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Gynecologic Cancers (RJ Morgan, Section Editor)

Making Sense of Cervical Cancer Screening Guidelines and Recommendations

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Opinion statement

Since the publication of the American Cancer Society (ACS)/American Society for Colposcopy and Cervical Pathology (ASCCP)/American Society for Clinical Pathology (ASCP) clinical guidelines in 2012, the majority of practice organizations have reached a consensus on screening recommendations for a low-risk population. These guidelines were based on a thorough review of the evidence with reproducible methods to obtain high-quality, generalizable guidelines. Despite the strength of the evidence based recommendations comprising these guidelines, limitations in physician understanding and compliance remain with respect to reaching an unscreened population and defining and caring for women who are at "high risk." "High-risk" patients are poorly characterized but should include women with a history of a prior abnormal screening, as data has shown a subsequent increased risk of cervical intraepithelial neoplasia grade 2 (CIN2) or greater, even after treatment. These women warrant more intense screening than the general population—though there are no evidence-based guidelines for optimized screening protocols in this population. Emerging data in cervical cancer screening this year includes the FDA approval of primary high-risk human papillomavirus (HPV) testing. While the data is promising, its role in clinical practice, impact on rates of colposcopy in a non-study population, and long-term outcomes are not fully understood, and ongoing research is needed. Challenges remain in this shifting environment on the optimal interval and modality for cervical cancer screening to provide the greatest benefit in detection of precancerous lesions while minimizing the harm of overtreatment. While rapid advancements in research provide improved knowledge on how to treat and prevent this disease, it is often difficult for providers across multiple specialties to remain abreast of these changes and to educate their patients about the most current recommendations. Ultimately,

provider and patient education is critical both for improving primary prevention with HPV vaccination, as well as for the uptake of evidence-based screening and management guidelines aimed at detecting and treating precancerous changes of the cervix.

Introduction

Cervical cancer, once a leading cause of mortality in reproductive age women in the USA as recent as the 1940s, has since been dramatically reduced as a result of screening. The incidence of cervical cancer was 38 per 100,000 women in the 1940s; however, since the advent of the Papanicolaou test by Dr. Papanicolaou, that incidence has decreased to 8.3 per 100,000 in the 1980s [1]. Since 1998, the rates of cervical cancer have remained relatively unchanged with 12,800 new women diagnosed with cervical cancer and 4800 cancer related deaths in the USA annually [2, 3]. While this reduction has been attributed to screening, barriers to effective screening remain, and disparities in care and access translate into discrepancies in cancer-related outcomes and plateauing mortality rates [3].

Historically, cervical cancer screening recommendations have changed relatively rapidly, reflecting emerging data and understanding of the pathogenesis of cervical cancer. According to the American Cancer Society (ACS), prior to 1980, a Pap smear was recommended "as part of a regular check-up" [4]. From 1980 to 1987, Pap smears with cervical cytology were recommended yearly for women over the age 20 (younger if sexually active) and if there are two negative Pap tests, this could be spaced to every 3 years. This was revised in 1987 to recommend yearly Pap testing for women 18 years and older with spacing of screening at the discretion of the provider. In 2002, following the ASCUS-LSIL triage group randomized control trial adding reflex human papillomavirus (HPV) testing to abnormal cytology, screening parameters again changed, increasing in complexity, now reflecting age-based variations with the addition of HPV co-testing in women over the age of 30 as an alternative to conventional cytology [4, 5]. Despite these changes in recommendations, providers and patients have been slow to change practice [6].

The evolution of screening has paralleled the discovery and evolving understanding of the role of HPV in cervical dysplasia. In the 1980s, HPV was found to be the causative agent for cervical cancer, with nearly 100 % of cervical cancer cases testing positive for HPV [7, 8]. HPV is acquired through sexual transmission with the highest prevalence at the age of sexual debut; however, more than 90 % of cases are "cleared" within 2 years of exposure, which implies that the virus is no longer actively replicating, although it may lie dormant for years [9•, 10]. Persistent positive testing for high-risk HPV subtypes such as 16 and 18 is linked to cervical cancer precursor lesions such as cervical intraepithelial neoplasia grade 3 (CIN3) which if left untreated may progress to invasive cancer [9•, 10, 11]. HPV 16 is the most carcinogenic subtype resulting in 55–60 % of all cervical cancers, followed by HPV 18 accounting for 10–15 % with a high association with adenocarcinoma, and 12 other high-risk subtypes contributing to the remaining 25–35 % of cases [8, 9•]. The natural history of cervical cancer is such that persistence of HPV 16 is a strong predictor of severe dysplasia within 5 years, and untreated CIN3 has a 30 % risk of progression to invasive cancer over 30 years, as compared to a 1 % risk of progression in treated patients [9•, 11].

In 2012, the ACS, American Society for Colposcopy and Cervical Pathology (ASCCP), and the American Society for Clinical Pathology (ASCP) developed a set of guidelines with the goal of providing unified, evidence-based recommendations aimed at detecting precancerous lesions while reducing the risk of overtreatment [9•]. Despite general agreement among 11 national and international organizations around these guidelines, there remain challenges in uptake and adherence. In a study by Teoh et al. looking at provider adherence to the 2012 guidelines, in a cross-sectional survey, 12.1 % of providers were not aware of the changes made in these guidelines and only 5.7 % were able to answer questions correctly regarding the information in the 2012 guidelines [6]. Since that time, more changes have been made to screening recommendations after the FDA approved the cobas HPV test in April of 2014 for use in primary HPV testing. The aim of this article is to review the current guidelines and recommendations for cervical cancer screening including the evidence behind the recommendations, the limitations, and the variations between guidelines. In addition, we will discuss the emerging data for primary HPV testing and address the evidence for screening high-risk populations. Although

screening is a vital part of a successful prevention program, a complete program should include primary prevention with vaccination as well as management of abnormal screens with diagnostic testing such as colposcopies and biopsies with treatment of persistent or high-grade abnormalities.

Summary of the current guidelines

The goal of a screening protocol is to optimize the detection of precancerous lesions at a time when they are treatable while limiting the harm of overtreating benign disease. Ten prominent organizations have published guidelines in the last 4 years to guide clinicians and improve screening practices. This has been led by the updated guidelines released by the ACS, the ASCCP, and the ASCP. The ACS/ASCCP/ASCP guidelines were developed with the intent to provide an evidence-based optimal screening strategy. They followed a rigorous process laid out by the Institute of Medicine to perform an unbiased review of the literature using the Grading Recommendations Assessment, Development, and Evaluation (GRADE) system. Preliminary results were posted for public comment prior to submission to add strength and transparency to the guidelines. Benefit was defined as a higher detection of CIN3+ at baseline screening and a reduction in CIN3+ at subsequent rounds of screening. Harm was defined as an increased number of colposcopies. Table 1 outlines the screening recommendations currently available for each organization.

Onset of screening

Among the ten organizations, there is consensus among nine of the organizations that screening should begin at the age of 21 regardless of sexual debut [9•, 12–14, 17]. The incidence of cervical cancer in women under 20 is 1–2 cases per 1,000,000 females and further; screening may not be preventative in this population as the incidence of cervical cancer in adolescents has remained unchanged despite initiation of screening, unlike the remainder of the population which has shown a 60 % reduction in cervical cancer following the initiation of screening [9•, 12, 20]. Furthermore, the incidence of HPV is highest following the initiation of sexual intercourse but usually "clears" spontaneously in 90 % within 2 years [9•, 10]. Thus, many organizations, in particular the US Preventive Service Task Force (USPSTF) and American College of Physicians (ACP), cite the increased harm of overtreatment in this age group and the associated pain, anxiety, cost of treatment, and the risk of preterm delivery from multiple cervical treatments [14, 17]. The USPSTF also notes the prevalence of CIN3 in women under 21 is estimated at 0.2 % while the false-positive cytology rate is reported at 3.1 % again emphasizing the potential harm of early screening [14]. Overall, the consensus for adolescents is to focus on primary prevention with education and universal vaccination [9•, 12–14, 16, 17, 20].

Screening modality and interval for women aged 21–29

All of the organizations except for the WHO recommend screening for women aged 21–29 with cervical cytology (either with conventional or liquid-based cytology) every 3 years [9•, 12–14, 16, 17, 20]. The 2012 guidelines

Table 1. Cervical cancer screening guidelines from major organizations

Organization	Date	Onset of screening	Preferred method of screening	Cessation of screening	Definition of high-risk patients	Screening for high-risk patients[a]	Prior hysterectomy	HPV vaccination
ASCCP/ASCP/ACS [9•]	2012	21	Ages 21–29: cytology q3 years Ages 30–65: -Cytology with HPV co-testing q5 years -Alternative q3 years of cytology	65—if adequate prior negative screening[a]	-Hx of CIN2 or more -Hx of cervical cancer -DES exposure -Immunocompromised women	Excluded	No screening Caveat: 1. retention of the cervix 2. Hx CIN2 or more requires 20 years of screening	Continue routine screening as per age-specific guidelines
ACOG- PB 131 [12]	2012	21	Ages 21–29: cytology q3 years Ages 30–65: -Cytology with HPV co-testing q5 years preferred -Q3 years of cytology is acceptable -Regardless of screening interval, annual well women visits recommended	65—if adequate prior negative screening[a]	-HIV infection -Immunocompromised women -DES exposure -Women with prior treatment for CIN2 or greater	-Recommend annual screening for immunosuppression (immunosuppression not defined—ex. solid organ transplant) -DES discussed but no recommendations for optimal screening	No screening Caveat: 1. retention of cervix 2. Hx CIN2 or more recommendation q3 years of cytology for 20 years	Continue routine screening as per age-specific guidelines
NCCN guidelines panel for cervical cancer screening [13]	2012	21	Ages 21–29: -Cytology q3 years With reflex HPV (ASCUS, HPV+colpo, ASCUS, HPV neg rescreen with cytology in 3 years) Ages 30–65: -Cytology with HPV co-testing q5 years is preferred -Cytology with 3 years is also acceptable -Screening with HPV alone is not recommended	65—if adequate prior screening[a] (and no Hx of prior abnormal cytology) -Continue screening for women with high-risk features -May discontinue in women with life-threatening conditions	-HIV infection -Immunocompromised women -DES exposure -Women with prior treatment for CIN2 or greater	HIV, solid-organ transplant, or long-term steroid use may need more frequent screening -HIV: q6 months for 1 year after diagnosis then annual screening (does not specify cytology versus HPV) -DES exposure: Recommend more frequent screening, usually annually as determined by their physician	No screening Caveat: 1. retention of cervix 2. Hx CIN2 or more requires 20 year of screening	Continue routine screening as per age-specific guidelines
USPSTF [14]	2012	21	Ages 21–65: Recommend screening with q3 years cytology -If desired lengthening of screening interval may consider HPV co-testing q5 years "as a reasonable alternative" after age 30 -Recommends against primary HPV or HPV	65—Caveat: after 65 may be indicated if no prior screening or for high-risk patients	High-grade precancerous lesions or cervical cancer -DES exposure -Immunocompromised women	Excluded	No screening Caveat: 1. retention of cervix 2. Hx CIN 2 or more requires 20 year of screening	Continue routine screening as per age-specific guidelines

Table 1. (Continued)

Organization	Date	Onset of screening	Preferred method of screening	Cessation of screening	Definition of high-risk patients	Screening for high-risk patients[a]	Prior hysterectomy	HPV vaccination
			co-testing in women <30 year					
AMA [15]	2014	21	Ages 21–29: Cytology q3 years Ages 30–65: -Cytology with HPV co-testing q5 years is preferred -Cytology q3 years is an alternative	65—if adequate prior negative screening[a]	-HIV infection -Immunocompromised women - DES exposure -Women with prior treatment for CIN2 or greater	Not addressed	No screening	Not addressed
WHO [16]	2014	30	Adolescent to age 30: -Primary prevention with HPV vaccination and education Ages 30–49: Screen and treat at least once: -Options include --HPV testing and treatment for positive results (with or without triage) -If negative for HPV rescreen in minimum 5 years --Visual inspection with acetic acid (VIA) in women who have a visible transformation zone --Cytology -If negative for VIA or cytology, rescreen in 3–5 years -Concomitant screening for HIV in endemic areas	49 (or determined by national standards)	Women with HIV infection	For women with HIV: screen at diagnosis -If negative test q3 years -If treated for precancer lesion follow-up in 1 year	Not addressed	Continue routine screening as per age-specific guidelines
ACP [17]	2015	21	Ages 21 to 65: Cytology q3 years or HPV co-testing q5 years beginning in women aged 30–65	65—if adequate prior negative screening[a] -Ending screening prior to age 65 in women with life-limiting comorbid conditions is	-High-grade precancerous lesions or cervical cancer -DES exposure -Immunocompromised women (including HIV)	Excluded -American Society of Nephrology recommends against screening women with end stage renal disease on dialysis with limited life expectancy	No screening Caveat: 1. retention of cervix	Continue routine screening as per age-specific guidelines

Table 1. (Continued)

Organization	Date	Onset of screening	Preferred method of screening	Cessation of screening	Definition of high-risk patients	Screening for high-risk patients[a]	Prior hysterectomy	HPV vaccination
				reasonable (limited evidence)				
ACOG US Pacific Island—PB 624 [18]	2015	Not addressed	Alternative screening methods in resource poor settings: -VIA with subsequent cryotherapy if abnormal -HPV testing followed by treatment with cryotherapy if positive	Not addressed	Not addressed	Not addressed	Not addressed	Not addressed
SGO/ASCCP-Interim clinical guidance [19••]	2015	21	Ages 21–25: Cytology q3 years Ages 25–65: -Option for q3 years of primary HPV testing (triage for positive test): hr Genotyping 16/18 1. If positive → colposcopy. 2. If "other high-risk types"→ cytology, if ASCUS+ colposcopy 3. If negative→repeat in 1 year Ages 30–65: Cytology with HPV co-testing q5 years or q3 years of cytology or primary HPV testing as above	65—if adequate prior negative screening[a]	Not addressed	Not addressed	Not addressed	Not addressed

ASCCP American Society for Colposcopy and Cervical Pathology, *ASCP* American Society for Clinical Pathology, *ACS* American Cancer Society, *ACOG* American Congress of Obestrics and Gynecology, *SGO* Society of Gynecologic Oncology, *AMA* American Medical Association, *NCCN* National Comprehensive Cancer Network, *USPSTF* US Preventive Services Task Force, *ACP* American College of Physicians, *WHO* World Health Organization

[a]Adequate prior negative screening is defined as three consecutive negative cytology results or two negative co-tests in the last 10 years with the most recent evaluation in the last 5 years. Note: Guidelines demonstrate the least agreement and most limited evidence on screening for high-risk patients and are excluded in the majority of the guidelines

recommend against HPV testing in this population either as primary testing or co-testing [9•, 12–14, 16, 17, 20]. The evidence behind these recommendations largely comes from modeling studies [9•, 21]. The estimated lifetime cervical cancer risk in the absence of screening is 31–33 per 1000 women [21]. Modeling studies compared the lifetime cervical cancer risk between annual, every 2-year, and every 3-year screening interval and found that while the lifetime risk of cancer diagnosis is slightly decreased with annual screening (3 per 1000 versus 4–6 per 1000 versus 5–8 per 1000 for annual, every 2-year, and every 3-year screening, respectively), the predicted lifetime risk of death due to cervical cancer is essentially unchanged at 0.03 versus 0.05 versus 0.05 per 1000 women [9•, 21, 22]. In contrast, the risk of harm was significantly higher in the annual screening mode with more than double the colposcopies compared to every 3 years [9•]. There was no significant difference in the odds ratio of the risk of invasive cancer following the last negative cytology between a 2- and 3-year interval (OR 1.2, CI 0.65–2.21); however, there was a rise in cancer risk at intervals over 3 years, suggesting that a 3-year screening interval is the optimal balance between benefit and harm in this age group [9•, 23]. It was also noted that the harm of HPV testing in this population outweighed the benefit, suggesting that higher rates of largely transient infections with a higher sensitivity with HPV testing would lead to unnecessary procedures. The WHO recommends primary prevention strategies with education and vaccination up to age 30 [16].

Screening modality and interval for women aged 30–65

The ACS/ASCCP/ASP, ACOG, Society of Gynecologic Oncology (SGO), National Comprehensive Cancer Network (NCCN), and American Medical Association (AMA) recommend screening every 5 years with cervical cytology and HPV co-testing as the preferred method for women 30–65, although screening with cytology every 3 years is an acceptable alternative [9•, 12, 13]. There is a body of evidence that suggests that the addition of HPV testing results in an increased sensitivity and only slightly decreased specificity, resulting in an increased detection of CIN3 while providing a similar or lower cancer risk than screening cytology alone every 3 years [9•, 12, 24, 25]. Four European randomized control trials have compared co-testing to cytology screening, and in each trial, the co-testing arm showed an absolute increase in detection of CIN3 and an absolute decrease in cancer in the second round of screening [9•, 12, 26, 27•, 28, 29]. The ARTISTIC trial, which followed patients to a third round of screening (6 years out from the initial screen), found the cumulative rate of CIN2+ was 1.41 % for negative cytology and 0.87 % for negative HPV [20, 30]. This evidence supports the recommendation for increased screening intervals with co-testing while improving detection of adenocarcinoma compared to cytology [9•, 12, 27•]. HPV testing has further shown improved efficacy in post-treatment surveillance of adenocarcinoma in situ compared to cytology (OR 12.6) highlighting the additional value in HPV testing [27•, 31].

A modeling study further supported increased screening intervals with HPV co-testing, demonstrating that over a 10-year study period, there was only a modest decrease in lifetime cancer risk (0.39 %) with every 3-year screening compared to co-testing every 5 years (0.61 %) while there was a significant increase in harm [9•, 21]. In a pooled analysis of seven European studies,

Dillner et al. reported the cumulative incidence rate of CIN3+ after 6 years following a baseline negative HPV test was 0.27 % which was considerably lower compared to a cumulative incidence rate of 0.51 % following a negative cervical cytology [24]. In a US population-based study by Katki et al. looking at over 330,000 women, the 5-year cumulative incidence of cancer was 3.2 per 100,000 for negative cytology with HPV co-testing versus 7.5 per 100,000 with negative cytology alone [25]. This data suggests that with the added sensitivity of HPV co-testing, an extended screening interval allows for a minimal risk while decreasing the harm of increased colposcopies with shorter screening intervals.

The USPSTF, on the other hand, recommends cytology every 3 years as the preferred modality for screening with HPV co-testing only for those wishing to extend the screening internal [14]. For the development of their guidelines, the USPSTF performed a decision analysis to clarify screening intervals as well as to address the benefits and harm of over- versus under-screening [14]. While it is recognized that both modalities demonstrate a comparable balance between benefit and harm, the USPSTF suggests that HPV co-testing may prolong surveillance for women nearing the end of screening who test positive for HPV with otherwise negative cytology resulting in increased harm with minimal benefit [14]. This is based on data that upwards of 11 % of women aged 30 to 34 years and 2.6 % of women aged 60 to 65 years will fall into the category of cytology negative, HPV positive, who then require repeat evaluation in 1 year, potentially extending screening intervals [14, 32].

The American College of Physicians (ACP) recognizes all published guidelines and suggests that either cytology every 3 years or co-testing every 5 years are viable options for women aged 30–65 [17]. The ACP does address the cost of screening, citing a lower cost with cytology but a cost benefit with increased screening intervals [17, 29]. The ACP also warns against the significant increased cost of annual screening in a low-risk population [17]. Goldie et al. reviewed the cost-effectiveness and reduction in cancer risk of varying screening models in cytology alone every 1, 2, 3, or 4 years and co-testing every 1, 2, 3, or 4 years and found that co-testing every 3 or 4 years had a 89–91.3 % reduction in cancer risk with a slightly higher incremental cost-effectiveness ratio than cytology alone every 3 years [29]. This study does not provide cost-effectiveness data for co-testing every 5 years as recommended in the guidelines. In 2014, in response to the guidelines released by the USPSTF, the AMA also petitioned for third party payers to amend metrics to reflect these recommendations (as seen in Table 1) to aid in physician uptake.

Cessation of screening

In regard to exiting from screening, all US organizations recommend the discontinuation of screening at age 65 with adequate prior negative screening [9•, 12–14, 16, 17, 20]. Adequate prior negative screening is defined as three consecutive negative cytology or two consecutive negative HPV results in the last 10 years with the most recent test within the last 5 years. All US guidelines agree that women with a history of CIN2+ should continue routine screening for at least 20 years following the initial increased period of surveillance even if

this extends beyond age 65 as these women retain a five- to tenfold increase risk of cervical cancer compared to the general population [9•, 12, 14, 16, 17, 33]. The evidence for discontinuation of screening is based primarily on a single modeling study with a model of continued screening up to age 90 [21]. A prolonged screening model only resulted in the reduction of 1.6 cancer cases and 0.5 cancer deaths per 1000 women compared to an additional 127 colposcopies per 1000 women [9•, 21]. ACOG also suggests that vulovaginal atrophy contributes to a higher rate of false-positive cytology which is supported by data from Sawaya et al. who reported that only 1 out of 110 post-menopausal women with abnormal cytology (following a previously normal screen) had dysplasia on biopsy (PPV 0.9 %)[12, 34]. The ACP does address the possibility of early discontinuation for women with life-limiting co-morbidities given an estimated 10 years for disease progression, though evidence is limited [17].

Screening following hysterectomy

All US guidelines are in agreement recommending the discontinuation of screening, regardless of age, for women undergoing hysterectomy for benign disease without a history of CIN2+ [9•, 12, 14, 16, 17]. These patients do not require adequate prior negative screening because the risk of vaginal cancer is so low (reported at 0.18 per 100,000 women) and additionally, the positive predictive value for vaginal cytology is poor [9•, 12]. In a systematic review of 19 studies of patients undergoing total hysterectomy both with and without a history of CIN, for women without CIN, 1.8 % had abnormal cytology and 0.12 % had vaginal intraepithelial neoplasia (VAIN) on biopsy and for women with a history of CIN2+, 14.1 % had abnormal cytology, 1.7 % had VAIN, and one patient had vaginal cancer [12, 35, 36]. A patient who undergoes a supra-cervical hysterectomy should continue routine screening, and diagnostic cytology should still be performed for all symptomatic patients.

Screening following HPV vaccination

All of the organizations recommend following routine screening guidelines for women vaccinated against HPV [9•, 12, 14, 16, 17]. Three vaccines are currently FDA approved which target the high-risk HPV (hrHPV) genotypes 16 and 18, including a non-avalent vaccine which includes five additional hrHPV subtypes to broaden the range of immunity [37, 38]. In a study setting HPV vaccines have been shown to be almost 100 % effective against hrHPV among previously unexposed patients; however, even almost 10 years following vaccine implementation, in practice the vaccination rates remain low [12]. In a meta-analysis of 20 studies looking at herd immunity of the HPV vaccine, in areas where vaccination rates were 50 %, vaccination decreased infection with hrHPV 16 and 18 by 68 %, reduced other hrHPV types, and reduced anogenital warts in males and in women in a different population, suggesting a cross protection and herd immunity [39]. While cross protection has been suggested, vaccination has not been proven to be protective against the 30 % of cervical cancers not caused by HPV 16 and 18 and has a decreased efficacy (reported at 44 %) in women vaccinated following HPV exposure [9•, 13, 37, 40]. Modeling studies suggest an expected reduction in CIN3 rate of 47–95 % 15–17 years after vaccination programs are operating at greater than 70 % [9•, 12, 40]. This is a

level that is still not being reached in the USA, reported at only 34.8 % in 2011, limiting alterations in screening practices in a vaccinated population.

Screening for high-risk populations

One of the limitations of the majority of the guidelines, including the ACS/ASCCP/ASCP, the AMA, the SGO, the ACP, and the USPSTF, is they were developed specifically to guide screening for the general population and do not address screening for high-risk populations defined in these studies as patients with immunosuppression, patients exposed to diethylstilbestrol (DES), or patients with prior abnormal cytology with CIN2+ [9•, 14, 17]. The guidelines that do discuss screening of high-risk patients do so limitedly, with recommendations based primarily on expert opinion [12, 13, 16]. ACOG cites the Center for Disease Control (CDC) guidelines for screening for women with HIV: initiation of screening at the time of diagnosis (regardless of age) with screening twice in the first year and subsequent yearly screening, and suggests this is a reasonable option for high-risk patients [12]. The WHO recommends screening women with HIV every 3 years if the initial test is negative [16]. Immunosuppression increases the risk of persistent HPV infection in women with HIV and thus has been shown to expedite the progression to invasive cervical carcinoma from 15.7 years in the general population to 3.2 years in women with acquired immunodeficiency syndrome (AIDS) [41]. While antiretroviral therapy has decreased rates of other AIDS-associated malignancy, the rates of cervical cancer have remained unchanged, and studies on antiretroviral therapy and cervical dysplasia have conflicting results, suggesting the importance of more rigorous screening guidelines in this population [41].

Screening recommendations for women with HIV have been extrapolated to apply to all women who are immunocompromised, but there are no evidence-based guidelines to direct this care. The standardized incidence ratio (SIR) for cervical cancer is 2–5 in women who have received a kidney transplant compared to the general population, and the rates of HPV in this population range from 22 to 63 % [41, 42]. The American Society of Transplantation recommends annual cytology and pelvic examination in this population, though these recommendations are not evidence driven [41]. The data regarding lupus remains mixed with some increases in cervical dysplasia reported, and similar increases in risk have been reported with rheumatoid arthritis [41]. In a meta-analysis looking at women with inflammatory bowel disease on immunosuppressive therapy, there was a modest increased risk of high-grade dysplasia and cervical cancer compared to the general population, OR 1.34 [43, 44]. ACOG reports that annual screening cytology beginning at age 21 is a reasonable screening strategy, and the NCCN suggests that women with immunosuppression may require more frequent screening, though an optimal interval is left to the discretion of the provider [13]. No recommendations are made on the role of HPV in this population in any of the above guidelines.

For women with prior high-grade dysplasia, after a period of increased surveillance, the guidelines suggest they may return to routine screening to continue for 20 years [9•]. The question remains if these patients and patients with a history of abnormal testing are appropriate for routine screening. In a Danish study, women testing HPV 16 positive during the first and second round

of screening had a 47.4 % risk of CIN3+ during the 12-year follow-up [45]. Other studies have supported the notion that patients with past positive tests or an unknown prior screening history had a significantly higher risk of CIN2+ in subsequent years even after treatment compared to patients who had an entirely normal screening history [45–48]. Obtaining a thorough and accurate screening history is thus a vital portion of an effective screening program to triage patient risk. The USPSTF addresses the need for research on how clinicians may tailor practices based on low- and high-risk individuals.

Emerging data

At the time of publication of the majority of the guidelines in 2012, primary screening with HPV testing was not recommended, based on the limited number of studies with long-term follow-up, limited data on actual cancer prevention, and no clear recommendations for triaging an abnormal test [9•, 12, 14, 16, 17, 26, 27•, 49]. Estimates of the number of colposcopies performed if all positive HPV tests were triaged to evaluation suggest an absolute increase in the number of colposcopies by 4 %, such that the harm would outweigh the benefit [9•].

The available evidence regarding HPV testing has consistently demonstrated an improved sensitivity as compared to cytology (95 % versus 40–70 %), a slightly lower rate of CIN3 following a negative test, but also a lower specificity (94 versus 97 %, respectively) [9•, 24, 25, 49]. This prompted an ongoing investigation into primary HPV screening, and in 2015, interim guidance from the SGO and ASCCP was published regarding the use of HPV for primary screening [19••]. The majority of data on primary HPV testing has been from large European studies; however, the publication of the ATHENA trial in 2015 lead to the consideration of primary HPV as a viable screening option in the USA [24, 27•, 50••, 51]. In the ATHENA trial, Wright and colleagues analyzed over 40,000 women over the age of 25 who received both primary HPV and cytology testing. The triaging strategy proposed in the ATHENA trial was for repeat screening in 3 years for HPV-negative patients and immediate colposcopy for HPV 16- or 18-positive patients, and for women with other hrHPV positivity, reflex cytology was recommend with colposcopy if the results were ASCUS or greater. Women with negative triage cytology would have a repeat co-test in 1 year. At baseline, 10.5 % of women were HPV positive with 6.4 % demonstrating cytology abnormalities. The 3-year cumulative incidence rate for CIN3+ with a negative test was lowest with co-testing at 0.3 versus 0.38 % with primary HPV versus 0.8 % with cytology. HPV also improved detection of cancers, as well as adenocarcinoma in situ, compared to cytology alone [50••]. While HPV was more prevalent in women 25–29, they also found an increased sensitivity for detection of CIN3+ over cytology in this age group. Both the hybrid co-testing strategy and primary HPV were associated with absolute increased number of colposcopies; however, there were a similar number of colposcopies per case of CIN 3+ detected at 12.8 versus 10.8 for cytology [50••].

Based on the above evidence, the SGO/ASSCP along with 13 expert representatives suggest that primary HPV may be an appropriate screening alternative in women aged 25–65 if managed according to the algorithms in the

ATHENA trial [19••]. Recommendations for initiation of screening with primary HPV at a younger age are based on the relatively higher rate of cases of CIN3+ found in this population with more than half of these women having normal cytology [50••]. While the data on primary HPV testing appears promising in detecting and reducing CIN3+, no cost-effective data currently exists and the incorporation of HPV clinically, including the number of visits and rates of colposcopies, is not fully understood as the ATHENA algorithm may not be feasible in some practice settings [52]. Additionally, the data remains preliminary including only 3 years of follow-up, such that more research is needed on long-term outcomes and translation into clinical practice.

Although the guidelines are evidence based and generally in agreement regarding screening average risk women, questions remain. Women with prior abnormal results and those who are immunocompromised are probably at higher risk and may need adjustments to the screening frequency and duration. There also still remains variable provider update with the additional problem of reaching an unscreened population. In a shifting environment, there are many tools to maximize benefit and minimize the harm screening, though ongoing challenges warrant further investigation to optimize prevention of cervical cancer.

Compliance with Ethical Standards

Conflict of Interest

The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
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•• Of major importance

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