test positivity and detection of cervical abnormalities that will initially result from HPV testing in women aged 25 to 29 years, there is growing recognition of the important role of adherence to conservative management guidelines. Either observation or immediate treatment of CIN2 is an acceptable strategy in patients who are concerned about the effects of treatment on a future pregnancy.<sup>21</sup>

In making its recommendation for cervical cancer screening with primary HPV testing as the preferred screening strategy in women aged  $\geq 25$  years, including specifically for women aged 25 to 29 years, the GDG placed a higher value on the greater cancer incidence reduction associated with higher detection of precursor abnormalities and the benefit in life-years gained, over the burden and harm measured by additional colposcopies. Consideration also was given to making a recommendation for primary HPV screening that applies to all women aged  $\geq 25$  years; and, for women aged 25 to 29 years, consideration also was given to the value of simple, less complex guideline

recommendations to improve adherence by both providers and patients.<sup>107</sup>

## When to Stop Cervical Cancer Screening

**The ACS recommends that individuals with a cervix who are older than age 65 years, who have no history of CIN2+ within the past 25 years, and who have documented adequate negative prior screening in the prior 10 years discontinue cervical cancer screening with any modality (qualified recommendation).**

- Adequate negative prior screening is currently defined as 2 consecutive negative HPV tests, or 2 consecutive negative cotests, or 3 consecutive negative cytology tests within the past 10 years, with the most recent test occurring within the recommended interval for the test used. These criteria do not apply to individuals who are currently under surveillance for abnormal screening results.
- Individuals aged >65 years without conditions limiting life expectancy for whom sufficient documentation of prior screening is not available should be screened until cessation criteria are met.
- Cervical cancer screening may be discontinued in individuals of any age with limited life expectancy.

Randomized trials and observational studies have demonstrated the effectiveness of cervical cancer screening in women up to age 65 years,<sup>4,43</sup> but the evidence for the effectiveness of screening beyond age 65 years is limited, based solely on observational and modeling studies. However, as noted in the 2012 guideline update,<sup>5</sup> the viral etiology of cervical cancer offers the opportunity to identify individuals who may be able to discontinue screening because they have had serial negative HPV test results and/or negative cytologic findings and thus are at very low risk for subsequently developing and dying from cervical cancer.

The 2012 joint guideline recommended against continued screening in women who had a history of adequate negative screening and no history of CIN2+ within the past 20 years.<sup>5</sup> Adequate negative screening was defined as 3 consecutive negative cytology results or 2 consecutive negative cotests within the past 10 years, with the most recent test having taken place within the past 5 years.<sup>5</sup> The rationale statement stressed that cervical cancer in the United States was most commonly diagnosed in unscreened and under screened individuals, whereas, in individuals with a history of routine screening, the prevalence of CIN2+ was low, cervical cancer was rare, and it was improbable that incident HPV infections and newly diagnosed CIN3 after age 65 years would progress to an

invasive cancer in an individual's lifetime. The statement emphasized that the benefit of continuing screening in regularly screened women was low relative to the potential harms associated with discomfort during sampling, false-positives, and the potential for overtreatment. The specific age to discontinue screening was based on observational and modeling data and the opinions of the expert panel members.

On the basis of recommendations in the 2002 and 2012 ACS guidelines for cervical cancer screening,<sup>5,20</sup> and in the absence of new evidence, the GDG reaffirms that individuals without a cervix and without a history of CIN2+ in the past 25 years (extended from 20 years in the 2012 recommendation<sup>5</sup>) or of cervical cancer ever, should not be screened.<sup>21</sup> Individuals of any age who have undergone hysterectomy with removal of the cervix and who have no history of CIN2+ should not be screened with cytology or HPV testing for lower genital tract malignancies, such as vaginal cancer.<sup>5</sup>

## Disease Burden and Risk in Older Individuals

Approximately 1 in 5 new cases of cervical cancer are diagnosed in women  $\geq 65$  years (Fig. 1). When considering the implications of an age to cease screening, it is important to examine incidence-based mortality, ie, cervical cancer deaths attributable to diagnoses in women after a proposed age for screening to cease. A substantial fraction of deaths in women  $\geq 65$  years result from diagnoses before age 65 years as well as incident cases that occur after age 65 years, each of which is largely attributable to a lack of screening.<sup>64,65,108</sup> Cervical cancer deaths from diagnoses in women aged  $\geq 65$  years account for approximately 1 in 4 deaths from cervical cancer each year (Fig. 3), whereas deaths from cervical cancer in women aged  $\geq 65$  years diagnosed at any age account for more than 1 in 3 deaths from cervical cancer (Fig. 2). The highest proportion of unscreened women within the ages recommended for screening is among women aged 60 to 65 years.<sup>4</sup>

## Impact of Prior Screening on Risk of Cervical Cancer in Women Older Than 65 Years

The GDG examined evidence of differential disease burden between regularly screened, underscreened, and unscreened women. Most of the evidence published since 2012 is from retrospective cohort, case-control, and modelling studies that examined outcomes associated with cytology-alone cervical cancer screening, whereas the evidence examining outcomes associated with primary HPV and cotesting in older women is more limited. Cytology-based studies have uniformly demonstrated a protective effect of prior screening on the likelihood of being diagnosed with cervical cancer,<sup>65,82,108-111</sup> often with less strict criteria compared with



the recommendation<sup>5</sup> for 3 consecutive, negative screening examinations over the 10-year period before reaching age 65 years.<sup>82,108,109,111</sup> Findings across these studies are similar, ie, cervical cancer among women aged  $\geq 65$  years is uncommon in a highly screened population; underscreening or no screening is associated with the large majority of cervical cancer diagnoses after age 65 years; and fulfilling conventional cytology cessation criteria appears to be highly protective.<sup>65</sup>

Few studies have examined the effect of primary HPV testing or cotesting on the subsequent risk of cervical cancer in older women, and the majority of those studies examined various histories of prior screening tests rather than the recommendation for 2 serial negative tests over a 10-year period before reaching age 65 years.<sup>5</sup> Nevertheless, recent evidence indicates that the protective effect from negative cotesting is even stronger than for cytology alone in women who have undergone a single cotest or multiple cotests at or near age 65 years.<sup>65,100,101,112</sup> In an observational cohort study from Kaiser Permanente Northern California that examined cotest results for almost 1 million women from 2003 to 2014,<sup>100</sup> investigators observed that 5-year CIN3+ risks in women aged  $\geq 50$  years decreased after each successive negative cotest screening round (0.060%, 0.036%, and 0.024%). For women aged  $\geq 50$  years with successive negative HPV tests as part of the cotest, regardless of cytology results, the decline in the 5-year CIN3+ risk was similar (0.073%, 0.042%, and 0.027%, respectively); and the CIN3+ risk associated with an HPV-negative test nearly matched the performance of a negative cotest, regardless of the cytology result. In another study of the Kaiser Permanente Northern California population, investigators observed that the 5-year risk of CIN3 after 1, 2, or 3 negative cotests in the 10-year period before age 65 years was 0.034%, 0.041%, and 0.016%, respectively.<sup>112</sup> No woman with 1 to 3 negative cotests was diagnosed with cervical cancer in the 5-year follow-up period. These results support the conclusion that sequentially negative HPV testing, with or without cytology, is associated with a very low risk of cervical cancer in older women. However, a more definitive answer to the question of how many negative cervical cancer screening tests provide sufficient safety over an individual's remaining life requires longer follow-up of existing cohorts.<sup>112</sup>

Although the preponderance of evidence suggests that sequential negative screening before age 65 years confers a low risk for subsequently developing and dying from cervical cancer, uncertainty remains regarding the duration of protection. A population case-control study based on National Health Service databases in England and Wales found that adequate cytologic screening up to age 65 years—defined as 3 negative screens between ages 50 and

64 years with at least 1 of these tests between ages 60 and 64 years, a history of screening similar to recommended cessation criteria in the current guideline<sup>5</sup>—conferred a low risk for developing cervical cancer over the ensuing 20 years.<sup>108</sup> The 20-year absolute risk of cervical cancer was 8 per 10,000 among regularly screened women, compared with 49 per 10,000 women not screened between ages 50 and 64 years (odds ratio [OR], 0.16; 95% CI, 0.13-0.19).<sup>108</sup> There are no observational studies examining the protective effect of negative primary HPV screening or cotesting on cervical cancer risk in older women beyond 5 years of follow-up, although modeling provides compelling evidence for very low lifetime cervical cancer risk after a negative HPV screening (see Modeling Age to Stop Screening, below).<sup>113</sup> However, some have questioned the durability of protection in adequately screened women aged  $>65$  years based on the possible role of HPV reactivation and progression of previously undetectable latent infections, as well as the risk conferred by newly acquired infections.<sup>114</sup> These are related to concerns about the potentially increased risk conferred by the increased lifetime number of sexual partners and later-in-life new partners of the generation now entering the cohort aged  $>65$  years.<sup>115</sup> Latent infections and reactivation at older ages, perhaps because of immune senescence, could theoretically contribute to the development of a small fraction of cervical cancers later in life. This possibility warrants continued study over the coming decades. The available evidence suggests that few persons aged  $>65$  years are likely to develop new infections that will follow a life-threatening course.<sup>115,116</sup> This is supported by a sensitivity analysis done for one modeling study demonstrating a low absolute risk even assuming double the current HPV prevalence in older women (see Modeling Age to Stop Screening, below).<sup>113</sup> The GDG reaffirms the conclusion of the 2012 guideline that, once screening is discontinued, it should not resume for any reason, even if an individual reports a new sexual partner.<sup>5</sup>

### Efficacy of Screening in Older Individuals

How well cytology and HPV screening perform in individuals aged  $>65$  years, principally those who have not met cessation criteria before age 65 years, compared with younger individuals, is incompletely understood, but the potential benefit of cervical cancer screening is likely diminished with increasing age by reported anatomic, hormonal, and immunologic changes and musculoskeletal disorders. These changes and vaginal atrophy may make positioning for an examination difficult, cause examinations to be painful, and limit access to the transmission zone for adequate sampling.<sup>117,118</sup> Visualization with colposcopy of the cervical transformation zone also declines.<sup>117,118</sup> In one

observational study of HPV prevalence and HPV-related dysplasia in elderly women aged 60 to 89 years, the transformation zone was not visible during colposcopy in about two-thirds of women, was only partly visible in one-third, and no study participants were reported to have a fully visible transformation zone.<sup>119</sup> In another study, screening between ages 55 and 64 years demonstrated a clearly protective effect against cervical cancer death up to age 79 years (OR, 0.18; 95% CI, 0.06, 0.57), whereas screening in those aged >65 years was associated with a nonsignificant protective effect (OR, 0.47; 95% CI, 0.14, 1.63), although the precision of this observation was affected by low screening numbers.<sup>120</sup> Analyses of data from 2 US health care delivery systems demonstrated a 78% to 84% reduced risk of cervical cancer in screened versus unscreened women aged ≥65 years,<sup>110</sup> and another observational study linking Surveillance, Epidemiology, and End Results registry and Medicare claims data reported a strongly protective effect of cytology screening in women aged ≥65 years when controlling for hysterectomy status.<sup>111</sup> However, neither of those studies examined the effect of prior screening history. Moreover, there is a lack of empirical evidence examining outcomes associated with primary HPV screening or cotesting after age 65 years. Finally, although anatomical changes associated with older age are purported to reduce the sensitivity of screening, no studies were identified that examined differential performance of cytology, primary HPV testing, and cotesting in older individuals. Although the available data suggest that screening older women is effective overall and that some individuals will likely benefit from continuing screening, it is likely that most of the benefit would be realized in the large subset of individuals who have not been adequately screened before age 65 years.

### Harms and Risks of Screening in Older Individuals

In regularly screened individuals, screening becomes less *efficient*, meaning that the additional number of colposcopies (as a surrogate for harms) required to achieve an additional unit of benefit increases with advancing age beyond 65 years, suggesting that the benefit-harm balance becomes less favorable.<sup>44</sup> In addition, as noted above, musculoskeletal disorders and vaginal atrophy can make the examination more painful in older women,<sup>117</sup> and the risks associated with biopsy, excisional, and ablative procedures are greater in older individuals.<sup>118</sup> Finally, given the slow progression from CIN to invasive disease, overdiagnosis and overtreatment are particular concerns in older individuals.<sup>119</sup>

### Modeling Age to Stop Screening

Given the absence of randomized trials that address the optimal age to stop cervical cancer screening and the limitations of available observational data, 3 recent modeling

studies contribute additional evidence to address this question. To support the Australian National Cervical Screening Program's evaluation of potential screening strategies, Lew and colleagues modeled primary HPV testing, cotesting, and cytology screening with a range of starting and stopping ages.<sup>121</sup> Overall, screening until age 69 years was associated with a 5% to 8% reduction in cancer mortality compared with screening until age 64 years, although the authors did not present their results in terms of absolute risk. A model using a Canadian provincial registry and survey data estimated the risks of cervical cancer incidence comparing cytology, primary HPV, and cotesting and examined stopping ages of 55 and 70 years.<sup>113</sup> Assuming typical adherence, extending cytologic screening from age 55 to age 70 years reduced the remaining lifetime risk of cervical cancer from 1 in 440 to 1 in 1206. In contrast, extending HPV screening from age 55 to age 70 years reduced the risk from 1 in 1940 to 1 in 6525. Given speculative concerns about reactivation or newly acquired HPV infections among successive cohorts of women currently approaching the age of screening cessation, these estimates of low risk with a history of HPV screening provide reassurance of low future cervical cancer risk in the period after screening ceases in individuals who meet cessation criteria.<sup>114</sup> Moreover, the model did not examine the effect of serially negative screens before stopping screening, which has been recommended since 2012.<sup>5</sup>

The modeling analysis performed for the USPSTF 2018 guideline update found efficient strategies for extending screening to ages 70 and 75 years.<sup>44,45</sup> However, the absolute benefit in terms of life-years gained was very small. For example, in a strategy of a single cytology screen at age 21 years transitioning to 5-year HPV testing at age 25 years, cessation of screening at age 65 years conferred 99.6% of the life-years gained from extending screening to age 70 years.<sup>45</sup> In addition, the corresponding harm-benefit ratios—measured as the number of colposcopies required to achieve an additional year of life—increased with increasing end age, indicating that screening becomes less efficient beyond age 65 years.<sup>44</sup> For example, achieving a very small gain in life-years by extending the screening strategy described above from age 65 to age 70 years would come at a cost of 3% more colposcopies.<sup>44</sup> The authors cautioned that their modeling results related to the age at which to end screening should be considered exploratory in light of the uncertainties regarding the natural history of HPV infection and regarding screening effectiveness in older women.<sup>44</sup>

### Individuals With a History of CIN2, CIN3, or AIS

On the basis of data from long-term follow-up studies, the 2019 ASCCP risk-based management consensus guideline<sup>21</sup> recommends that individuals previously treated for histologic high-grade squamous intraepithelial lesions, CIN2, CIN3, or AIS should continue cervical cancer

surveillance for at least 25 years. If patients with a history of CIN2, CIN3, or AIS have completed the initial 25-year surveillance period when they reach age 65 years, continued surveillance at 3-year intervals is acceptable and may continue as long as the patient is in reasonably good health. The management guideline recommends discontinuation of screening if a patient has limited life expectancy.<sup>21</sup> According to the Society for Gynecologic Oncology's (SGO) 2020 recommendations, for patients who initially underwent fertility-sparing management for AIS and have completed childbearing, either hysterectomy or continued surveillance is acceptable for those who have had consistently negative HPV test results during surveillance. For patients who have had positive HPV test results during surveillance, hysterectomy after completion of childbearing is preferred.<sup>122</sup>

Although no screening approach will entirely prevent the occurrence of cervical cancer in older individuals, assuring an adequate history of screening before cessation is likely to be one of the most effective strategies to reduce the relatively substantial disease burden from cervical cancer in older individuals. The identification of inadequately screened individuals must be a priority of clinicians and health systems. If documentation of recent screening cannot be obtained, as will often be the case, given the absence of screening registries in the United States and the lack of shared medical records between providers and health systems, screening tests should be performed until the criteria are met for cessation.

## Clinical Considerations

At the most basic level, the success of a cancer screening program depends on a high rate of regular attendance by the target population and the accuracy of the screening test. However, there are many ancillary issues that go beyond the screening recommendations that also are integral to successful outcomes, such as attention to individual risk of developing cervical cancer, quality assurance, elimination of access barriers, patient/clinician communication, management of abnormal findings, implementing new features of a guideline, and adoption of new technology.

## Management of Abnormal Screening Test Results

The performance of screening and the balance of benefits and harms importantly depend on adherence to protocols for management of positive screening results. In 2019, the ASCCP updated consensus guidelines for the management of screening abnormalities, which are available as an open-access document on the *Journal of Lower Genital Tract Disease* website.<sup>21</sup> Clearly defined risk thresholds based on the results of HPV tests, alone or in conjunction with cytology, are used to guide management (more or less frequent surveillance, colposcopy, or treatment; or return to routine screening).<sup>21</sup> Risk estimation tables and

decision aids also have been provided to estimate a patient's risk of having or developing CIN3+ (as a surrogate endpoint for developing cervical cancer), based on a current screening test result and previous screening tests and biopsy results. The patient's age also is a consideration in the context of reproductive decisions. As noted above, the growing prevalence of individuals who receive timely vaccination against hrHPV types will result in a decrease in the prevalence of HPV infections, which, in turn, will influence management recommendations. It cannot be stressed too emphatically that the updated ASCCP management guidelines should be regarded as integral to the success of this screening guideline, because failure to follow-up a positive screening test in a manner that is adherent to the ASCCP management guidelines undermines what is achieved with screening and can result in harm to the patient.

## Individuals at Increased Risk

This guideline update applies to average-risk adults who are initiating screening, or have had only normal cervical cancer screening results in the past, or have been returned to routine cervical cancer screening based on follow-up recommendations from the risk-based management consensus guidelines.<sup>21</sup> This guideline does not address screening or surveillance in persons at higher risk for developing cervical cancer (see Table 1).

The higher risk of cervical cancer in individuals who are immunosuppressed because of HIV infection is well established in the literature.<sup>123</sup> For these individuals, the recommendations for screening from the Centers for Disease Control and Prevention, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America,<sup>124,125</sup> and the US Department of Health and Human Services<sup>126</sup> should be followed. Although the evidence on the increased risk of cervical cancer among non-HIV-immunosuppressed individuals is more limited, clinicians should give attention to the potential increased risk of patients who are solid organ or stem cell transplantation recipients or are undergoing immunosuppressant therapy. Screening recommendations for these subgroups and others potentially at higher risk than the general population because of immunosuppression have been the same as those for people living with HIV.<sup>126</sup> More recently, Moscicki and colleagues have provided detailed guidance on screening various subgroups of non-HIV-immunocompromised individuals.<sup>127</sup>

Individuals with a cervix who were exposed to diethylstilbestrol in utero are at greatly increased risk of developing clear cell adenocarcinoma of the lower genital tract, a very rare cancer with the majority of the incidence occurring before age 30 years, but with elevated risk remaining into the 40s.<sup>128</sup> In addition, those exposed to in-utero DES are at increased

risk of developing abnormal cells in the cervix and the vagina that are precursors of cancer (dysplasia, CIN, and squamous intraepithelial lesions).<sup>129,130</sup> Screening recommendations for these individuals have included pelvic examination with visualization of the cervix and vaginal wall, annual cytology, and consideration of colposcopy.<sup>103</sup> Comprehensive screening recommendations for this group have not been recently updated, nor has consideration been given to the aging of the diethylstilbestrol-exposed population.

### Adequate Screening and Documentation Before Cessation

A majority of cases of invasive cervical cancer occur in individuals who have never been screened or have not been adequately screened.<sup>64,131</sup> According to the 2018 National Health Interview Survey data, 90% of respondents aged 30 to 39 years reported being up to date with screening; this rate declines to 80% among women aged 50 to 65 years.<sup>132</sup> The underscreening of those aged 50 to 65 years is particularly concerning because individuals with a 10-year history of normal screening results may discontinue screening after age 65 years. A history of prior normal screening tests is a crucial marker for reduced risk of developing cervical cancer or precancer. The criterion for cessation is adequate negative prior screening, currently defined as 2 consecutive negative HPV tests, or 2 consecutive negative cotests, or 3 consecutive negative cytology tests within the past 10 years, with the most recent primary HPV test, cotest, or cytology-alone test occurring within their recommended intervals.

The structure of health care in the United States presents enduring challenges in addressing the decline in screening with age and the difficulty obtaining documentation of screening history to assess criteria for screening cessation, particularly for individuals who have changed their residence or health care provider. In a national administrative database capturing almost one-half of employer-sponsored US health insurance plans, only 29% of the 110,961 potentially eligible women met cessation criteria based on available documentation; limiting the analysis to women who were continuously enrolled for  $\geq 10$  years increased the proportion meeting cessation criteria, but only to 53%.<sup>133</sup> Clinicians and health care systems should implement programs to identify and screen the subgroup of individuals who have not initiated screening or who have had inadequate recent screening, with ample time to meet cessation criteria. Further efforts should be devoted to electronic health record interoperability across all clinical settings so that it will be easier for clinicians to obtain relevant medical and screening history data to identify persons who need to extend screening to meet cessation criteria or avoid overscreening because the medical

record cannot be accessed. In the absence of such accessible confirmation of recent negative screening results, clinicians should continue to offer screening to individuals without conditions limiting life expectancy until criteria for cessation are confirmed.

### Implementation of Primary HPV Testing

This guideline explicitly acknowledges a period of transition toward the availability and utilization of primary HPV screening in all clinical settings. Two primary HPV tests are FDA-approved specifically for primary screening in the United States. As of 2017, primary HPV testing was available only in a limited number of US laboratories,<sup>134</sup> and it may take time and financial resources for laboratories currently using other HPV testing platforms to add platforms using the tests approved for primary screening.<sup>135</sup>

The inclusion of cotesting and cytology-only testing as screening strategies in this update should be viewed as provisional: an acknowledgment of the variability that may exist in access to preferred testing technology across health care settings in the United States, and the time that will be required for primary HPV testing to replace cotesting and cytology-only testing in all clinical settings and laboratories that process specimens for cervical cancer screening. Clinicians are often unaware of which testing platform is offered by the laboratory used by their practice or health system, and most clinicians do not have any control over the choice of laboratory or testing platform. Hence, it is incumbent on laboratory directors and clinical practice medical directors to lead local efforts to transition to primary HPV screening.

HPV tests should both be FDA-approved and meet specific established benchmark criteria for clinical performance, including high sensitivity, high specificity, and high intralaboratory and interlaboratory reproducibility.<sup>136</sup> Tests not meeting these standards of performance and not FDA-approved as a stand-alone primary HPV test should not be used for primary screening. As uptake of primary HPV testing proceeds, health care providers are advised to ascertain whether the HPV tests available in their clinical setting are FDA-approved for primary HPV screening to ensure that patients are being screened with a test that has met the appropriate performance standards.

### Future Directions Vaccination Impact

As the proportion of vaccinated individuals increases, the prevalence of hrHPV types is expected to decrease,<sup>137</sup> which will reduce the positive predictive value of both cytology and primary HPV testing. This reduction in prevalence, along with potential reductions in CIN3+ prevalence (attributable



to protection from vaccination), may increase the relative proportion of false-positive screening results. There are ongoing RCTs to evaluate the performance of primary HPV testing versus cytology screening for cervical cancer in HPV vaccinated women.<sup>138</sup> However, as noted above, there is an inherent logic to the expectation that HPV vaccination will decrease the efficiency of cytology for cervical cancer screening, and early empirical indications provide support for this expectation.<sup>34</sup> Although it is not the case now, with increased vaccination coverage in the screening population and the existence of comprehensive vaccination registries, screening strategies could be tailored to vaccination status where feasible.

### Primary HPV Testing and the Diminishing Role of Cytology Screening

Despite known limitations in accuracy and quality-assurance challenges, the burden of cervical cancer, particularly squamous cell cervical cancer, has been successfully reduced since the middle of the last century in populations with widespread access to cytology. However, the development of molecular assays for detecting HPV is an advance in cervical cancer screening that offers improved sensitivity and better reassurance of low future cancer risk from a negative screening test for a causative agent compared with cytology.

Primary HPV testing was not included as an option for screening in the 2012 ACS guideline update due to several factors, including lack of an FDA-approved test for primary screening and because the evidence for the effectiveness of primary HPV testing in the majority of studies was limited to a single round of screening.<sup>5</sup> Since 2012, several RCTs have been published on the effectiveness of primary HPV testing for cervical cancer screening that include subsequent rounds of screening,<sup>43</sup> and there are now FDA-approved tests for primary screening. Although the FDA approved the first test for primary HPV screening in 2014, as of 2017, only 40.6% percent of laboratories reported that they offered primary HPV screening, and, among those that did, primary HPV screening was a very small fraction of all HPV-associated testing.<sup>134</sup> Furthermore, the survey reported variability in the settings where HPV genotyping (for management of positive results, not primary HPV screening) was available. The majority (>70%) of reporting laboratories were large hospital/medical centers, regional/local independent laboratories, or laboratories affiliated with university hospital/academic medical centers.<sup>22</sup> Laboratories in public health agencies or affiliated with local, state, or federal agencies represented the lowest numbers offering HPV testing.<sup>22</sup> The 2016 to 2017 survey<sup>134</sup> did not include questions related to all HPV testing, so it is unclear at this time whether access has increased. However, although we expect that laboratory capacity has increased with the

increase in FDA-approved tests and several guidelines endorsing primary HPV screening, we may continue to see the availability of FDA-approved HPV testing being location-dependent and small laboratories and those in lower resource settings transitioning to full access later than larger laboratories and those in health care systems with greater resources.

The implementation of primary HPV testing for screening in all health care settings in the US will be a major undertaking that is expected to take some time. Insofar as the disease burden of cervical cancer is disproportionately borne by minority and underserved populations,<sup>60,139,140</sup> the unequal diffusion of a superior screening test could impede cervical cancer prevention services among medically underserved populations and further worsen health inequities. The countries where primary HPV testing was recently introduced have the benefit of nationwide screening programs and centralized laboratory services in which changes could be implemented simultaneously in all settings.<sup>121,141</sup> However, it cannot be stressed too strongly that the delay in implementing new, more sensitive screening technology, even when an effective technology already is in place, can be costly in terms of new cases and deaths that could have been prevented. Castanon and colleagues estimated that a 1-year delay in replacing cytology cervical screening with primary HPV testing in England would miss the opportunity to prevent 581 cases of cervical cancer and lead to a loss of 1595 quality-adjusted life-years.<sup>142</sup>

### Self-Sampling

The introduction of HPV cervical cancer screening has ushered in a new potential for self-sampling for cervical cancer screening. In studies conducted from the mid-1990s through the first 2 decades of the 2000s, HPV self-sampling in cervical cancer screening has been shown to be feasible and acceptable and is a viable approach to screening in never-screened and under screened populations.<sup>143,144</sup> HPV self-sampling is superior to self-sampling for cytology testing for several reasons; in particular, the adequacy of specimen collection (source and adequacy of cells, including morphologic features) essential for cytology testing is more likely to be adversely affected by self-sampling compared with sampling by a trained professional. In contrast, molecular testing for HPV DNA or RNA uses assays that are less affected by specimen adequacy,<sup>145</sup> and there is a growing body of evidence demonstrating the validity of HPV self-sampling compared with cervical samples collected in a clinical setting.<sup>75,146,147</sup> Several different methods for specimen collection may be used, including brushes, swabs, vaginal patches, and lavage, among others.<sup>144,148</sup>

Evidence supporting the usefulness of HPV self-sampling includes substantial increased participation of

hard-to-reach women in home-based screening programs. In addition to greater uptake of screening, the reported advantages of HPV self-sampling include convenience, privacy, less embarrassment and anxiety, ease of use, and less discomfort and pain compared with in-office specimen collection.<sup>143,146,149</sup> The method of dissemination of self-sampling test kits has an impact on screening uptake—the most effective impact is achieved with HPV self-sampling kits offered door-to-door by health workers, whereas mailing kits directly to the homes or requiring women to pick up their own kits is less effective in achieving screening uptake.

Self-sampling offers lower cost screening opportunities with a choice of screening location, often the home, and potentially greater access, convenience, and privacy. In low-income and middle-income countries and populations, as well as in settings where some groups of women are hard to reach, self-sampling has the potential to save many lives.<sup>150-152</sup>

Although self-sampling offers great potential to expand the scope of cervical cancer screening, it has not been approved by the FDA, and a recommendation for self-sampling outside of research studies is not included in this guideline update. Furthermore, when self-sampling is approved, it will be important to identify populations most likely to benefit and to ensure that there is strict adherence to protocols and that patients have unimpeded access to appropriate follow-up and management in clinical settings. We anticipate that self-sampling will play an increasingly prominent role in cervical cancer screening once regulatory and clinical prerequisites are in place and as supporting evidence continues to accumulate.

## Discussion

### Changes from the Previous Guideline

The recommendations in this guideline continue to build on the decades-long contribution of cervical cancer screening to reducing incidence and mortality from cervical cancer. Based on the accumulation of evidence, the ACS now recommends primary HPV testing at a 5-year interval as the preferred screening strategy *for all individuals being screened*, replacing the recommendation for cytology testing, with a switch to cotesting at age 30 years as the preferred strategy. The ACS GDG relied on evidence demonstrating the effectiveness of screening with primary HPV testing and the high sensitivity for detecting precancers and predicting future risk.

Compared with primary HPV testing, cytology testing—the former mainstay of cervical cancer screening—has inferior sensitivity and provides lesser assurance regarding future risk. The combination of cytology and HPV testing (cotesting) offers very little incremental benefit in detection but increases the number of procedures

and the risk for harms. Therefore, the GDG concluded that primary HPV testing should be designated as the preferred screening test.

In this update, the use of cotesting (at a 5-year interval) or cytology alone (at a 3-year interval) are included as acceptable options for screening through what is expected to be a period of transition in the availability of and access to tests that are FDA-approved for primary HPV screening. The GDG chose not to prioritize among these 2 screening strategies because they are expected to be phased out as primary HPV screening becomes uniformly available. It is expected that the availability and use of primary HPV testing for cervical cancer screening will increase in all health care settings in the United States; but, in the meantime, screening utilization and adherence are prioritized, thus continuing the use of cytology and cotesting is acceptable if primary HPV testing is not available.

The other major change from the previous guideline is the recommendation that all average-risk individuals with a cervix initiate screening for cervical cancer at age 25 years rather than 21 years, with primary HPV testing preferred. The GDG examined the evidence on disease burden, the efficacy and effectiveness of available screening tests, and the harms of screening in women aged <30 years. The disease burden of cervical cancer among individuals aged <25 years is very low, and the modeling study suggested that any incremental benefit conferred by starting screening at age 21 years with cytology and then switching to primary HPV testing at age 25 years would be very small compared with strategies starting at age 25 years with any screening test. Additional burdens associated with a starting age of 21 years are the higher number of colposcopies because of transient infections and the associated stress along with the possible increased risk of adverse obstetrical outcomes in those who undergo cervical excisional procedures.

Some have expressed concerns that unvaccinated women aged 21 to 24 years (or individuals in the adjacent age group) will unduly experience higher disease burden as a result of increasing the starting age for screening to 25 years. The recommendation for screening beginning at age 25 years with primary HPV testing applies to both vaccinated and unvaccinated women, based on the evidence of superior sensitivity and negative predictive value of HPV testing, the very low disease burden at young ages in unvaccinated and vaccinated women, the overall balance of benefits and harms, and the considerable implementation obstacles to any screening policy tailored to individual vaccination status. Inadequate record keeping and faulty recall would severely limit the feasibility of a recommendation based on vaccination status. It is hoped that a single recommendation for individuals aged 25 to 65 years will minimize confusion and contribute to

enhanced implementation and adherence. Furthermore, we can anticipate increasingly lower HPV prevalence in these younger individuals as prior and new vaccinated cohorts reach the age of 21 years.

### Comparison With Other Guidelines

The USPSTF updated their cervical cancer screening recommendations in 2018.<sup>15</sup> Screening for cervical cancer received an “A” rating and was recommended every 3 years with cytology alone for women aged 21 to 29 years and, for women aged 30 to 65 years, every 3 years with cervical cytology alone, every 5 years with primary HPV testing alone, or every 5 years with cotesting. The USPSTF considers cytology alone and HPV testing alone strategies for those aged 30 to 65 years as preferred; cotesting is considered an alternative strategy. Like the ACS, the USPSTF does not recommend screening for cervical cancer in individuals aged >65 years who have had adequate prior screening and are not otherwise under surveillance; screening also is not recommended for individuals who have had a hysterectomy with removal of the cervix and do not have a history of a high-grade precancerous lesion or cervical cancer. The primary difference between the USPSTF and ACS recommendations is the ACS’s strong recommendation to begin screening at age 25 years with primary HPV testing preferred (with cytology and cotesting as acceptable options). In contrast, the 2018 USPSTF recommends beginning screening at age 21 years with cytology alone, with transitions at age 30 years to using 1 of the 3 screening options described above.<sup>15</sup>

In 2015 a panel convened by the SGO and the ASCCP published guidance and information on primary HPV testing as a strategy for screening for cervical cancer.<sup>16</sup> This was the first guidance on screening after the FDA-approved the first HPV test for primary cervical cancer screening. The panel indicated that the test showed effectiveness equivalent or superior to that of the current cytology-based cervical cancer screening methods and thus concluded that HPV testing for cervical cancer screening starting at age 25 years can be considered as an alternative. On the optimal interval for primary HPV testing, they indicated that rescreening after a negative primary HPV screen should occur no sooner than every 3 years. The interim guidance also stated that cytology alone and cotesting remain as screening options specifically as recommended in major guidelines. The American College of Obstetricians and Gynecologists’ current cervical cancer screening guidelines encompass screening with cytology alone, cotesting, and primary HPV testing, with ages to begin and end screening and to initiate HPV-based screening consistent with ASCCP and SGO interim guidelines.<sup>16,103,153</sup> In 2015, the American

College of Physicians<sup>154</sup> issued a best-practice advice article that was largely concordant with the 2012 consensus guidelines,<sup>5</sup> although no preference was stated for cytology alone every 3 years versus cotesting every 5 years, in line with the USPSTF recommendation at that time. The American Academy of Family Physicians endorses the 2018 USPSTF recommendations.<sup>155</sup>

### Limitations

The recommendation for cervical cancer screening with primary HPV testing is based on RCT data limited to one or two rounds of screening, with screening intervals varying from 3 to 5 years, and the reporting of harms (colposcopy and biopsy rates) was not consistent across these studies.<sup>43</sup> The RCTs generally were conducted in settings with organized cancer screening programs, so it is reasonable to believe that participants were more uniformly up to date or adherent to screening than can be assumed in the US setting. Continued accumulation of data over several rounds of HPV primary screening will provide greater confidence in the performance of primary HPV testing at the recommended screening interval. However, given the wide screening interval, the accumulation of serial testing data with longer versus shorter screening intervals will require a lengthy observation period. In the US health care setting, where screening is opportunistic, the higher sensitivity of primary HPV testing and increased detection of CIN3+ may be especially beneficial to individuals who do not undergo regular screening. There is disparity in the cervical cancer disease burden in the United States, with higher rates of disease among Black and Hispanic women and women of lower socioeconomic status: populations not optimally represented in the RCTs. Although screening tests are not expected to perform differently in these individuals, this limitation in the data is acknowledged.

Projections from modeling studies were also considered as evidence to guide these new recommendations. Although model-based studies are used to synthesize the best available epidemiologic, clinical, and resource data from various empirical studies and databases, there are invariably uncertainties in the data and model structures that are unavoidable. Limitations of the 2018 USPSTF model that was also used to provide supplemental evidence to the ACS GDG have been documented previously.<sup>44,45</sup>

Questions remain about the age and criteria for cessation of screening, and there is a lack of good evidence on the effectiveness of continued screening in well screened older women on which to base a recommendation for continued screening. Areas of remaining uncertainty include the effect of persistent HPV infection, reactivation, and the course after acquisition of new infections at older ages. In addition, increasing life expectancies and potential cohort

effects because of changes in lifetime sexual behaviors of US women over time have been suggested as points to consider in formulating recommendations for the cessation of screening.<sup>114</sup> These considerations will be revisited in future guidelines as evidence addressing these issues accumulates, with the potential that future recommendations related to cessation of screening could be increasingly tailored.

### Research Needs

There is strong consensus that successful screening and management of precursors of cervical cancer have led to substantial reductions in cervical cancer incidence and mortality. However, there are enduring and new research challenges related to effective intervention strategies to improve screening utilization and guideline adherence among inadequately screened and unscreened subpopulations.<sup>156</sup> For example, although the potential for self-sampling to increase screening rates in hard-to-reach populations has been demonstrated, there is a need to systematically address any remaining uncertainties so that this screening strategy can be implemented with confidence in appropriate settings.

There is a need for better understanding of the risk for early onset cervical cancer. Also of particular importance is identifying effective strategies that ensure women accumulate the history of normal screening examinations that would provide the opportunity to cease screening at age 65 years. Another important question for continued research concerns the effectiveness of screening tests in a vaccinated population as the uptake of HPV vaccination increases, including the incorporation of new genotyping tests and opportunities to extend screening intervals.

Recent trends show increasing rates of adenocarcinoma,<sup>2</sup> which is less likely to be prevented by cytologic detection (and treatment) of its precursors compared with squamous cell carcinoma. Although there is limited evidence of the effectiveness of screening strategies specific for AIS and adenocarcinoma, there is some indication that primary HPV testing may improve early detection.<sup>157</sup> The most effective screening strategy for the early detection of adenocarcinoma is still unclear and an area of research need.

### Communication and Transition Challenges

A guideline change necessitates a communications strategy directed to medical professionals and the target population. The ACS will be working with other national organizations to promote the necessary changes in system capacity and processes, as well as the educational and communication efforts that will be necessary to accomplish the transition to high-quality, FDA-approved primary HPV cervical cancer screening with minimal disruption.

Although there is indication that the most influential factors in clinicians' cervical cancer screening practices are

screening guidelines,<sup>158</sup> in many health care settings, the current cervical cancer screening recommendations are not consistently followed, do not match women's preferences, or do not reflect efforts to educate women about new, recommended protocols.<sup>54</sup> A national survey of different provider groups (family physicians, nurse practitioners, obstetricians and gynecologists, and certified nurse-midwives) revealed considerable disparities and variation between and among provider groups in the use of cervical cancer screening tests.<sup>159</sup> Despite recommendations against annual cervical cancer screening from major guideline developing groups, and many years since annual cytology screening was recommended, it is reported that annual cytology testing still is common.<sup>160,161</sup> Likewise, adoption of the 2012 preferred strategy of cotesting for women aged 30 to 65 years had been slow, although recent reports show an upward trend in cotesting among individuals aged 30 to 65 years,<sup>24,25,162</sup> which varied geographically, from 27.5% in Utah to 49.9% in the District of Columbia.<sup>163</sup> Not only is guideline adherence an enduring challenge; but, as noted previously, concerns about lack of universal access to preferred screening tests overall, and more so outside of urban and academic settings, have been borne out by national surveys of laboratories.<sup>22,134</sup>

The GDG acknowledges the implementation challenges posed by recommending a new strategy for cervical cancer screening. Although the transition to primary HPV testing is occurring, the GDG is hopeful that the recommendation of a single test with a single screening frequency will facilitate broader adherence. The new recommendation diverges from older, but still current, recommendations from other organizations, thus the ACS will actively provide clear communication and rationale about of the new recommendation to clinicians and the public (cancer.org). The transition to primary HPV testing will take time, and it is our hope that this transition will be facilitated by health plans providing coverage for primary HPV testing or cotesting beginning at age 25 years. Health care providers can play an important role in counseling patients who are uncomfortable with longer screening intervals or who have concerns about recommended starting and stopping ages. Health care providers also can direct efforts to improve the still limited public understanding of the prevalence and course of HPV infection and its association with cervical abnormalities and cancer, which may exacerbate psychological and psychosexual consequences among individuals who receive a positive HPV result after screening.<sup>52,164</sup>

Ensuring that individuals adhere to a 5-year screening interval poses challenges for patients, clinicians, and payers. For patients, keeping track of when they are due for screening may be, and likely will be, more difficult than keeping track of short-interval testing. For clinicians, harnessing registries to monitor the screening status of all women is crucial



but may be more difficult for longer interval testing because of changing practice enrollment and insurance coverage.

The expectation that all individuals can be efficiently screened for cervical cancer precisely 5 years after their previous screening examination is unrealistic and impractical. Therefore, to remain up to date with the recommended 5-year screening interval, individuals should be able to be screened in the months leading up to the end of the interval. Insurance coverage must be flexible enough to support these real-life considerations, including an opportunity for screening coincident with a clinical encounter for other reasons.

The ACS will collaborate with professional societies and other stakeholders to assist in supporting the transition to primary HPV testing for cervical cancer screening. The ACS also will work with key organizations to

overcome the barriers to screening that contribute to the persistence of avoidable morbidity and mortality from cervical cancer. ■

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