New Cervical Cancer Screening Guidelines, Again

Nicole Karjane, MD, David Chelmow, MD*

KEYWORDS

• Pap smear • HPV • Cervical cancer screening • Cervical cytology • Guidelines

KEY POINTS

- Several major organizations, including the American Cancer Society, the US Preventative Services Task Force, and the American College of Obstetricians and Gynecologists, have recently revised their guidelines for cervical cancer screening and prevention.
- Cervical cancer screening should begin at 21 years of age, regardless of risk factors.
- Women aged 21 to 29 years should be screened with cytology alone at 3-year intervals.
- Women aged 30 to 65 years should be screening with cytology and high-risk human papilloma virus cotesting at 5-year intervals or cytology alone every 3 years, with cotesting specifically preferred by all but the US Preventative Services Task Force.
- Women older than 65 years with adequate negative prior screening should not undergo further screening for cervical cancer.

INTRODUCTION

Over the past year, cervical cancer screening guidelines have undergone a series of important revisions by major organizations. In March, the American Cancer Society (ACS), the American Society for Colposcopy and Cervical Pathology (ASCCP), and the American Society for Clinical Pathology revised their recommendations (referred to as *ACS guidelines* in this article).[1] At the same time, the US Preventive Service Task Force (USPSTF)[2] (referred to here as *USPSTF guidelines*) revised their guidelines. In addition, the American College of Obstetricians and Gynecologists (ACOG) released a revised practice bulletin in November 2012 (ACOG practice bulletin). Each of these major organizations used slightly different methodologies to arrive at their recommendations. This article discusses and summarizes these recommendations and the rationale for them.

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Department of Obstetrics and Gynecology, Virginia Commonwealth University School of Medicine, 1250 East Marshall Street, PO Box 980034, Richmond, VA 23298, USA
* Corresponding author.
E-mail address: dchelmow@mcvh-vcu.edu

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RATIONALE FOR REVISIONS

Each of the organizations listed earlier recognized the need to revise existing recommendations. Cervical cancer screening has been a true preventative medicine success. The introduction of cervical cancer screening programs has resulted in marked reductions in cervical cancer incidences whenever and wherever they have been implemented.[3,4] Cervical cytology was initially recommended arbitrarily on an annual basis as early as the 1940s. This recommendation was done without supportive data and without understanding the pathophysiology of cervical carcinogenesis. By the 1960s, annual Papanicolaou screening became the basis for the annual well-woman visit. Given the extraordinary success in cancer reduction and tradition of annual visits, annual screening became deeply entrenched in medical practice and patient expectations.

Guideline revisions are not new and, in fact, have occurred regularly over the last 25 years. Given the importance of cervical cancer screening and prevention, major societies have developed screening recommendations and guided their evolution as new data has become available. The frequency of screening has been a major focus. As early as 1976, the Walton report from Canada suggested that every 3-year screening was as effective as annual screening. The ACS included every 3-year testing in their guidelines in 1987. The ACOG first suggested an increased interval in their practice bulletin revision in 2003.

The need to yet again revise the guidelines came from new data in several areas. First, when cytology was initially implemented, it was without the knowledge of the role of the human papilloma virus (HPV). It has become clear that HPV is necessary for the development of squamous cell carcinoma of the uterine cervix. HPV infection, however, is incredibly common; most people who are infected are unaware of their infection and do not suffer any consequences, let alone develop cancer. The current model[5,6] assumes that HPV infection of the cervix behaves in 2 different ways. Most infections are transient. In women with transient infections, the immune system clears the virus; these women are not at an increased risk for cervical cancer. These infections may be manifested by low-grade squamous intraepithelial lesion (LSIL) cytology and cervical intraepithelial neoplasia (CIN) 1 histology. In a second, much smaller group of women, the virus persists. These persistent infections are manifested by high-grade squamous intraepithelial lesion (HSIL) cytology and CIN 2 and 3 histology. These patients do have appreciable risk of developing cervical cancer if the precursors are not detected and treated. In a tragically misguided observational study of women with high-grade cervical dysplasia who were observed without treatment, 31.3% went on to develop cervical cancer over 30 years of follow-up.[7] Second, it has been recognized that there are harms related to screening. These harms include discomfort from examinations, anxiety, and potential morbidity. There is emotional impact from labeling patients with sexually transmitted infections. In addition, there is evidence[8] that women treated with excisional procedures for neoplasia may have an increased risk for premature birth. Although some recent evidence has begun to question this risk,[9,10] treatment that does not lead to a reduction in cancer risk should still clearly be avoided. Although all of the major organizations explicitly did not consider costs in their recommendations, costs would inevitably be reduced if the same cancer reduction could be reached with less intensive testing and treatment. Given the current health care environment, it is extremely important that we avoid unnecessary screening. Third, the understanding of the role of HPV in cervical carcinogenesis has led to the Food and Drug Administration (FDA) approval of tests for high-risk HPV types. Prior screening recommendations did not effectively integrate

HPV testing. Guideline revision was necessary, therefore, to integrate the understanding of HPV in carcinogenesis and the ability to test for HPV, while minimizing harms of testing too frequently.

Since the last set of revisions, vaccines for the prevention of infection with high-risk HPV subtypes have been approved and recommended by the Advisory Committee on Immunization Practices.[11–13] However, given the pathogenesis of HPV infection and cervical cancer, it is expected that a significant impact on cervical cancer incidence will not occur until approximately 20 or more years after widespread vaccination begins. Both the ACS and the ACOG explicitly state that HPV vaccination should not alter cervical cancer screening at this time.

DIFFERENCES BETWEEN GUIDELINES

In the past, the guideline updates occurred at different times unrelated to one another. This year, the USPSTF and the ACS released guidelines almost simultaneously; the ACOG released their guidelines immediately after reviewing both.

It is important to realize that there are some noteworthy differences between each organization's guidelines. These differences stem from the differing goals and methodologies of the organizations developing them. In the past, guidelines from the USPSTF, ACS, and ACOG have differed significantly in several important areas. The USPSTF makes recommendations about the effectiveness of specific clinical preventative services. These recommendations are extremely important because under the Affordable Care Act, new private insurance plans and Medicare are required to cover USPSTF-recommended preventative services without patient cost sharing. The USPSTF's guidelines focus on effectiveness, however, and are not intended to contain adequate detail for implementation in clinical settings. The ACS provides a much greater level of detail, with the intent to provide guidance for the implementation of cervical screening for typical patients. Although they provide evidence-based guidelines for the populations and situations within the scope of the guidelines, they make no comment about the areas outside the guidelines. The ACOG, which adopted the ACS guidelines, provides additional guidance to providers based on expert opinion for some areas outside the scope of the ACS's guidelines. All of the guidelines are evidence based, but the ACOG provides a larger amount of expert opinion to fill the gaps between evidence to allow for more complete implementation. Despite the differences in methodologies and aims, all 3 guidelines ended up with very similar recommendations.

INITIATION OF SCREENING

The USPSTF explicitly recommends against screening for cervical cancer in women younger than 21 years. They base this recommendation on a decision analysis that they commissioned.[14] The ACS and ACOG make the same recommendation, stipulating that women younger than 21 years should not be screened regardless of the age of sexual initiation or other behavior-related risk factors. Of note, this differs from the Centers for Disease Control and Prevention's (CDC) recommendations for women who are human immunodeficiency virus (HIV) positive,[15] which states that women who are HIV positive should be screened starting at the time of diagnosis, with no exception for adolescents. The ACS's recommendations were carried forward from the Practice Improvement in Cervical Screening and Management Symposium[16] and were not actually new recommendations.

The recommendations for age at initiation of cervical cancer screening make sense in light of the extreme rarity of cervical cancer before 21 years of age, which is

estimated at 1 to 2 cases per million girls aged 15 to 19 years.[5] In addition, studies examining the initiation of screening in younger populations have not shown a decrease in cervical cancer rates.[17,18] In light of the lack of evidence for the prevention of cancer and that abnormal screening tests are incredibly common in this age group, screening leads to harm without benefit. Cervical cancer prevention efforts in this age group should be directed at compliance with the ACIP's recommendations for HPV vaccination, not screening.

APPROPRIATE TESTS FOR SCREENING

The FDA has approved several tests for high-risk HPV types over the past several years. The use of these tests in addition to cervical cytology (cotesting) was not included in the USPSTF's prior guidelines. The ACS's earlier guidelines recommended screening with either cytology alone every 2 to 3 years or cotesting every 3 years in women older than 30 years. The addition of HPV testing in women aged 30 years or older makes sense in light of HPV's role in cervical carcinogenesis. Previous recommendations were arbitrary, however, and incompletely guided by evidence. It is known that HPV testing increases the sensitivity for high-grade lesions while decreasing specificity.[19,20] Given this trade-off, the rationale for the ACS's prior guidelines recommending either testing with cytology or cotesting at similar intervals was not optimal.

The ACS, USPSTF, and ACOG are all in agreement regarding using cytology alone in women aged 20 to 29 years. Each of the guidelines specifically states that cytology and HPV cotesting should not be performed in women younger than 30 years for screening purposes. The rationale for avoiding the use of cotesting in women younger than 30 years is that the prevalence of high-risk HPV infection is high, and the incidence of cervical cancer is extremely low in sexually active women in this age group. Because HPV testing is so much more sensitive and less specific than cervical cytology,[19] cotesting women younger than 30 years would largely detect transient HPV infections that have little to no clinical significance. Detecting infections that do not have carcinogenic potential would lead to large amounts of additional testing and potential treatment with minimal to no impact on cervical cancer prevention.[21]

The selection of appropriate tests for women aged 30 to 65 years is the area in which the major society guidelines have the most significant difference. The ACS's guidelines specifically state that HPV and cytology cotesting is preferred in women aged 30 years and older. They state that cytology alone every 3 years is acceptable.[1] The ACS argues that HPV testing is more sensitive but less specific than cytology for identifying women with CIN 3 or greater.[19] In addition, women with negative HPV tests have a lower subsequent risk of CIN 3 or greater[22,23] as well as a lower subsequent risk of cervical cancer.[24]

Since the previous guideline update, no less than 4 randomized trials have compared cytology with cotesting. Three of them focused on women aged 30 to 65.[25–27] Each of the studies used slightly different protocols and evaluation schemes for abnormal cotests, but all had similar results. In all 3 trials, cotesting detected a greater proportion of high-grade dysplasia in the first round of screening, and lower rates in subsequent testing compared with cytology alone. Rijkaart[26] demonstrated a statistically significant reduction in cancer in the second round of screening (4 of 19 579 in the cotesting group vs 14 of 19 731 cytology alone; RR 0.29, 95% confidence interval [CI] 0.10–0.87), and Ronco[21] showed a statistically significant reduction from .03% to 0%. Naucler[25] did not report the difference in cancer detection.

The ACS states that "While co-testing is preferred to cytology alone based on risks and harms assessment, such a strategy might not be feasible in all clinical settings in

the United States due to a lack of payment for co-testing or due to local policies."[1] Cytology alone is acceptable in circumstances when it is the only option; but when available, cotesting is clearly preferred.

The initial draft of the USPSTF's guidelines posted on the Internet for public comment gave cotesting a grade I statement, meaning, "Current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, poor quality, or conflicting and the benefits of benefits and harms cannot be determined."[28] Their rationale was that current evidence was insufficient to assess the relevant benefits and harms for cotesting with HPV. This decision would have had profound implications because without a grade A or B rating of effectiveness by the USPSTF, cotesting would not have been on the list of approved preventative services covered without cost sharing by the Affordable Care Act. Fortunately, additional data became available, and cotesting was given a grade A recommendation in the final document.

Even in their final document, however, the USPSTF does not distinguish between the two alternatives. They recommend cytology every 3 years or cotesting every 5 years equally. They specify cotesting as an option for women aged 30 to 65 years "who want to lengthen the screening interval."[2] They state that both strategies administered with the appropriate intervals provide a reasonable balance between benefits and harms. They caution that women who choose cotesting should be counseled that "positive screening results are more likely with co-testing than with cytology alone, and that some women may require prolonged surveillance with additional frequent testing if they have persistently positive HPV results."

The formal incorporation of cotesting into both the USPSTF's and the ACS's guidelines was likely the most profound change in this set of revisions. The ACS's guidelines, which are more likely to be widely followed, specifically prefer cotesting, unlike their prior recommendations, which offered cytology or cotesting equally. In light of the randomized evidence suggesting decreased cancer in subsequent screening rounds, the availability of cotesting and its routine use should be a significant step forward in cervical cancer prevention. Even with the USPSTF's change in their final guidelines, this remains the area of most significant difference between the USPSTF and the ACS. In its latest practice bulletin on cervical cancer screening, the ACOG adopted the ACS's recommendation that cotesting be used whenever available and agreed that cotesting should be the preferred screening method for women aged 30 to 65 years.

AT WHAT INTERVAL SHOULD PATIENTS BE TESTED?

The USPSTF, ACS, and ACOG all agree on the interval at which patients should be screened. Women without special risk factors should be tested with cytology alone every 3 years from 21 years of age until they reach 30 years of age. Women aged from 30 to 65 years should be tested with cotesting every 5 years, assuming negative results for both tests. If cotesting is not available, cytology alone should be performed every 3 years. This guideline represents a significant change from the ACS's and ACOG's prior guidelines, which specified either cotesting or cytology alone every 3 years after 30 years of age. Between 21 and 30 years of age, prior guidelines recommended screening every 2 years.

The choice of a screening interval is a balance between benefits and harms. Testing needs to be sufficiently frequent to detect high-grade lesions before the development of cervical cancer. Conversely, it should be infrequent enough that transient infections of no risk to patients can be allowed to resolve, avoiding unnecessary diagnostic tests

and treatments that will not decrease patients' cancer risk. Both the USPSTF and the ACS acknowledged the need to balance screening risks and benefits and to decrease the harms from overtesting compared with previously recommended screening intervals and, most importantly, to stop annual screening.

The interval is particularly important with cotesting. The initiation of HPV testing significantly increases the sensitivity of HPV detection while decreasing specificity.[19] Repeating cotesting too frequently will result in the detection of large numbers of transient infections and result in much additional testing. There are a few studies specifically addressing intervals at any age. Both organizations relied heavily on a modeling study by Kulasingam and colleagues[14] in making their recommendations. Stout[29] modeled outcomes for women 20 years of age screened over 10 years and predicted that screening every 3 years compared with 1 year would reduce colposcopy by half (187 vs 403 per 1000) while only slightly changing lifetime cancer risks (0.69% vs 0.33%). Kulasingam and colleagues[14] compared outcomes for screening every 1, 2, or 3 years. Compared with intervals of every 2 years, screening every 3 years negligibly changed cancer risks (37 vs 39 cancer cases per 100,000 women) and led to significantly more colposcopies (176 vs 134 per 100 000). Sasieni[30] studied women in the United Kingdom who had been screened every 2 or 3 years after negative test results and noted no difference in risk. Given the compelling evidence that screening annually in this age group leads to significantly greater colposcopies with only a slight advantage for cancer risk and that every-2-year and every-3-year intervals seem to behave similarly and were both a better balance than annual screens, all organizations recommended every-3-year testing with cytology alone in this age group.

In women aged 30 to 65 years, all 3 organizations again recommended every 3 years as the appropriate interval for screening with cytology alone. Previously, the ACS recommended screening every 2 to 3 years without specifying a preference for one interval versus the other. At least 4 studies[30–33] compared annual to every-2-year or every-3-year interval screening in organized programs and noted no advantage to annual screening. Both the Stout[29] and Kulasingam[14] modeling studies again noted very low cervical cancer rates with either 1- or 2-year screening and significantly more testing with more frequent screening. Screening with cytology every 3 years yielded a slightly higher cancer rate but required much less diagnostic testing.

In developing their guidelines, the ACS used a principle that women at similar cancer risk should be managed similarly. Further, they acknowledged that the cancer risk achieved with every-3-year screening was the accepted standard and should be the benchmark. They chose every-5-year cotesting as optimal because it has the same or lower cancer risk as compared with testing with cytology alone every 3 years. Cotesting achieved slightly lower cancer rates with less screening and fewer follow-up colposcopies than cytology alone in both a pooled analysis of small studies and a single large population study. Dillner and colleagues[22] pooled 7 studies conducted in Europe and reported a 0.28% risk of CIN 3 + 5 years after negative cotesting compared with 0.51% 3 years after negative cytology alone. In an analysis of the Kaiser Permanente of Northern California database, Katki[23] noted a 0.016% risk of cervical cancer in women 5 years after a negative cotest compared with 0.037% after negative cytology alone. Using modeling, Kulasingam[14] noted cotesting every 5 years had similar or fewer cancer cases, cancer deaths, and colposcopy than cytology performed every 3 years.

There is abundant evidence that despite recommendations to stop annual testing made by the ACS years ago and by the ACOG in 2003, many providers are still performing annual cytology testing or cotesting more frequently than every 3 years.[34] This practice has the potential to cause significant harm, particularly by detecting

low-grade lesions of no appreciable risk of becoming cancer. Detecting these low-grade lesions generates further unnecessary testing and treatment of lesions that will likely spontaneously resolve. Although all 3 organizations explicitly did not consider cost in their recommendations, extra testing clearly leads to extra cost, which is of significant concern in today's health care economic environment. The ACOG and the ACS explicitly state that annual testing should not be performed.

CESSATION OF SCREENING

All 3 major society guidelines are in agreement that under usual circumstances, screening should stop at 65 years of age. The USPSTF recommends against screening for cervical cancer in women older than 65 years who have had adequate prior screening and are not otherwise at a high risk for cervical cancer. In a separate clinical consideration section, they state that the clinician should base the decision to end screening on whether patients meet criteria defined by established guidelines and specifically cite the ACS's guidelines, reiterating their criteria.

The ACS's guidelines state women older than 65 years with evidence of adequate prior screening and no history of CIN 2 or greater 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. In addition, the ACS's guidelines state that 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 performed within the past 5 years. Women older than 65 years with a history of CIN 2, CIN 3, or adenocarcinoma in situ (AIS) should continue routine screening for at least 20 years, even if this extends screening past 65 years of age. These guidelines state that the 20 years should start after spontaneous regression or completion of appropriate management for the abnormality. The ACOG adopted this component of the ACS's guidelines without change.

The rationale for ceasing screening is twofold. First, there is little benefit of screening older women. Given the natural history of cervical cancer, which requires a median of 15 to 25 years after acquisition of HPV to develop, it is tremendously unlikely that someone who has not developed cytologic abnormalities by 65 years of age will live long enough to develop cervical cancer.[14] The study included 3 separate models. These models suggest that in women who were well screened, defined as cytology every 3 years until 65 years of age, only approximately 1.6 cancers per 1000 women and 0.5 cancer deaths per 1000 women would be prevented by continuing screening to 90 years of age. Over the course of this continued testing, many colposcopies and additional testing would be required without evidence of benefit. The rationale for not restarting screening, even when new risk factors are identified, is again motivated by the natural history of cervical cancer. Even if patients were infected with carcinogenic HPV strains at 65 years of age, they would be unlikely to live long enough to develop cervical cancer.

In addition to scant benefit of continued screening beyond 65 years of age, there is risk and inconvenience. Epithelial atrophy makes interpreting cervical cytology much more difficult after menopause; and there are many false-positive lesions, particularly low-grade lesions. Sawaya and colleagues[33] studied women from the Heart and Estrogen/Progestin Replacement Study and noted a rate of 23 new cytologic abnormalities per 1000 person years of women studied. Of the 130 women in the study with known histologic diagnoses, only one had confirmed mild to moderate dysplasia for a positive predictive value of 0.9% over 2 years. Thus, although a significant amount of

abnormal cytology was diagnosed, only a tiny fraction had true histologic abnormalities. The combination of low yield and high false positives makes screening in older women ineffective; therefore, it is not recommended.

SPECIAL CIRCUMSTANCES

All of the major society guidelines are intended for typical women without special risk factors. Certain groups have been excluded from each of the major society guidelines. The USPSTF specifically states that their recommendations do not apply to "women who have received a diagnosis of high-grade precancerous cervical lesion or cervical cancer, women with in utero exposure to Diethylstilbestrol (DES), or women who are immunocompromised (such as those who are HIV positive)."[2] The ACS's guidelines do address women with a prior diagnosis of high-grade lesions but do not address women with a history of cervical cancer, exposed to in utero DES, or who are immunocompromised. The ACS recommends that women with a history of prior CIN 2, CIN 3, or AIS should first have completion of surveillance after treatment or documentation of spontaneous lesion regression according to the 2006 consensus guidelines for the management of women with CIN or AIS.[35] For women with a history of CIN 2, CIN 3, or AIS, they recommend that routine age-based screening continue for at least 20 years after spontaneous regression or completion of appropriate management, even if this extends the screening until after 65 years of age. The reason for continued screening in this population is that these women have a residual risk of significant recurrent disease that extends for this time period. Soutter[36] performed a meta-analysis and showed that women who had prior treatment of CIN 2 or CIN 3 had a 2.8-fold increased risk of invasive disease that persisted for up to 20 years after treatment. Although these patients do need continued screening, once they are out of the immediate surveillance period, they do not need increased frequency of testing; the recommendation is to follow the general age-based screening recommendations.

The CDC makes recommendations for women infected with HIV.[15] They recommend that women infected with HIV be screened every 6 months for the first year after HIV diagnosis, then annually thereafter. Screening should be with cytology alone. They recommend performing colposcopy for any abnormal cytology. They do not state an age at which screening should be stopped. They also do not stipulate a minimum age at which to start. If read literally, these recommendations are impractical. For instance, according to the recommendations, a female child who had vertical transmission of HIV would be screened at 6 and 12 months of life and then annually thereafter. If following the CDC's guidelines, clinical judgment should be used regarding when to start screening adolescents with HIV. The ACS's guidelines do make a specific statement that may apply to other populations, including those with HIV. They specifically recommend against screening anyone before 21 years of age, regardless of risk factors; therefore, the ACS's recommendations would suggest 21 years as a reasonable age to begin testing women infected with HIV.

The ACOG does provide some guidance for women with DES exposure and for those who are immunocompromised, such as solid organ transplant recipients. They comment that characteristics of HPV testing have not been determined for these populations and recommend against cotesting. They recommend screening with cytology alone annually starting at 21 years of age and do not specify an age at which to cease.

SCREENING AFTER HYSTERECTOMY

The USPSTF specifically states that their recommendations apply only to women who have a cervix. ACS states that women who have undergone hysterectomy and have

had no history of CIN 2 or greater should not be screened for vaginal cancer using any modality. They specify that evidence of adequate negative prior screening is not required and that once screening is discontinued, it should not resume for any reason, including a woman's report of having a new sexual partner. They do not make recommendations for women who had a history of CIN 2 or greater before their hysterectomy. The ACOG adopted the ACS's recommendations but provide additional guidance for patients with a prior history of CIN 2 or greater.

The rationale for discontinuing screening in women without a cervix and with no history of CIN 2 or greater is that vaginal cancer is exceedingly rare. As with extremely rare diseases, screening is ineffective. A systematic review of 19 studies including 6543 women with prior hysterectomy and with no history of CIN[37] noted that 1.8% had abnormal vaginal cytology screening after hysterectomy and only 0.12% had vaginal intraepithelial neoplasia (VAIN) on biopsy. In 5822 women with CIN 3 before their hysterectomy, 14.1% had abnormal cytology, but VAIN was confirmed by biopsy only in 1.7%, and there was only one case of cancer. Screening after hysterectomy generates significant additional testing with negligible impact on the detection of an extremely rare disease. The few lesions that are detected seem confined to women with a history of prior high-grade disease. The ACOG's guidance reflects these observations. They recommend routine screening with cytology alone for up to 20 years after spontaneous regression of the lesion or completion of the ASCCP's recommended posttreatment surveillance period.[35] Because there is no data for cotesting in this setting, they recommend testing with cytology alone. The choice of a 20-year time period is a generalization of the data from which the recommendation was made for patients who still have their cervix and have a history of prior high-grade lesion.[36]

MANAGING COTESTING RESULTS

The use of cotesting will yield several combinations of results. The USPSTF does not include management of test results at all within their recommendations. The ACS does provide some guidance. Cytologic abnormalities with a significant risk of CIN 3 are managed as per the ASCCP's 2006[38] recommendations. These recommendations include results such as atypical squamous cells–cannot exclude high grade squamous intraepithelial lesion, LSIL, HSIL, and AIS, which all merit colposcopy regardless of the HPV test result. The ASCCP's 2006 recommendations are currently being revised. The consensus meeting took place in September 2012, and the publication of the recommendations is anticipated in March 2013. The ACS does make recommendations for common screening test results with low risk for CIN 3, particularly atypical squamous cells of uncertain significance (ASC-US) with negative HPV test results and cytology that showed no intraepithelial lesion or malignancy (NILM) with a positive HPV test. Although management of these test results was included in the screening guidelines, they could also be considered elements of management. Draft revisions of the ASCCP's 2006 guidelines for the management of abnormal screening tests posted for comment on the Internet included revised management recommendations for HPV-negative ASC-US cytology, which may supersede the ACS's recommendations.

The ACS recommended that women with ASC-US cytology with negative HPV test results should be managed the same as women with negative cotesting, with continued follow-up as per age-appropriate recommended screening. This recommendation was based on the risk of CIN 3 at the time of colposcopy and over 5 years of follow-up, both of which are extremely low. In the **A**ddressing **THE N**eed for **A**dvanced HPV Diagnostics trial, the risk of CIN 3 at colposcopy was 0.28%.[39] In the Kaiser Permanente of Northern California Database, the incidence of CIN 3 was

0.54% over 5 years of follow-up. For comparison, women with NILM cytology alone had a risk of 0.36%, which is only slightly smaller. Thus, ASC-US with a negative HPV cotest has similar risk to normal cytology; if it has higher risk, the increment is small, leading to recommendations to manage both the same way. The draft revisions to the ASCCP's 2006 guidelines posted for public comment on the Internet included a recommendation to repeat age-appropriate screening 3 years after this finding. Although the final revised guidelines are not available at the time of this writing, if the draft recommendation is adopted, the recommendations discussed here will change.

The larger challenge with cotesting is the management of NILM cytology with a positive HPV cotest. The ACS recommends that these women should be followed as per the ASCCP's recommendations,[38,40] which offer 2 options. One option is to repeat cotesting in 1 year, with colposcopy if either repeat test is abnormal. Alternatively, HPV-16 or HPV-16/18 genotyping can be performed with immediate colposcopy if either HPV-16 or -18 is present. They also clearly state that colposcopy should not be performed at the initial cotest. The ACOG adopted this recommendation.

This recommendation is particularly important because these results will be common when cotesting is performed. In the Kaiser Permanente Northern California Database,[23] NILM cytology with positive HPV testing occurred in 4.7% of screenings. In their guideline document (2011), the ACS summarized the results of 11 prospective studies that followed patients up to 16 years and noted that the risk of developing CIN 3 in the year after this finding ranged from 0.8% to 4.1%. These risks are much lower than typical thresholds for recommending colposcopy. Data for the recommendation are based on expert opinion and extrapolation from other data. In particular, data suggest that most HPV will clear, and the risk of having a significant pathologic condition occurs in the small fraction where the HPV persists. Two studies[24,41] noted approximately two-thirds of patients with NILM cytology and positive HPV cotest were HPV negative by 6 to 12 months. In the study by Rodriguez and colleagues,[24] 21% of women who had persistent HPV at 12 months developed CIN 2 or CIN 3 by 30 months. The selection of 1 year as the interval to wait before repeating the cotest was based on expert opinion and was the balance of allowing time for low-risk lesions to resolve while testing soon enough that high-risk lesions did not progress. The rationale for HPV-16 or HPV-16/18 genotype testing is that the risk of CIN 3 is significantly higher with these types than other HPV types. Several studies[42–45] noted an approximately 10% risk of CIN 3 over several years after the detection of HPV-16 or -18. Because a 10% risk of having a high-grade lesion is the threshold typically chosen for colposcopy, proceeding to immediate colposcopy in the presence of HPV-16 or -18 was thought to be reasonable. Logistic difficulties and limited availability of genotyping, however, have limited the use of this triage option.

IMPLICATIONS OF LESS FREQUENT TESTING

In the decades since its introduction, the annual Papanicolaou test became a ritual to which patients and providers have become deeply attached. This tradition has allowed the development of the annual well-woman visit, which is routinely covered by insurance and allows women better access to preventative care. With the recommendations by all major societies that annual cervical cytology is no longer required, concerns have been expressed that the annual visit is threatened. Increasing the interval of cervical cancer screenings is clearly the right thing to do because it decreases the harms of testing without negatively impacting cancer rates. Rather than posing a threat to women or the annual well-woman visit, the decrease in cervical cancer

screening requirements presents an opportunity to further enhance the annual visit.[46] There are many other preventative screening and counseling requirements recommended by other guidelines from the ACS, ACOG, and USPSTF. It is difficult to cover them effectively in the limited time available. The time previously devoted to cervical cancer screening can instead be devoted to these other important issues. The ACOG[12] has clearly stated that the well-woman visit remains important despite the diminished need for cervical cancer screening.

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