American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology Screening Guidelines for the Prevention and Early Detection of Cervical Cancer

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■ **Abstract:** An update to the American Cancer Society (ACS) guideline regarding screening for the early detection of cervical precancerous lesions and cancer is presented. The guidelines are based on a systematic evidence review, contributions from six working groups, and a recent symposium co-sponsored by the ACS, American Society for Colposcopy and Cervical Pathology (ASCCP), and American Society for Clinical Pathology (ASCP), which was attended by 25 organizations. The new screening recommendations address age-appropriate screening strategies, including the use of cytology and high-risk human papillomavirus (HPV) testing, follow-up (e.g., management of screen positives and screening interval for screen negatives) of women after screening, age at which to exit screening, future considerations regarding HPV testing alone as a primary screening approach, and screening strategies for women vaccinated against HPV16/18 infections. ■

Cervical cancer screening has successfully decreased cervical cancer incidence and mortality. The ACS Guideline for the Early Detection of Cervical Cancer was last reviewed and updated in 2002; for the first time, those recommendations incorporated human papillomavirus (HPV) DNA testing [1]. Since that time, numerous studies have been published that support changes to recommended age-appropriate screening as well as the management of abnormal screening results, as summarized in Table 1 [2].

BACKGROUND

High-quality screening with cytology (Pap testing) has markedly reduced mortality from squamous cell cervical cancer, which comprises 80–90% of cervical cancers [3–5]. Since the introduction of cervical cytology in the United States in the mid-20th century, cervical cancer, once the most frequent cause of cancer deaths in women, now ranks 14th for cancer deaths [6]. This reduction in mortality through screening is due to 1) an increase in detection of invasive cancer at early stages, where the five-year survival rate is approximately 92% [7] and 2) detection and treatment of pre-invasive lesions, which reduces the overall incidence of invasive cancer. In 2012, an estimated 12,170 cases of invasive cervical cancer will be diagnosed, and an estimated 4,220 women will die [6].

It is now understood that persistent cervical infection with high-risk human papillomavirus (HPV) genotypes ("types") is necessary for the development of cervical cancer and its immediate precursor lesion ("precancer"), cervical intraepithelial neoplasia (CIN) grade 3 (CIN3). Epidemiologic case series have shown that nearly 100% of cervical cancer cases test positive for HPV [8]. HPV16

is the most carcinogenic HPV genotype and accounts for approximately 55–60% of all cervical cancers [8–10]. HPV18 is the next most carcinogenic HPV genotype, and accounts for approximately 10–15% of cervical cancers [8–10]. Approximately 10 other HPV genotypes cause the remaining 25–35% of cervical cancers. HPV causes all common and most rare histologic types of cervical cancer. HPV18 causes a greater proportion of glandular cancers, adenocarcinoma and adenosquamous carcinoma, than squamous cell carcinoma (approximately 32% vs. 8%, respectively) [9]. The establishment of the causal link between HPV and cervical cancer, along with an understanding of the epidemiology and natural history of HPV infection, has led to a new model for cervical carcinogenesis: HPV acquisition, HPV persistence (versus clearance), progression to precancer, and invasion [11, 12], which helps guide age-appropriate interventions to prevent cervical cancer.

Genital HPV is acquired through sexual and genital skin-to-skin contact. In most populations, prevalence peaks within a few years after the median age of sexual debut, which in the U.S. is 17 years [13]. Most (~90%) HPV infections are transient, becoming undetectable within one to two years [14, 15]. Women whose infections persist are at significant risk of developing precancerous lesions. One-year [16] and two-year HPV persistence [17], especially by HPV16, strongly predict CIN3 or more severe diagnoses (CIN3+) in the subsequent years (e.g., 20–30% risk of CIN3+ over 5 years for one-year or two-year persistent HPV16). Untreated CIN3 has a 30% probability of becoming invasive cancer over a 30-year period, although only about 1% of treated CIN3 will become invasive [18].

The fundamental goal of cervical cancer screening is to prevent morbidity and mortality from cervical cancer. The optimal screening strategy should identify those cervical cancer precursors likely to progress to invasive cancers (maximizing the benefits of screening) and avoid detection and unnecessary treatment of transient HPV infection and its associated *benign* lesions that are not destined to become cancerous (minimizing the potential harms associated with screening). Cytology (Pap test) screening has been very successful in lowering cancer incidence and mortality in countries where good quality screening is available, yet false-positive results are common, since most abnormal (atypical squamous cells of undetermined significance or more severe) cytology is not associated with concurrent CIN3 or cancer, and is therefore still a concern [19, 20]. Increased understanding of the association between HPV and cervical cancer

Table 1. Summary of Recommendations

Population	Page number	Recommended screening method[a]	Management of screen results	Comments
<21 Years	7	No Screening		HPV testing should NOT be used for screening or management of ASC-US in this age group.

21–29 Years	8–9	Cytology alone every 3 years	HPV-Positive ASC-US[b] or cytology of LSIL or more severe:
			    Refer to ASCCP Guidelines [2]
			Cytology Negative or HPV-Negative ASC-US[b]:
			    Rescreen with cytology in 3 years
				HPV testing should NOT be used for screening in this age group

30–65 Years	9–16	HPV and Cytology "Cotesting" every 5 years (Preferred)	HPV-Positive ASC-US or cytology of LSIL or more severe:
			    Refer to ASCCP Guidelines[2]
			
			HPV Positive, Cytology Negative:
			    Option 1 – 12-month follow-up with cotesting
			    Option 2 – Test for HPV16 or HPV16/18 genotypes
			        if HPV16 or HPV16/18 positive: refer to colposcopy
			        If HPV16 or HPV16/18 negative: 12-month follow-up with cotesting
			
			Cotest Negative or HPV-Negative ASC-US:
			    Rescreen with cotesting in 5 years
				Screening by HPV testing *alone* is not recommended for most clinical settings.

		Cytology alone every 3 years (Acceptable)	HPV-Positive ASC-US[b] or cytology of LSIL or more severe:
			    Refer to ASCCP Guidelines [2]
			
			Cytology Negative or HPV-Negative ASC-US[b]:
			    Rescreen with cytology in 3 years	

>65 Years	16–17	No Screening following adequate negative prior screening		Women with a history of CIN2 or a more severe diagnosis should continue routine screening for at least 20 years.
After Hysterectomy	17–18	No Screening		Applies to women *without* a cervix and *without* a history of CIN2 or a more severe diagnosis in the past 20 years or cervical cancer ever.
HPV Vaccinated	18–19	Follow age-specific recommendations (same as unvaccinated women)		

[a]Women should not be screened annually at any age by any method.
[b]ASC-US cytology with secondary HPV testing for management decisions.

risk has led to the development of molecular tests for HPV* that offer increased sensitivity albeit lower specificity compared to cytology. HPV tests may better forecast which women will develop CIN3+ over the next 5–15 years than cytology [21–23]. Incorporation of HPV testing into cervical cancer screening strategies has the potential to allow both increased disease detection (improving benefits) and increased length of screening intervals (decreasing harms such as psychosocial impact of screening positive, additional clinical visits and procedures, and treatment of lesions destined to resolve). In the development of this evidence-based review and guideline update, we considered the tradeoffs of benefits and harms of screening while considering different screening modalities and ages.

*HPV refers only to high-risk HPV. Other HPV types are unrelated to cervical cancer and should not be used in cervical cancer screening. Testing for low-risk HPV types has no clinical role in cervical cancer screening or evaluation of women with abnormal cytology.

Of note, approximately half of the cervical cancers diagnosed in the United States are in women never screened, and an additional 10 percent of cancers occur among women not screened within the past five years [24–26]. The current opportunistic approach to cervical cancer screening in the U.S. fails to reach sub-populations of women mainly living in low-resource, medically underserved regions, and thus invasive cervical cancer is one among a complex of diseases strongly linked to socioeconomic, geographic, and/or racial disparities. Annual rates of cervical cancer incidence and mortality in these populations are several-fold higher than the rates in the general U.S. population and are similar to the rates observed in some lower-income countries [24–26].

Technologic improvements in screening are unlikely to have a substantial impact on mortality if they do not reach this population [27]. While this new ACS-ASCCP-ASCP screening guideline includes a review of molecular screening tests and strategies, perhaps the largest immediate gain in reducing burden of cervical cancer incidence and mortality could be attained by increasing access to screening (regardless of the test used) among women who are currently unscreened or screened infrequently. Incorporation of HPV testing may offer advantages over what is already a successful screening strategy if utilized, i.e., cytology. For example, HPV testing provides longer-term safety following a negative test than cytology, a useful characteristic for the women who are screened infrequently.

METHODS

Guideline Development and Organization

From 2009 to 2011, the ACS, ASCCP, and ASCP worked collaboratively to convene an expert panel to develop new screening recommendations based on a systematic review of the available evidence. The process was overseen by a Steering Committee composed of representatives from the sponsoring organizations, other stakeholder organizations and agencies, and experts representing multiple disciplines *(see pages 22–23 for names of all committee members)*. An independent Evidence Evaluation Committee (the "Data Group") composed of experts in literature reviews, evidence evaluation, and data analysis had primary responsibility for overall development and implementation of the guidelines process, and for providing feedback and guidance to the Working Groups. Six topic areas to be addressed by the recommendations were identified by the Steering Committee.

A Working Group consisting of experts on a particular topic and representing different disciplines was assigned to each area, with each Working Group having a member of the Data Group serving as a liaison. Each group met regularly via teleconference, including web-based conferences for all participants to review specific methodologic issues.

The six working groups addressed the following topic areas:

(1) Optimal cytology screening intervals
(2) Screening strategies for women 30 years and older
(3) Management of discordant combinations of cytology and HPV results (e.g., HPV positive, cytology negative and HPV negative, atypical squamous cells of undetermined significance (ASC-US) results)
(4) Exiting women from screening
(5) Impact of HPV vaccination on future screening practices
(6) Potential utility of molecular screening (Specifically, HPV testing for primary screening was assessed as a potential future strategy.)

The working groups were instructed to propose evidence-based cervical cancer prevention strategies that best serve women, specifically balancing benefits and harms of screening and, in some cases, management of screening results. They were specifically directed not to consider financial cost in making their recommendations.

Conflict of Interest

In planning this workshop, the Steering Committee critically examined some of the issues involved in defining conflict-of-interest (COI) and recognized that all interests – whether directly financial or more indirect such as an affiliation with a company, the success of one's clinical practice, or the prominence of a professional specialty – represent potential conflicts. Steering Committee members, Working Group and Data Group co-chairs, and members of the Writing Committee were required not to have any financial ties to companies that market or sell screening tests or devices (e.g., methods to visualize the cervix such as colposcopes). All participating individuals were required to disclose all real or potential conflicts of interest. Employees or representatives of industry and insurance companies were not invited to participate in the development of these guidelines because of their significant, direct financial interests in the outcome of these guidelines. The complete COI policy can be found in the online supplement (http://links.lww.com/LGT/A5).

Benefits and Harms

The six Working Groups independently considered a series of screening and management questions. We recognized that different groups of experts could evaluate the same data for related questions and reach different conclusions because of differences in weighing benefits and harms of screening. Therefore we harmonized the main outcomes for benefits and harms across Working Groups as defined below.

Benefit Outcomes. Ideally, the screening test(s) should efficiently and accurately identify women with precancer who are at significant risk for developing cancer, so that appropriate intervention will prevent progression to invasive cancer. We used detection of CIN3 as the measure of a screening test's sensitivity for precancer because a substantial proportion of women with CIN3 would develop invasive cervical cancer if left untreated [18]. Also, given the natural history of cervical carcinogenesis and the relative rarity of cervical cancer in screened populations, it is the most feasible directly measurable outcome in controlled clinical studies. By contrast, CIN2 is an equivocal diagnosis that includes some precancer lesions (CIN3) but also some lesions (e.g., CIN1) that would regress on their own [28–30]. Although CIN2 is the widely accepted threshold for treatment [2] – to provide an additional margin of safety – we posited that CIN2 should not be the primary target of cervical cancer screening.

Ideally, the screening interval for a particular testing modality should be chosen such that development of invasive cancer is highly unlikely before the next screen. Because few studies have sufficient numbers of cancer cases to assess cancer risk directly, we considered the absolute risk of CIN3, including the rare cases of cancer (CIN3+) before or at the next visit as our best measure of incident cervical cancer risk. When available and appropriate, we also noted the risk of invasive cancer, especially in relationship to screening intervals, following a negative screening test.

Thus, for these guidelines, we judged that a screening test or modality provided greater benefit if more CIN3 was detected immediately by the screening test, and risk of CIN3+ was reduced in the interval before the next screening test.

Harm Outcomes. Most episodes of HPV infection and many CIN1 and CIN2 cases are transient and will not develop into CIN3 or cancer [28–30]. The potential harms associated with detecting these transient lesions include the anxiety associated with a "positive" cancer screening test, potential stigmatization from the diagnosis of a sexually transmitted infection, discomfort from additional diagnostic and treatment procedures, bleeding from treatment, and, longer term, an increased risk of pregnancy complications such as preterm delivery due to treatment [31]. Having a positive test at any point in one's life may contribute to a perception of an increased risk of cancer, and a subsequent desire for more testing, further increasing the likelihood of another positive test [32]. Although any false positive test has the potential for inducing anxiety or other psychological distress, quality-of-life instruments are rarely included in controlled clinical trials of screening. Because of this, we used the number of colposcopies, both alone and relative to CIN3+ and cancer detected, as the primary measure of harm, since colposcopies themselves are associated with physical discomfort, and are a necessary pre-requisite to more invasive treatments with greater short- and long-term risks of harms. Since the number of subjects undergoing colposcopy is usually reported in controlled studies, and more screening leads to more screen positives and therefore more colposcopy, it provides a surrogate for potential harm of screening analogous to the use of the detection of CIN3 as a surrogate for cervical cancer for potential benefits of screening.

Risk-Based Strategies. Our basic tenets regarding risk and risk-based interventions were as follows:

(1) *Preventing all cervical cancer is unrealistic.* No screening test has perfect sensitivity, and therefore there will always be a residual cancer risk following any round of screening. More rapidly progressive cervical cancers, such as those occurring in women in their teens and early twenties, may not be preventable through feasible screening strategies [33].

(2) *Reasonable risk is determined by the strategy of cytology alone as a benchmark.* Cytology alone at 2 to 3 year intervals is consistently included in current guidelines of major professional societies [1, 2, 34] and is generally accepted as the standard of care in the United States. Screening strategies that achieve equivalent or better reduction in cervical cancer incidence and mortality– without an undue increase in harms – compared to cytology would be acceptable options for consideration. The optimal balance of benefit and harm should be chosen so that equipoise is achieved between screening too frequently and finding mostly benign HPV infections or correlates of HPV infection (e.g., low-grade squamous intraepithelial lesions [LSIL]), or too infrequently and thereby exceeding the reasonable interval cancer risk threshold.

(3) *Women at similar cancer risk should be managed alike*. Independently of how the risk is measured (i.e., screening modality), women with similar cancer risk share the same tradeoffs of benefits and harms from routine screening, increased surveillance, referral to colposcopy, or treatment. It is therefore rational to provide the same care for similar women at similar cancer risk.

We recognize that the women at different ages may have different tradeoffs in benefits and harms from screening. These differences are addressed through the development of age-specific screening recommendations.

Considerations Regarding Cytology

Based on good evidence showing similar sensitivity and specificity of conventional and liquid-based cytology for CIN grade 2 or more severe diagnoses (CIN2+) [35, 36], we included studies that used either cytology method. We found no data to suggest a need to analyze data from studies using liquid-based cytology separately from those using conventional cytology.

Considerations Regarding HPV Testing

The hallmarks of HPV testing are greater sensitivity but lower specificity for CIN3+ and CIN2+ [37–43] and better reproducibility than cytology [44–46]. Benchmarks for clinical performance of HPV testing are described in detail elsewhere [47, 48]. Our general assumptions are that the sensitivity of HPV testing for CIN3+ and CIN2+ should be ≥90%, and the percent of women in the general population who test (screen) positive, as a measure of false positives, should be less than or equal to established thresholds from well-validated HPV DNA tests [47, 48].

Several U.S. Food and Drug Administration (FDA)-approved HPV tests are commercially available, though none is yet approved for primary, stand-alone screening. The performance characteristics vary among these HPV tests, and comparability cannot be assumed. For use in the U.S., HPV tests should both be FDA approved (for validity) and meet specific criteria for *clinical* performance as described above [47, 48]. Other well-validated tests (e.g., GP5+/6+ EIA) are commercially available in Europe, and data using these tests were included in our review [39, 40], but these are not FDA-approved. HPV tests not meeting these standards of performance (including FDA-approved tests) should not be used. In particular, compared with the current benchmarks, excessive analytic sensitivity is a significant concern, as it will be unlikely to improve already very high clinical

sensitivity for CIN3+ but may increase harms due to poorer specificity [49]. The updated guidelines for cervical cancer screening described here were developed based on HPV tests that have performance characteristics similar to those of the HPV tests used in the supporting evidence. The guidelines cannot be expected to perform as designed (i.e., to balance benefits and harms) when using HPV tests with different performance characteristics.

Laboratory-developed tests (LDTs), which are currently exempt from the FDA regulatory oversight, rarely have undergone the necessary evaluation using clinical endpoints of CIN3+ and CIN2+ in properly designed studies. Therefore, we recommend against the use of LDTs for cervical cancer screening.

HPV tests should be used in accordance with their package labeling. Professional medical organizations with clinical expertise in gynecological cancer may recommend off-label applications of FDA-approved tests (e.g., HPV testing for post-treatment follow-up as recommended by the ASCCP) [2]. Laboratory standard operating procedures and robust quality assurance programs should accompany the use of any HPV test. Interlaboratory or proficiency testing to ensure quality results across laboratories should be established [50]. Although well validated in the research setting, additional studies of interlaboratory comparability of HPV testing in the clinical laboratory setting would be helpful.

Evidence Review

We utilized the Grading Recommendations Assessment, Development, and Evaluation (GRADE) system [51–56] to provide a framework for the guidelines development process. An initial literature search for terms relevant to all the Working Groups was performed, and abstracts were reviewed by Data Group members. Papers meeting initial inclusion criteria were retrieved and distributed to each Working Group as appropriate. The search included articles from 1995 through July 5, 2011. (See online supplement, Figure 1 and Figure 2 for details http://links.lww.com/LGT/A5).

Each Working Group took the initially defined areas and formulated specific questions using the GRADE framework [51–56]. From an initial list of potential outcomes identified by the Data Group, each Working Group defined 3–4 outcomes as "Critical," 3–4 as "Important," and 3–4 as "Useful" (see online supplement for list of outcomes). Members of the Working Groups then reviewed each article to determine whether data were available on critical or important outcomes. We did not

perform formal data synthesis or meta-analyses to create single summary estimates for each outcome/intervention pair. Instead, summary data from each included article, along with a quality grade of "high, moderate, low, or very low" were presented to the group, with a subsequent quality grade for the entire body of evidence for a given outcome/intervention pair.

The GRADE system does not specifically address modeling studies, which were frequently the only evidence available for comparing alternatives, particularly different screening intervals. Because modeling integrates evidence from a wide range of sources of varying quality, we considered individual modeling studies as "low" quality evidence, but, if the individual studies followed best practices for model-based analyses, and the results were consistent across studies done by different groups using different methods, the rating of the overall body of evidence based on modeling could be graded as of "moderate" quality.

Strength of Recommendation

Based on the initial grading of evidence, each Working Group formulated an initial summary recommendation, graded as "Strong" or "Weak," based on the overall quality of the evidence for outcomes considered "Critical," as well as additional criteria such as variation in patient preferences (if data were available) and feasibility of obtaining additional evidence. A "strong" recommendation means that the group is confident that further research would be unlikely to change the recommendation, based on the overall quality of the available evidence, the prospect of obtaining better evidence, and the balance between benefits and harms. A "weak" recommendation means that there is substantial uncertainty surrounding the balance of benefits and harms, and further research is needed to increase confidence in the results, or that benefits and harms are closely balanced, with decisions based largely on individual preferences and values.* Members of the Steering Committee and Data Group, as well as the other Working Groups, reviewed these recommendations and corresponding rationale and provided feedback. After revision, the draft recommendations and rationale were posted on the ASCCP website for public comment from October 19, 2011 to November 9, 2011. The public comments were distributed to each Working Group, and revisions were made to address or clarify issues raised. However, each Working Group had the ultimate authority and responsibility for the (revised) draft recommendations presented at the symposium for consideration.

Consensus Conference

A symposium was held November 17–18, 2011 to discuss, revise as necessary and vote on the final recommendations. In addition to the members of the Steering Committee, Data Group and Working Groups, representatives from other stakeholder organizations were invited (*see online supplement for list* http://links.lww.com/LGT/A5). Each Working Group presented its evaluation of the evidence and draft recommendations. After the presentation, there was an open discussion, followed by voting on the recommendations, including both the wording of the recommendation and the strength of the recommendation. A two-thirds majority was required for a recommendation to be accepted—if this threshold was not achieved, the recommendation was revised by the Working Group and brought back to the plenary participants for voting.*

Special Populations

These guidelines were developed to address cervical cancer screening in the general population. These guidelines do not address special, high-risk populations who may need more intensive or alternative screening. These special populations include women 1) with a history of cervical cancer, 2) who were exposed *in utero* to diethylstilbestrol (DES), and 3) who are immune-compromised (e.g., infection with human immunodeficiency virus) [57].

RECOMMENDATIONS, RATIONALE, AND EVIDENCE

The following recommendations are based on review and assessment of the published peer-reviewed literature available at the time of the symposium. It is anticipated that they will be reviewed on an ongoing basis and revised as new evidence becomes available about the impact of alternative strategies on the balance of benefits and harms associated with cervical cancer screening.

Age to Begin Screening

The question of when to begin screening was addressed at the 2009 Practice Improvement in Management (PICSM) Symposium on Management of Cervical Abnormalities in Adolescents and Young Women [33] and was not part of the current review. The following recommendation has been previously endorsed by the several organizations that participated in that meeting.

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*The majority of recommendations are ''strong.'' The strength of each recommendation is noted in the individual Working Group reports in the online supplement.

Recommendation. Cervical cancer screening should begin at age 21 years. Women under the age of 21 should not be screened regardless of the age of sexual initiation or other risk factors.

Rationale and Evidence. Cervical cancer is rare in adolescents and young women [58] and may not be prevented by cytology screening [59]. The incidence of cervical cancer in this age group has not changed with increased screening coverage over the last 4 decades [58]. Screening adolescents leads to unnecessary evaluation and potentially to treatment of preinvasive cervical lesions that have a high probability of regressing spontaneously and that are on average many years from having significant potential for becoming invasive cancer. This overtreatment, and subsequent increased risk of reproductive problems, represents a net harm [33].

Adolescent cervical cancer prevention programs should focus on universal HPV vaccination, which is safe, highly efficacious, and when used in adolescents before becoming sexually active, highly effective and cost-effective [60, 61]. Even without cervical cancer screening, it is crucial that adolescents continue to have access to appropriate health care, including assessment of health risks, family planning and contraception, and prevention counseling, screening and treatment of sexually transmitted infections [33].

Screening Periodicity

Over time, growing evidence and the improved understanding of the natural history of cervical cancer have led to growing recognition that earlier recommendations for annual screening were excessive and led to an increased rate of harms. Today, there is little evidence to support annual screening of women at any age by any screening test, method, or modality. Annual screening leads to a very small increment in cancers prevented, at the cost of a very large excess of unnecessary procedures and treatments [62, 63] due to the high prevalence of transient, benign HPV infections and associated lesions, most of which will regress within a year or two or, of those that do not, are many years on average from causing cancer. Women at any age should NOT be screened annually by any screening method; rather, recommended screening intervals for women are based on age and clinical history.

WOMEN AGES 21–29

Recommendation

For women 21–29 years of age, screening with cytology alone every 3 years is recommended. For women 21–29 years of age with 2 or more consecutive negative cytology results, there is insufficient evidence to support a longer screening interval (i.e. >3 years).

HPV testing should not be used to screen women in this age group, either as a stand-alone test or as a cotest with cytology.

Rationale

For women under 30 years of age, there are few studies specifically addressing the optimal interval for cytology-based screening. Those studies meeting selection criteria were mainly modeling studies. While affording slightly greater cancer risk reduction, annual screening results in twice the number of colposcopies compared to screening every 3 years [63]. Only one study modeled the trade-offs between cancers detected and colposcopies for screening every 2 years versus every 3 years in this age group [62]. The results for both intervals conducted over a 10-year interval were similar for reducing the lifetime

Table 2. Evidence for Screening Women Aged 21–29[a]

Outcome	Main result	Number of studies	Quality of evidence[b]	Comments
CIN3+				
Cancer incidence	Increase in lifetime number of cancers per 1000 women from 3/1000 to 5–8/1000	5 [62, 63, 68–70]	Moderate	Modeling studies—indirect evidence, but consistent across studies; results for every 2 years intermediate between every 1 and every 3 years
Colposcopies	Decrease in lifetime colposcopies per 1000 women from 2000/1000 to 760/1000[c]	2 [62, 63]	Moderate	Modeling studies—indirect evidence, but consistent across studies; results for every 2 years intermediate between every 1 and every 3 years

CIN3+ indicates cervical intraepithelial neoplasia of grade 3 or more severe diagnosis.
[a]Patients/population comprises women aged 21 to 29 years. The intervention was screening with cytology every 3 years, and the comparator was screen with cytology every year.
[b]GRADE (Grading Recommendations Assessment, Development, and Evaluation) system Working Group grades of evidence: high (we are confident that the true effect lies close to what was found in the research), moderate (the true effect is likely to be close to what was found, but there is a possibility that it is substantially different), low (the true effect may be substantially different from what was found), and very low (we are uncertain about the effect).
[c]Indicates risk of multiple colposcopies over lifetime with annual screening.

cancer burden. Combining these results with findings of other studies [64, 65] that showed no significant difference in cancer reduction between a 2- and 3-year screening interval, we determined that screening every 3 years provided the best balance of benefits and harms of screening in this age group.

Because of the high prevalence of HPV in women under the age of 30 [25, 66, 67], HPV testing should not be used to screen women in this age group due to the potential harms as described above.

Evidence

Table 2 [62, 63, 68–70] shows patient outcomes, number of studies and quality of the evidence. In the absence of screening, modeling predicts a lifetime risk of cervical cancer in the U.S. of approximately 31–33 incident cancers per 1000 women [63, 70]. In addition, these studies predict a lifetime risk of cancer associated with screening every 3 years of approximately 5 to 8 incident cancers per 1000 women [62, 63, 68–70]. Screening every 2 years is associated with a lifetime cancer risk ranging from 4 to 6 incident cancers per 1000 women [63, 69]; screening annually is associated with a lifetime risk of about 3 per 1000 women [63, 69]. Early stage cervical cancer has a very high 5-year survival rate of 90%. The predicted lifetime risks of death due to cervical cancer associated with screening every 3 years, every 2 years and annually are even lower: 0.05, 0.05, and 0.03 per 1000 women, respectively.

With respect to harm, screening every 3 years is associated with a lifetime prediction of about 760 colposcopies per 1000 women, screening every 2 years with about 1080 per 1000 women (a 40% increase vs. screening every 3 years), and screening every year with about 2000 per 1000 women (i.e., two colposcopic evaluations per woman), or nearly three times the number of colposcopic referrals expected from screening every 3 years.

A modeling study that examined outcomes for women 20 years of age screened over a subsequent 10-year time period [62], predicted that there would be a doubling of the colposcopies (using ASC-US as the threshold for referral) per 1000 women with annual screening compared with screening every 3 years. These results are similar to those reported by Kulasingam [63] who examined outcomes associated with screening every 2 years. Compared to screening every 3 years, screening every 2 years (starting screening at any age between 15 and 25) was associated with little additional patient benefit in terms of reduced lifetime risk of cancer modeled over a slightly shorter time period than reported by Stout (9 versus 10 years) [62].

There is insufficient high-quality evidence from randomized controlled trials (RCT) to increase screening interval based on prior negative cytology results for any age group. Miller [71] calculated the risk of invasive cervical cancer associated with different intervals since the last negative cytology test. The odds ratio comparing a 3-year vs. 2-year interval was 1.20 (95% confidence interval [0.65, 2.21]). Adjusting for a history of abnormal cytology or prior consecutive negative cytology tests did not substantially change the results. The authors also reported an incremental rise in cancer risk (≥3.16) over time as the interval from the last negative cytology test moved beyond three years [72] and did not find a significantly reduced risk of CIN3+ associated with increasing numbers of prior negative cytology tests after controlling for time since last normal cytology test.

WOMEN AGES 30–65

Recommendation

Women ages 30–65 years should be screened with cytology and HPV testing ("cotesting") every 5 years (preferred) or cytology alone every 3 years (acceptable). There is insufficient evidence to change screening intervals in this age group following a history of negative screens.

Rationale

Cytology Only

For women 30–65 years of age, even with a history of negative cytology tests, the limited available evidence does not support a screening interval longer than 3 years. Studies of screening intervals in women with a history of negative cytology results report an increased risk of cancer after 3 years even after controlling for prior number of negative cytology tests [71]. Furthermore, the only modeling study that examined the screening interval among U.S. women with a history of prior normal cytology results compared screening every year to screening every 3 years [73]. A longer interval was not examined in this review, although some countries (e.g., The Netherlands) use a 5-year interval. Modeling studies have shown a stepwise increase in cancer risk with increasing interval from 1 year to 3 years to 5 years [62, 63]. As such, we concluded that a 3-year interval for cytology provides an appropriate balance of benefits and harms and that there was insufficient evidence to support a longer interval than every 3 years utilizing cytology alone in women aged 30 years or older, even with a screening history of consecutive negative cytology tests.

Table 3. Evidence for Cotesting With HPV and Cytology vs Cytology Alone

Outcome[a]	Main result	Number of studies	Quality of evidence	Comments
CIN3+	Absolute increase in detection of CIN3+ ranging from 17–31% in first round of screening	3 [39–41]	High	High-quality RCTs from Europe—indirectness based on population
Cancer incidence	Absolute decrease in cancer detected at 2nd round of 0.03–0.05%	2 [40, 41]	High	High-quality RCTs from Europe—indirectness based on population
Colposcopies	No direct evidence			Not reported in RCTs

Outcome[b]	Main result	Number of studies	Quality of evidence	Comments
Cancer deaths (lifetime risk per 1000 women)	Decrease from 1.6–1.7/1000 to 1.4/1000	1[c]	Moderate-low	Modeling study, results consistent in sensitivity analysis using different inputs for sensitivity/specificity. Results consistent with other models showing relationship between sensitivity, specificity, and test frequency
Cancer incidence (lifetime risk per 1000 women)	Decrease from 8.5–8.9/1000 to 7.4–7.7/1000	1[c]	Moderate-low	Modeling study, results consistent in sensitivity analysis using different inputs for sensitivity/specificity. Results consistent with other models showing relationship between sensitivity, specificity, and test frequency
Colposcopies (lifetime risk per 1000 women)	Decrease from 416–758/1000 to 323–573/1000	1[c]	Moderate-low	Modeling study, results consistent in sensitivity analysis using different inputs for sensitivity/specificity. Results consistent with other models showing relationship between sensitivity, specificity, and test frequency

[a]Patients/population comprises women aged 30–65 years. The intervention was screening with cotesting (cytology and HPV), and the comparator was screening with cytology alone at the same interval.
[b]Patients/population comprises women aged 30–65 years. The intervention was screening with cotesting with HPV and cytology every 5 years, and the comparator was screening with cytology alone every 3 years.
[c]Unpublished data (Kulasingam, Shalini L. Personal correspondence. November 2011).

HPV and Cytology (Cotesting)

In the majority of studies reviewed, the addition of HPV testing to cytology resulted in an increased detection of prevalent CIN3 with a concomitant decrease in CIN3+ or cancer detected in subsequent rounds of screening [39–41]. This increase in diagnostic lead-time with cotesting translates into lower risk following a negative screen, permitting a longer interval between screens with incident cancer rates similar to or lower than screening with cytology alone at shorter intervals. If the incident cervical cancer rates associated with cytology at 3-year intervals are acceptable, cotesting at 5-year intervals provides similar or lower cancer risk [22, 74].

The addition of HPV testing to cytology also enhances the identification of women with adenocarcinoma of the cervix and its precursors [42, 74]. Compared to squamous cell cancers, cytology has been relatively ineffective in decreasing the incidence of invasive adenocarcinoma of the cervix [75, 76]. A strategy of cotesting may become increasingly important based on evidence of increasing incidence of adenocarcinoma, which has been observed in several European countries [76] and the U.S. [77] that have exclusively or primarily used cytology-only screening.

Cotesting at a 3-year interval, as recommended in interim guidelines from 2002 and 2004 [1, 78], resulted in a significantly smaller diagnostic yield of CIN3+ in the second round of cotesting following a prior negative cotest [74], supporting the recommendation to use a longer interval between cotests. Modeling studies have shown that cotesting in 40-year-old women at a 3-year versus a 5-year interval over a 10-year period only slightly decreases lifetime cervical cancer risk (0.39% vs. 0.61%, respectively) while significantly increasing the number of colposcopic evaluations [62]. In the same modeling study, the lifetime cancer risk estimates for 40-year-old women undergoing 3-year cytology versus 5-year cotesting over a 10-year period were comparable (0.69% vs. 0.61%, respectively). Cotesting more frequently than at 3-year intervals, and especially annual screening, is predicted to further exacerbate the harms by increasing the number of colposcopic referrals and treatments [62]. Unfortunately, there is evidence that cotesting is being used at shorter intervals than 3 years [79]. The lack of greater benefits and the increase in potential harms associated with screening more frequently support a recommendation of cotesting every 5 years.

Evidence. Table 3 [39–41] shows patient outcomes, number of studies and quality of the evidence.

Increased Sensitivity of Cotesting

Compared with cytology, HPV testing is more sensitive but less specific for identifying women with prevalent CIN3+ [80]. In a meta-analysis [80], the sensitivity of HPV testing for CIN3+ was 37% greater than that of cytology using a positive cut point of LSIL (i.e., LSIL or more severe cytologic abnormalities were considered screen positive), while the specificity of HPV testing was 7% lower. The sensitivity of HPV tests for CIN3+ was 28% greater than that of cytology at a positive cutpoint of ASC-US, while the specificity of HPV tests and cytology were the same.

When compared with women with negative cytology, those with negative HPV tests have a lower subsequent risk of CIN3+ [22, 74] and, more importantly, cancer [41]. Results from FDA-approved or well-validated HPV tests are also more reproducible (intra-assay reliability) than cytology [45, 46, 81].

There are four RCTs [39–41, 82] in which two rounds of screening are reported comparing cotesting with cytology and HPV testing to cytology alone; three of those trials provided adequate evaluation of HPV-positive, cytology-negative results. Each of the trials had a complex protocol and each differed in the way that HPV-positive women were evaluated. ARTISTIC (a randomized trial of HPV testing in primary cervical screening) differed from the other three in that the lower age limit of eligible women was 20 years, while for the other three trials, it was 32 years, 29 years, and 35 years [39–41]. The ARTISTIC trial [82] also differed in that women in ARTISTIC who tested HPV positive, cytology negative were referred to one-year follow-up, similar to the interim guidelines in the U.S. [1, 78], rather than being immediately referred to colposcopy as was done in another trial [41]. As the added benefit of HPV testing is only realized with thorough follow-up of and disease ascertainment in women with HPV-positive, cytology-negative results, it is not surprising that ARTISTIC did not show a benefit to cotesting versus cytology alone, with only half of the HPV-positive, cytology-negative women returning in a year. Saseini [83] pointed out that if all of the HPV-positive, cytology-negative women had been evaluated and disease rates in those who were lost to follow-up had been comparable to those found among the women evaluated, ARTISTIC would have demonstrated increased sensitivity with the addition of HPV testing to cytology, as observed in other studies, compared to cytology alone [83]. The other three trials [39–41] were powered to detect differences in the rate of CIN3+ in the second round of screening, but not powered to detect differences in the rate of cancer in the second round of screening. Their protocols and results are described in detail in the online supplement.

In each of the three trials considered [39–41], the cotesting arm detected a greater proportion of CIN3+ in the first round of screening compared to cytology alone. The difference in the incidence of cancer in the second round of screening was not stated in Naucler *et al.* [39], showed a trend towards declining incidence (not statistically significant) in Bulkmans *et al.* (0.08% vs. 0.02%) [40], and showed a statistically significant decrease in Ronco *et al.* (0.03% vs. 0%, $p = 0.004$) [41]. The number of colposcopy referrals in the three studies was not clearly stated, so the increased number of colposcopies must be inferred based on modeling.

Based on the significant increase in sensitivity in detection of CIN3+ at the first round of screening and the reduction in invasive cancer in the second round of screening in Ronco *et al.* [41], we concluded that the addition of HPV testing to cytology is beneficial. The main harms associated with adding HPV testing– the increased referral to colposcopy and diagnosis of CIN2, some of which would regress without intervention– can be mitigated by extending the screening interval to 5 years (as discussed below) and thereby reducing the detection of transient HPV infections and related lesions that would trigger clinical follow-up in low-risk women [62].

While cotesting is preferred to cytology alone based on risks and harms assessment, such a strategy might not be feasible in all clinical settings in the U.S. due to a lack of payment for cotesting or due to local policies. With regards to the primary goal of cervical cancer screening, which is prevention of cervical cancer, a cytology-based screening strategy in women over 30 has been and continues to be an acceptable option. As mentioned previously in this document, a more frequent, cytology-only strategy does lead to more colposcopy and other harms including the potential need for prescribing shorter screening intervals due to equivocal cytology results that have minimal cancer risk.

Rationale for and Safety of Interval Extension

Cotesting has increased sensitivity for detecting CIN3+ compared with cytology. Consequently, women screened with cotesting also have a lower subsequent risk of CIN3+ and invasive cancer, permitting a lengthening of screening intervals. Seven observational studies involving 24,295

women were pooled to examine the long-term predictive values of HPV testing and cytology [22]. The 6-year risk of CIN3+ following a negative HPV test was 0.27%, compared to 0.28% among cotest negatives. By comparison, the 6-year risk of CIN3+ following a negative cytology alone was significantly greater at 0.97%. The authors also noted that the risk of CIN3+ at a 3-year screening interval, the most commonly used screening interval in Europe, after negative cytology was 0.51%. In a retrospective observational study of 330,000 women aged 30 years and older undergoing cotesting (at 3-year intervals) in routine clinical practice [74], the 3-year risk of CIN3+ following negative cytology alone (regardless of the HPV result) was 0.17%; the 5-year risk of CIN3+ following a negative HPV test alone (regardless of the cytology result) was 0.17%; and the 5-year risk of CIN3+ following a negative cotest was 0.16%, essentially comparable results across each testing strategy. Likewise, the risks of cancer also were comparable (0.018%, 0.019%, and 0.016%, respectively).

In the same analysis [74], women who cotested negative at the initial screening and HPV and/or cytology positive 3 years later were at a lower risk of CIN3+ or cancer than women with a positive HPV and/or cytology result at the initial screen. This lower risk associated with previously negative findings presumably is due to the prolonged period of HPV carriage (chronic infections) required for invasive cancer to develop. Taken together, these reports indicate that healthcare providers can rely on the negative predictive value of the HPV test to assure women who cotest negative that they are at very low risk for CIN3 and cancer for at least 5 years after negative cotesting.

Risks Associated With Screening at Different Intervals

Modeling from several sources indicates that there is a dramatic increase in colposcopy rate with minimal change in invasive cancer incidence as screening intervals decrease below 3 years, regardless of the modality employed [63, 84, 85]. Despite differing assumptions, all three analyses indicated that the number of colposcopies more than tripled with annual cytology starting at age 21, in comparison to annual cytology for ages 21–29 and cotesting at 5-year intervals starting at age 30. The models also agreed that cotesting of women aged 30 and older at 5 years intervals involves fewer colposcopies with

similar or slightly lower cancer risk compared with 3-year cytology.

Detection of Adenocarcinoma of the Cervix and Its Precursors

Case control studies in Australia and Italy demonstrated that cytologic screening provides only modest protection against adenocarcinoma [86, 87]. More recently, the International Collaboration of Epidemiological Studies of Cervical Cancer Group pooled screening data from 12 studies involving 1374 women with adenocarcinoma and concluded that risk reduction of a preceding cytology test was greater for squamous cell carcinoma than for adenocarcinoma [88].

In Castellsague *et al.* [89], HPV was detected in 93% of 167 adenocarcinomas of the cervix (including 55 adenosquamous carcinomas). A case control study with these cases and 1881 controls was also reported. Testing HPV positive (vs. negative) was strongly associated (odds ratio = 81.3) with a diagnosis of cervical adenocarcinoma [89]. From Katki *et al.* [74], 63% of the adenocarcinomas diagnosed over a 5-year period followed an initial HPV-positive, cytology-negative cotest result.

Management of Women with HPV Positive, Cytology Negative Cotests

Recommendation. Women cotesting HPV positive, cytology negative should be followed with either (as noted in the interim ASCCP guidelines [78]: Option 1) repeat cotesting in 12 months, or Option 2) immediate HPV genotype-specific testing for HPV16 alone or for HPV16/18. If cotesting is repeated at 12 months, women testing positive on either test* should be referred to colposcopy; women testing negative on both tests** should return to routine screening. If immediate HPV genotype-specific testing is used, women testing HPV16 positive or HPV16/18 positive should be referred directly to colposcopy; women testing HPV16 negative or HPV16/18 negative should be cotested in 12 months, with management of results as described in option 1.

Women cotesting HPV positive, cytology negative should not be referred directly to colposcopy. Furthermore, they should not be tested for individual HPV genotypes other than HPV16/18. The use of HPV genotype-specific testing for HPV16 or HPV16/18 is recommended only for the management of HPV-positive, cytology-negative women. Currently, there is insufficient evidence to support the use of non-HPV biomarkers.

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*HPV positive OR LSIL or more severe cytology
**HPV negative AND ASCUS or negative cytology

Table 4. Evidence for Managing Women With HPV Positive, Cytology Negative or HPV Negative, ASC-US Cytology Results

Outcome[a]	Main result	Number of studies	Quality of evidence	Comments
CIN3+ (absolute risk)				
1 year	<1–4.1%	4 [93, 97–99]	Moderate-high	Observational studies, but consistency of results across multiple designs, settings
3 years	2.2–7.0%	3 [74, 100, 101]	Moderate	Large observational studies, consistent results
5 years	5.9–9.3%	2 [74, 100]	Moderate	Large observational studies, consistent results
10+ years	16.0–21.2%	2 [100, 102]	Moderate	Observational studies, consistent results

Outcome[b]	Main result	Number of studies	Quality of evidence	Comments
CIN3+ (absolute risk)				
Enrollment	ASCUS: 0.28% cytology negative: 0.30%	2 [93, 103]	Moderate-Low	Large observational studies, consistency of results, indirect comparison
2 years (cumulative)	ASCUS: 1.4–1.9%	2 [104, 105]	Moderate	Large observational studies, consistent results
5 years (cumulative)	ASCUS: 0.54% cytology negative: 0.16%	1 [74]	Moderate	Large observational study, direct comparison

ASC-US indicates atypical squamous cells of undetermined significance; CIN 3+, cervical intraepithelial neoplasia of grade 3 or more severe diagnosis; HPV, human papillomavirus.
[a]Patients/population comprises women aged 30–65 years with HPV-positive, cytology-negative cotesting results. The intervention was no treatment/referral within the specified time frame, and the comparator was 2-year risk of CIN 3 observed in Atypical Squamous Cells of Undetermined Significanxce-Low-Grade Squamous Intraepithelial Lesion Triage Study (ALTS) for women with HPV-positive ASC-US or LSIL cytology (10–11%).
[b]Patients/population comprises women aged 21–65 years with HPV-negative ASC-US results. The intervention was no treatment/referral within the specified time frame, and the comparator was no treatment/referral for women with HPV-negative, cytology-negative results.

Rationale. There are no RCTs that directly compare different management strategies for women cotesting HPV positive, cytology negative. Consistent, high-quality evidence from prospective observational studies indicates that the short-term risk of CIN3 in this population is far below the risk threshold of HPV positive ASC-US and LSIL used for referral to colposcopy (i.e., 2-year risk of 8–10% in the ASC-US/LSIL Triage Study) [20, 90]. For this reason, immediate colposcopy for all HPV-positive women (including HPV-positive, cytology-negative women) was strongly dismissed by the consensus conference participants as a potential management strategy. Repeat cotesting at 12 months is the current recommended management [2] for women testing HPV positive, cytology negative. This is supported by evidence from cohort studies showing the majority of transient infections clear by 12 months [15, 91], allowing the majority of women to return to routine screening without excessive risk.

Where available, HPV genotype-specific testing for HPV16 or HPV16/18 may be performed following HPV-positive, cytology-negative results. Large cohort studies [17, 92] and one industry-sponsored trial [93] have shown that HPV16-positive or HPV16/18-positive results are associated with clinically relevant short-term risk of CIN3 or cancer in HPV-positive, cytology-negative women, supporting immediate referral to colposcopy. In all studies, HPV16 conferred much higher absolute risk than any other carcinogenic type. HPV18 conferred the next highest absolute risk. Other types such as HPV31 and HPV58 were associated with short-term risks similar to those of HPV18 in some populations [17, 94]. However, large international case series studies of type attribution to cervical cancers have demonstrated that the etiologic fraction of HPV18 is much higher than that of any other type (except for HPV16) [9, 10, 95, 96], and the etiologic fraction is even higher in adenocarcinomas. Thus, including HPV18 in genotype-specific assays appears warranted.

Aside from management of HPV-positive, cytology-negative women, no other clinical indications have sufficient evidence to recommend HPV genotype-specific testing for HPV16 or HPV16/18. Further studies are likely to refine the risk estimates of specific test result combinations. There is also a lack of evidence to support the use of other molecular markers in HPV-positive, cytology-negative women. However, studies are ongoing, with results anticipated within 2–3 years.

Evidence. Table 4 [74, 93, 97–102] shows patient outcomes, number of studies and quality of the evidence. The prevalence of HPV-positive, cytology-negative screening results was reported in nine studies (online supplement, Working Group 3a report Table 1) [74, 93, 97–102, 106, 107] and ranged from 3.4% to 8.2% in women age 30 years and older. In a screening population of women age 30 years and older [74], the proportion of HPV-positive, cytology-negative results (3.7%) was more than twice that of HPV-positive, cytology-positive results (1.4%), implying a significant increase in referral to colposcopy if HPV-positive, cytology-negative women were referred for immediate colposcopy.

Cumulative risks of CIN2 or CIN3 among HPV-positive, cytology-negative women have been reported from 11 prospective studies with heterogeneous populations, varying disease ascertainment, and length of follow-up ranging from 1–16 years (online supplement, Working Group 3a report Table 2). The estimated 12-month risk of CIN3+ following an HPV-positive, cytology-negative cotest, relevant for management decisions, ranged from 0.8% [74] to 4.1% [93]. The estimated 12-month risk of cancer was 0.08% [74].

For HPV16 or HPV16/18 genotype-specific testing in HPV-positive, cytology-negative women, risk of CIN3 reaches 10% over 1–4 years for HPV16 positivity and over 2–5 years for HPV18 positivity [17, 92]. One industry-sponsored trial reported risk of prevalent disease (within 12 weeks) for HPV16/18-positive results as 11.4% for CIN2+ and 9.8% for CIN3+, and for HPV16-positive results as 13.6% for CIN2+ and 11.7% for CIN3+ [93]. The short-term risks associated with oncogenic HPV genotypes other than HPV16 and HPV18 were considerably lower [17, 92, 93]. While the risk estimates for oncogenic HPV genotypes other than HPV16 and HPV18 do not warrant immediate colposcopy, they are elevated compared to those for women cotesting negative; therefore, a reasonable approach for women who test negative for HPV16 or HPV16/18 following an initial HPV-positive, cytology-negative result is to follow with repeat cotesting at 12 months to identify women who are likely to have persistent HPV infection and are at an elevated risk of CIN3+ over many years [92, 100].

The potential utility of p16^{INK4A} immunocytochemistry for managing HPV-positive women has been demonstrated in an Italian screening trial [108], but this study did not directly evaluate women testing HPV positive, cytology negative. As more data from HPV-positive, cytology-negative populations become available for other biomarkers, revisions to recommendations may be warranted.

Management of Women With HPV-Negative, ASC-US Cytology Results

Recommendation. Women with ASC-US cytology and a negative HPV test result should continue with routine screening as per age-specific guidelines.

Rationale. The cytologic interpretation of ASC-US represents a category of morphologic uncertainty. The definition of ASC-US is "some, but not all" of the features of a LSIL and as such, includes both poorly sampled and poorly represented LSIL and the many morphologic mimics of LSIL. An ASC-US interpretation does not represent a specific cytologic interpretation. Because of its morphologically equivocal nature, the inter- and intra-observer reproducibility of an ASC-US interpretation is less than that for the reliable, unequivocal cytologic categories of LSIL and high-grade squamous intraepithelial lesion (HSIL) [81]. The current ASCCP recommendation [2] of HPV testing for the management of ASC-US cytology tests allows for the use of this more objective test to stratify the risk for the development of cervical cancer precursor lesions. The introduction of HPV testing for management of ASC-US and cotesting for primary screening over the last decade has led to an increased number of women being identified with HPV-negative, ASC-US-cytology results. The key question to provide rationale for this recommendation is as follows: Does the risk of precancerous lesions in women with HPV-negative, ASC-US-cytology results warrant increased surveillance in comparison to that of women who are HPV negative and cytology negative?

Data from published studies have shown that the risk of precancerous lesions following an HPV-negative, ASC-US cytology result is very low, and not qualitatively different from a negative cotest. Because of the very low cervical cancer risk observed in the HPV-negative, ASC-US cytology population, continued routine screening is recommended for this group: 3-year interval for cytology screening of women ages 21–29 or 30–65 years old, and 5-year interval for cotesting of women ages 30–65 years old.

Women with HPV-positive ASC-US or abnormal cytology more severe than ASC-US (LSIL or more severe) regardless of their HPV status should be referred to colposcopy [2]. The risks of CIN3+ and cancer following HPV-negative, LSIL+ cytology results are too great to warrant a return to routine screening [19].

Evidence. Table 4 [103–105] shows patient outcomes, number of studies and quality of the evidence. The risk of CIN3+ following HPV-negative, ASC-US cytology results is very low. In the largest study, the risk of CIN3 at enrollment in women with HPV-negative ASC-US cytology was 0.28% [103]. In a longitudinal follow-up study, the risk of CIN3+ in this population at 5 years was 0.54% [74]. Analyses from the ASCUS LSIL Triage Study showed that the 2-year cumulative risk of CIN3+ was less than 2% (1.4% to 1.9% depending on the HPV testing method used) [104, 105]. For comparison, two studies showed follow-up data on cotest-negative women

Table 5. Evidence for Screening With HPV Alone Compared to Cytology

Outcome[a]	Main result	Number of studies	Quality of evidence	Comments
Cancer				
Prevalent	Cytology 0.01%, HPV 0.02%	1 [109]	Low	Wide confidence intervals based on small number of cases, but consistent pattern
Incident cases after negative result	5 years: Cytology 7.5/100,000, HPV 3.8/100,000	1 [74]	Moderate–low	Wide confidence intervals based on small number of cases, but consistent pattern; 1 RCT, 1 observational
CIN3+				
Prevalent	Increase in prevalent CIN3+ detected with HPV 0–0.3%	4 [38, 74, 109, 110]	Moderate–low	Includes one RCT with CIN2+ as outcome
Incident cases after negative result	CIN3+ 5 year: Cytology: 0.36%; HPV: 0.17%[74] 6 year: Cytology: 0.68%; HPV: 0.28%[110]	2 [74, 110]	Moderate–low	Results consistent with multinational cohort study with joint database analysis[22]
Colposcopies	Absolute increase in colposcopies 0–4.2% with HPV at enrollment	2 [38, 109]	Moderate–low	Not universally reported; cumulative risks not reported

CIN2+ indicates cervical intraepithelial neoplasia of grade 2 or more severe diagnosis; CIN3+, cervical intraepithelial neoplasia of grade 3 or more severe diagnosis; HPV, human papillomavirus; RCT, randomized controlled trial.
[a]Patients/population comprises women aged 30–65 years. The intervention was screening with HPV alone, and the comparator was screening with cytology alone.

30 years and older. In these studies, the risks of CIN3+ ranged from 0.3% (prevalent) [93] to 0.16% with 5 years follow-up [74].

Overall, the absolute risk of a true precancerous lesion in the HPV-negative, ASC-US cytology population is very low (less than 2% overall, and less than 1% when based on the most robust studies). This level of risk does not warrant more frequent screening.

Screening With HPV Testing Alone

Recommendation. In most clinical settings, women ages 30–65 years should not be screened with HPV testing alone as an alternative to cotesting at 5-year intervals or cytology alone at 3-year intervals.

Rationale. Primary HPV testing has been prospectively assessed as a replacement for currently acceptable modalities of cervical cancer screening. RCTs of HPV testing alone have demonstrated that when compared to standard cytologic screening, HPV testing has increased sensitivity for detection of CIN3+ and CIN2+ after a single screening round. Greater sensitivity also means greater negative predictive value over a longer time period, because the absence of positive HPV findings is an indication of low risk of developing CIN3+. RCTs have been less successful at defining the specificity of HPV testing, and so the potential harms of primary HPV testing are poorly quantified.

Although HPV testing alone-based screening approaches appear promising, the lack of a well-defined and evaluated management strategy for positive tests precludes their practical implementation in the majority of clinical settings in the U.S. at this time. There are no data to estimate how the clinical performance of cytology (as a follow-up test) would be affected by *a priori* knowledge of positive HPV status. The lack of an internal standard for specimen adequacy for some HPV assays may provide false reassurance among a small number of women whose negative screening results may be a function of specimen inadequacy rather than true absence of disease. Such an event is less common with cytology since specimen adequacy assessment is a routine component of the evaluation, and inadequacy prompts intervention and follow-up on the part of the clinician and patient. Thus, the inclusion of cytology with HPV testing, i.e. cotesting, provides some additional reassurance against testing errors due to specimen inadequacy, although the benefits in terms of sensitivity and negative predictive values are only incremental. Implications, such as cost effectiveness of and adherence to implementing such a major change in the current U.S. opportunistic screening setting, require further evaluation and planning.

Evidence
HPV in Primary Screening
Table 5 [38, 74, 109, 110] shows patient outcomes, number of studies and quality of the evidence. HPV testing alone for primary screening appears promising in women aged 30 years and older, as this group may be at greatest risk for developing CIN3+. In single round screening studies, HPV testing is more sensitive for detection of CIN2+ and CIN3+ than cytology alone and is almost as sensitive as cotesting (2–5% additional CIN3+ are detected among women with HPV-negative, cytology-positive results, primarily in those with LSIL or more

severe cytology) [74, 80, 105]. And a negative HPV test provided greater reassurance against CIN3+ in the subsequent 5–7 years than cytology alone and is nearly as reassuring as a negative cotest. Therefore an acceptable screening interval for use of HPV testing alone should be comparable to that of cotesting.

However, the published studies of HPV testing alone for primary screening are limited by a lack of long-term follow-up, with only one reporting the second round of screening [41]. In that study, referral of all HPV-positive women to colposcopy led to a reduction in cancers in the second round of screening 4 years later compared to cytology screening. But more data are needed regarding the long-term impact of using HPV testing alone for cervical cancer screening.

HPV testing alone for primary screening is less specific than cytology alone and may identify clinically insignificant disease destined to spontaneously regress [41]. Thus, a strategy of immediate colposcopy of all HPV-positive women can be associated with significant harms, due to unnecessary diagnostic procedures or treatment, which may outweigh the benefits of the increased sensitivity. For this reason primary screening using HPV testing alone requires yet-to-be-defined appropriate tests for assessing a positive HPV result.

Currently, there are no published large-scale or population-based studies evaluating management strategies of HPV-positive women in an HPV testing alone for primary screening setting. A recent systematic review of the available published evidence concluded that HPV testing alone is very promising for primary screening of women aged 30 years and older, particularly when coupled with cytology testing (for follow-up) of HPV positive results, which may reduce the increase in false positives (and their related harms) that would result from HPV testing alone [111]. There are no direct data to estimate the performance of cytology in a triage (follow-up) setting, although a simulation analysis using data from a RCT found an improved positive predictive value using HPV testing followed by cytology compared to other combinations of cytology and/or HPV testing [38]. Specifically, it is unclear whether the interpretation of cytology in a real-world setting is affected by *a priori* knowledge of an HPV positive result and what impact this may have in a general population screening setting. In addition, as discussed in the Management of Women

with HPV-Positive Cytology-Negative Cotests section, rational clinical follow-up of HPV-positive, cytology-negative women is crucial to realizing the (sensitivity) benefits of using HPV testing (although the HPV-negative patients would still benefit from the added safety). Assessment of the full impact of a primary screening strategy using HPV with or without cytology follow-up may be possible only after implementation in selected clinical settings in a Western or high-resource setting and/or using modeling analyses [111].

Other strategies have aimed to improve specificity and reduce harm by interposing secondary testing for management decisions between a positive HPV test and colposcopy. Potential secondary biomarkers included HPV genotyping (for HPV16 or HPV16/18) [92, 100], HPV mRNA testing [112], and/or detection of other non-HPV biomarkers (e.g. p16^{INK4A}) [108]. Although promising, there are limited data regarding the test performance of these markers. Specifically, the cross-sectional and archival nature of most available molecular marker studies as well as the heterogeneity of clinical endpoints examined (CIN2+ vs. CIN3+) limits the current usefulness of these data. Finally, there are no direct comparisons of these various triage strategies and the specificity of such an approach, and the consequential potential harms (or benefits) have not yet been well defined.

Women Older Than Age 65

Recommendation. Women over 65 years of age with evidence of adequate negative prior screening and no history of CIN2+ within the last 20 years should not be screened for cervical cancer with any modality. Once screening is discontinued it should not resume for any reason, even if a woman reports having a new sexual partner.*

Women Older Than Age 65 With a History of CIN2, CIN3, or Adenocarcinoma *in Situ*

Recommendation. Following spontaneous regression or appropriate management of CIN2, CIN3, or adeno-carcinoma *in situ* (AIS), routine screening should continue for at least 20 years (even if this extends screening past age 65).

Rationale. In well-screened women older than the age of 65 in the United States, CIN2+ prevalence is low [29, 113] and cervical cancer is rare [1]. In the U.S., cervical cancer is most commonly diagnosed in unscreened and under-screened women [114–116]. In contrast, the potential

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*Adequate negative prior screening is defined as 3 consecutive negative cytology results or 2 consecutive negative cotests within the 10 years before ceasing screening, with the most recent test occurring within the past 5 years.

Table 6. Evidence for Stopping Screening

Outcome[a]	Main result	Number of studies	Quality of evidence	Comments
CIN3+	N/A			
Cancer incidence	Continued screening to age 90 prevents only 1.6 cancer cases and 0.5 cancer deaths per 1000 women	1 [63]	Moderate-low	Modeling study; consistent with other modeling studies
Colposcopies	Continued screening to age 90 results in an additional 127 colposcopies per 1000 women	1 [63]	Moderate-low	Modeling study

CIN3+ indicates cervical intraepithelial neoplasia of grade 3 or more severe diagnosis; N/A, not applicable.
[a]Patients/population comprises women older than age 65 years. The intervention was no further screening, and the comparator was screening with cytology every 3 or 5 years.

harms from screening of this population, in addition to those already specified, include discomfort during cytology sampling and false-positive screening tests. Based on the extended natural history of the disease, it is improbable that incident HPV infections and newly detected CIN3 after the age of 65 will have sufficient time to progress to invasive cancer in the woman's lifetime but it is unlikely that there will ever be a clinical trial to demonstrate this directly. Finally, one modeling study concluded that for women who have been screened every 3 years prior to age 65 years, the ratio of colposcopies to years of life gained associated with further screening was large (or the years of life gained per colposcopy small) because of the small gains in life expectancy [63].

The age at which to discontinue screening is based on the opinions of the expert panel members and was chosen to balance the benefits and harms of screening older women. Women who discontinue cervical cancer screening should continue to obtain age-appropriate health care.

While women with adequate negative prior screening have a very low risk of cervical cancer, those who have been treated for CIN2+ in the past 20 years (or had it resolve spontaneously) remain at approximately a 5- to 10-fold higher risk for cervical cancer than the general population [117, 118]. (We note that these studies were based on cytology alone; future studies incorporating HPV testing may yield different risks.) We endorse the ASCCP guidelines for continued regular screening of these women for 20 years after an initial period of more intense surveillance, even if that extends screening past age 65. We define *regular screening* as screening every five years using cotesting (preferred) or every three years using cytology alone (acceptable).

Recent evidence suggests that the natural history of incident HPV infections is unaffected by a woman's age at acquisition [94, 119]. A new carcinogenic HPV infection in a woman aged 65 years or older with a cervix should clear spontaneously in most cases, and only a small percentage of women should have a persistent infection. Since the transformation zone of older women is smaller and less accessible than in younger women, and since cervical cancer develops many years after an incident infection, screening this population would detect a very small number of new cases of CIN2+ and prevent very few cervical cancers and even fewer cancer deaths.

Evidence. Table 6 [63] shows patient outcomes, number of studies and quality of the evidence. Mathematical modeling [63] among women screened with cytology every three years prior to age 65 demonstrates that continued screening even to age 90 prevents only 1.6 cancer cases and 0.5 cancer deaths per 1000 women. Continued screening extends life expectancy by only one year per 1000 women, while resulting in 58 extra false positives, 127 extra colposcopies and 13 extra CIN2/3 diagnoses requiring treatment.

With respect to newly acquired HPV infection in women who have discontinued screening, indirect evidence regarding the risk of not resuming screening in this population is found in the report by Chen *et al*. In a large-scale community-based cohort of women followed for up to 16 years after receiving cytology and HPV testing at baseline and two years later, newly detected infections were associated with very low absolute risks of persistence and CIN3+ regardless of the woman's age. Furthermore, for women aged 55 and older who had two negative HPV tests two years apart, the risk of subsequently developing CIN3 or cervical cancer was only 0.08%, with only one woman developing CIN3 after 9.6 years [94]. In another large 7-year, population-based cohort study, newly detected infections were associated with very low absolute risks of HPV persistence or progression to CIN3+. The rate of progression to CIN2+ (or CIN3+) after 3 years of follow-up was not higher for women aged 34 years and older than for younger women [119]. Therefore, most new carcinogenic HPV infections in women age 65 years or older should clear spontaneously, and only a small percentage is likely to persist. Since the transformation zone of older women is smaller and less accessible than in younger women and since cervical

cancer develops at a median of approximately 20 to 25 years after an incident infection, screening this population would detect a very small number of new cases of CIN2+ and prevent very few cancers and even fewer cancer deaths. The risks associated with over-treatment in the elderly population outweigh the benefits.

Women Who Have Undergone Hysterectomy and Have No History of CIN2+

Recommendation. Women at any age following a hysterectomy with removal of the cervix who have no history of CIN2+ should not be screened for vaginal cancer using any modality. Evidence of adequate negative prior screening is not required. Once screening is discontinued it should not resume for any reason, including a woman's report of having a new sexual partner.

Rationale. In women who have undergone hysterectomy with removal of the cervix for reasons other than CIN2+, vaginal cytology screens for primary vaginal cancer. Vaginal cancer is an uncommon gynecologic malignancy. Its age-specific incidence is similar to or less than that of other cancers for which screening is not performed, such as breast cancer in men. Abnormal vaginal cytology is rarely of clinical importance. Therefore, there is no justification for continuing to screen these women for lower genital tract malignancies. Women who have had a hysterectomy for cervical intraepithelial lesions may be at increased risk of vaginal cancer, but the data are limited. Women who discontinue screening should continue to obtain age-appropriate preventive health care.

Evidence. The incidence rates for all vaginal cancers combined were 0.18 per 100,000 female population for *in situ* cases and 0.69 for invasive cases [120]. A retrospective cohort study of vaginal cuff cytology in 5,862 women post-hysterectomy for benign disease reported abnormal cytology among 79 women (1.1% of all tests). The mean length of time from hysterectomy to abnormal cytology result was 19 years. The positive predictive value of vaginal cuff cytology for detection of vaginal cancer was 0 (95% CI 0 to 33) [121]. A 10-year retrospective study among 697 women after hysterectomy for benign disease found that 663 vaginal cuff cytology tests were needed to detect one case of vaginal dysplasia [122]. A retrospective study of 220 women selected at random from 2,066 women with a previous hysterectomy for benign conditions and followed for an average of 89 months identified seven patients (3%) with intraepithelial cytologic abnormalities, but no vaginal cancers. No benefit in patient outcomes was observed [123]. A cross-sectional study of 5,330 screening cytology tests in women after a hysterectomy found one case of dysplasia and no cancers [124].

In a study of 193 women with CIN at hysterectomy, the incidence of abnormal vaginal cuff cytology at least two years after hysterectomy was 0.7 per 1,000; at 20 years, 96.5 percent of the women continued to have normal cytology [125]. Thus, even if women with hysterectomy were at an increased risk of vaginal cancer, there is no proven method to effectively intervene before vaginal cancer develops.

Screening After Vaccination: Looking to the Future

Recommendation. Recommended screening practices should not change on the basis of HPV vaccination status. *Rationale.* Two HPV vaccines have been licensed in the U.S.; both are highly effective at preventing infection with the two most carcinogenic HPV types, HPV16 and HPV18, which cause about 70% of all cervical cancers. Randomized clinical trials have also shown that HPV16/18 vaccination is highly effective in preventing CIN2 and CIN3 among women not previously exposed to these types. In vaccinated populations, it is plausible that women protected by vaccination could have less intensive screening and also start screening at a later age, since they will likely experience a lower risk of cervical cancer in the future. However, a number of arguments preclude a more permissive screening policy at this time among a vaccinated cohort in the US. About 30% of cervical cancers will continue to occur, because the first generation of vaccines covers only HPV16/18. As Advisory Committee on Immunization Practices (ACIP) recommendations include vaccinating women up to 26 years, many women may be vaccinated after HPV infection has already occurred, when efficacy declines. Moreover, coverage of HPV vaccination in the U.S. has yet to reach levels comparable to those of countries, like Australia and the United Kingdom, which have publicly-funded, school-based vaccination programs that guarantee high coverage of pre-adolescents and young women. On average for all states in the U.S. in 2010, only 32% of eligible girls and women had received all 3 doses of the vaccines, and HPV vaccination is largely opportunistic, not necessarily targeting girls and young women before the onset of sexual activity [126]. There are also geographic and socioeconomic disparities in vaccination coverage.

Thus, there are no data at this time that support changes in the age when screening is to be initiated or in the screening interval for U.S. women that have been

Table 7. Evidence for Women Who Have Been Vaccinated Against HPV Types 16 and 18

Outcome[a]	Main result	Number of studies	Quality of evidence	Comments
CIN3+				
Incidence in vaccinated women	HPV vaccine showed near 100% efficacy in reduction of HPV vaccine type CIN 3+ in women who are HPV naïve	7 [127–133]	Strong	Duration limited at this time at 7–9 years depending on vaccine type, women in RCT had limited number of partners to qualify, efficacy was significantly reduced in those not HPV naïve, no efficacy data are available on vaccinated children; overall efficacy in reduction of all CIN 3+ is much less since non vaccine types continue to contribute to CIN 3+
Population effects	Modeling studies show that vaccination at rates >70–75% is expected to result in 47–95% reduction of CIN 3+ . This reduction is likely not to occur until 15–17 years after vaccination programs have reached 70%.	7 [134–140]	Moderate	Modeling studies—indirect evidence, but consistent across studies. Long interval to reduction limits any recommendations to changes at the present time
Population vaccine coverage	Latest data from the CDC show that 32% of targeted female youth have received 3 doses of HPV vaccine	1 [126]	Strong	No data are available regarding whether the targeted youth including 'catch-up' have already initiated sexual activity and are less likely to benefit
Colposcopies	Studies have shown that PPV of cytology would be negatively impacted by the HPV vaccine. Modeling studies suggest fewer unnecessary diagnoses/treatments if screening recommendations revised to delay onset of screening or increase intervals.	11 [141–151]	Moderate	Modeling studies are indirect evidence. If women reduced screening, the effect of HPV vaccination would be negated. Some of the models suggest that altering strategies would not be cost-effective and potentially harmful. Results from RCTs not generalizable due to intensity of follow-up.

CDC indicates Centers for Disease Control and Prevention; CIN3+, cervical intraepithelial neoplasia of grade 3 or more severe diagnosis; HPV, human papillomavirus; PPV, positive predictive value; RCT, randomized controlled trial.

[a]Patients/population comprises women who have received HPV vaccination against types 16 and 18. The intervention was beginning screening at age 25 years and/or screening with cytology less frequently than every 3 years, and the comparator was current recommended guidelines for screening with cytology among nonvaccinated females (ie, cytology every 1–3 years starting at age 21 years).

vaccinated. The same recommendation applies to the individual woman who reports having been vaccinated. Overall practice recommendations for age to initiate screening, interval, and acceptable screening technologies are described elsewhere in this article and should be followed in populations with access to HPV vaccination as well as for individual women with known vaccination.

Evidence. Table 7 [126–151] shows patient outcomes, number of studies and quality of the evidence. The low HPV vaccine coverage in the U.S. remains a barrier for proposing population-based changes in cervical cancer screening among those receiving the vaccine. Moreover, the coverage threshold at which changes would be cost-effective for the population and yet safe for the individual remains unknown. At low coverage, herd immunity will not occur, and there will be little impact on HPV transmission rates and consequently on the incidence of CIN3+. Even in countries with high HPV vaccination coverage, changes to cervical screening practices are not immediately anticipated. Surveillance systems, such as the New Mexico HPV and Pap Registry [152], the establishment of sentinel CIN3 registries, and HPV Vaccine Impact Monitoring Project Across Connecticut (HPV-IMPACT), a sentinel surveillance system for monitoring HPV vaccine impact on HPV type-specific CIN2+ established by the Centers for Disease Control [153], will be crucial for monitoring the impact of vaccination.

Although mathematical models suggest that current cervical cancer screening recommendations could be modified following HPV vaccination, there is no consensus on screening recommendations in a vaccinated cohort. There is agreement among modelers that it will take more than a decade to see the full impact of vaccination on screening outcomes. As a result, changes in screening recommendations in the HPV vaccination era, although

attractive, will likely not be warranted in the immediate future. It is also important to ensure that the benefits of vaccination are not offset by reductions in screening coverage due to complacency or an erroneous belief that vaccination eliminates the need for screening. One study suggested that with vaccine coverage of 84% among 12-year-old girls, a reduction of screening from about 80% coverage to about 60% coverage could lead to reductions in life expectancy compared to no HPV vaccination with 80% screening coverage [147]. Likewise, another study found that the quality-adjusted life expectancy was lower for certain age groups under conditions in which there was lower participation in screening (<70%) and incomplete vaccine coverage (<75%) compared to current screening practice without vaccination [148].

Another important argument against modifying screening recommendations based on introduction of HPV vaccines is the lack of empirical data on the performance of screening tests among a vaccinated cohort. Mathematical models [149, 150] indicate that vaccination is expected to reduce the prevalence of high-grade cervical lesions over time, which will have a deleterious influence on the positive predictive value of screening tests, thus increasing the proportion of false positive results. Although not empirically based, these models provide insights concerning the role of cytology or other screening technologies and raise awareness about the need to reassess future screening practices to guarantee acceptable performance quality and safety. The guidelines presented elsewhere in this report emphasize the need for less intensive screening, setting the stage for reducing the harms that would come from the expected loss in screening test performance.

Despite the rationale for changes in screening practices among vaccinated women, agreement on a recommendation would have to be based on high quality evidence on the critical outcomes, including duration of protection and reduction of risk of CIN3+. A key question is the duration of protection following HPV vaccination, especially in girls ages 11–12, and the impact on age-specific cancer risks. In addition, reliable documentation of fully vaccinated status at an age likely to be prior to HPV exposure would be needed. Evidence is also needed on (1) the effect of vaccination on the HPV genotype distribution, (2) the impact of vaccination on the performance of cytology and HPV testing (the two methods recommended in the updated guidelines), and (3) the effect of vaccination on screening adherence. It is expected that epidemiologic surveillance via linkage of vaccination registries with screening and HPV testing databases or electronic medical records from managed care organizations, and collection and reporting of screening data by vaccination status will permit comparisons of HPV type distributions, screening behaviors, and lesion prevalence between vaccinated and unvaccinated individuals. Having such data sources would permit tailoring of screening recommendations for women with a documented history of HPV vaccination. In addition to registries, clinic-based systems and large screening programs such as Title X Family Planning, the CDC's National Center of Chronic Disease Prevention and Health Promotion, Planned Parenthood, and managed care organizations should begin reporting screening data by HPV vaccination status. Such guidance is already being provided by the Public Health Agency of Canada [154].

RECOMMENDATIONS FOR FUTURE RESEARCH

These updated guideline recommendations were motivated by an increased understanding of the natural history of HPV infection and cervical carcinogenesis, and by an expanding knowledge of the relative performance of different screening tests. Evident and important remaining research priorities include the following:

1. The most important research priority involves identifying strategies to increase screening coverage in unscreened or under-screened women, in whom a significant proportion of invasive cancers occur. Novel strategies utilizing HPV testing and other molecular approaches should be examined. Specifically, self-collection of cervico-vaginal specimens coupled with HPV testing can achieve sensitivity that is comparable to or better than that of cytology-based screening [155]. Self-collection with HPV testing might be used to increase screening coverage and address these cancer health disparities [156]. Future studies need to evaluate the scale-up, implementation, and acceptability of such programs targeting these populations.

2. How best to manage women with HPV-positive, cytology-negative cotesting results or more generally, HPV-positive results. We need to determine the relative performance of reflex HPV typing for the most carcinogenic types versus follow-up repeat cotesting at different intervals. Future research on the use of novel biomarkers is also necessary.

3. In available studies, most of the sensitivity of cotesting derives from the HPV test rather than the cytology test. Future research might support HPV testing alone for screening, especially if it can show that longer screening intervals offset the potential

harms that follow lower specificity of a highly sensitive test. It will be important to verify that the expected, very small decrement in sensitivity compared with cotesting is acceptable in the U.S.

4. Prospective studies among older women are needed to establish the optimal age to cease screening among known HPV-negative women. The incidence of new infections declines sharply with increasing age. They are usually benign regardless of a woman's age. It is long-term HPV persistence that causes cervical cancer, and carcinogenesis typically takes decades from infection to cancer. The great majority of cervical cancer cases arise from HPV infections that persist from acquisition at younger ages. Thus, it might be safe for consistently HPV-negative women to stop cervical cancer screening at younger ages than the 65 years recommended in these guidelines.

5. HPV vaccination decreases the efficiency of current methods of cervical cancer screening, but conference participants judged that it is premature to modify screening in the U.S. based on vaccination history. For example, it might eventually make sense to initiate screening in vaccinated cohorts at older ages (>21 years) because of their lowered risk of cancer. For proper integration of screening and prevention, we need to study how to modify cervical screening in optimally vaccinated women. To do so, it will be necessary to implement an epidemiologic surveillance system with vaccination and screening registries whose data can be linked for efficient assessment of the impact of vaccination on lesion incidence and screening performance and/or use data from managed care organizations with excellent electronic medical records.

6. There is a continuing need to validate HPV tests. Researchers must establish which ones are acceptably reproducible and accurate. We need to ensure that the HPV tests in clinical use afford the same protection against cancer at longer time intervals as those used in research studies.

7. Large trials are unlikely to be conducted to answer all of these applied research questions. Cervical cancer screening should become an active area of comparative effectiveness and cost-effectiveness analysis, including focused health decision modeling and efficient use of observational data from surveillance systems.

8. Acceptance of the extended screening intervals requires a change in thinking among women, their clinicians, and insurers. It will be important to study to what degree the guidelines are followed, and reasons for noncompliance, as part of fostering acceptance. In these screening guidelines, one of our underlying principles (see section on Risk-based strategies) is that women with equal risk of CIN3+ should be managed similarly. As part of guideline development, patient risks are considered explicitly (e.g., HPV-negative ASC-US has similar risk as HPV negative, cytology negative, and therefore both groups should be re-screened at the same interval) or else implicitly (when evaluating acceptable screening intervals). In the future, patient characteristics and their cervical cancer risk will change, e.g., HPV vaccination and a history of negative HPV tests. New screening tests will continue to be developed that may have different performance characteristics. These changes will need to be fit into recommended risk thresholds for clinical decision-making. Because of their central place in guidelines, more research on appropriate risk thresholds for referral to colposcopy and on performance of colposcopy in these referral populations is warranted. If feasible, the development of novel risk estimation software to support decision-making would be helpful.

CONCLUSION

The process used to develop these recommendations represents a transitional stage in guidelines development for the American Cancer Society. Previous guidelines have been developed using a consensus process involving experts in the field along with key stakeholders; although these recommendations were based on evidence, there was not a formalized process for evaluating the evidence and incorporating it into the recommendations. The group developing these guidelines also consisted of experts and stakeholders; the key difference was in the use of the principles of the GRADE guideline development process to more formally evaluate the evidence and incorporate the quality of the evidence into the recommendations. Beginning in 2012, the ACS will be using a new guidelines process, involving a standing group of non-specialists and a formal process for evidence review [157]; this change comes in response to Institute of Medicine (IOM) recommendations for improving guideline transparency and clarity, and reducing potential conflict of interest.

One of the key principles outlined in the IOM report was the need for timely updating of guidelines as new evidence becomes available. Particularly for areas where uncertainty remains, there are large ongoing trials that either were published after our final update for the conference [158], or will publish results in the next 1–2 years. One advantage of using a structured evidence

evaluation process such as GRADE is that it facilitates identifying the key research needs that will lead to changes in recommendations; this should help expedite the updating process.

Until the next update, these recommendations reflect the participants' judgment of the best evidence-based practice for the prevention of cervical cancer morbidity and mortality through currently available screening tests that maximizes protection against cervical cancer while minimizing the potential harms associated with false-positive results and overtreatment.

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