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Commentary

Precision Prevention: The 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors

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Abstract: The approach to cervical cancer prevention has evolved significantly over the past two decades. HPV immunization has decreased the specificity of screening modalities and HPV-based testing has been replacing our previously successful morphology-only approach. Additionally, there is much more emphasis on providing precision prevention, rather than the previously used "one-fits-all" management strategies. A number of new biomarkers are entering clinical practice and being integrated into cervical cancer screening and management in order to enable a more personalized assessment of the risk for precancer/cancer for an individual patient. The 2019 ASCCP Risk-Based Management Consensus Guidelines expand on the concept of "equal management for equal risk". They consider a patient's history in addition to current test results to provide recommendations for increased surveillance/treatment in patients at higher risk for CIN3+ while minimizing interventions for lower-risk patients who have new versus persistent HPV infection. Clinical management decisions are based on immediate risk and 5-year risk estimates for CIN3+, which are determined by referencing an extensive risk table compiled by the National Cancer Institute (NCI). The course of action for a given patient is recommended by comparison of the risk in the risk database, to the predetermined clinical action thresholds. These guidelines address the need for simplification and offer some stability for the provider while being conducive to the incorporation of anticipated continued technologic advances in methods for cervical cancer prevention. Their enduring nature will allow for changes needed based on risk reduction as HPV vaccination uptake increases and vaccinated women reach screening age. Similarly, the design allows for the addition of new tests into the risk assessment calculations after their approval by applicable regulatory agencies and review/consensus approval by the ASCCP new technology and enduring guidelines workgroups. As cytopathologists, we must be familiar with the scientific advancements in primary and secondary prevention, evolving screening and management guidelines, and participate actively in the multidisciplinary approach for the prevention of cervical cancer.

Keywords: cervical cancer; prevention; risk assessment; management guidelines; ASCCP; HPV; cervical cytology; HPV testing; molecular pathology; paradigm shift

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1. Background

The concept of "precision prevention," which emphasizes the biological basis of prevention efforts, what to target, and how to prevent in a safe and cost-effective manner is very relevant in the current landscape of health care delivery [1]. Accordingly, over the past two decades, there has been a significant paradigm shift in cervical cancer prevention. We now have both the scientific knowledge as well as the tools for the elimination of this disease, one that unfortunately is still a significant worldwide burden for women. The natural history of the causative agent for almost all cervical cancer, the human papillomavirus (HPV), has been well researched and understood and it is universal, irrespective of resource setting. However, primary and secondary prevention strategies do depend on the local infrastructure and resources. HPV infects the anogenital tract mostly as a self-limiting

infection and less commonly infection by persistent, high-risk genotypes progresses to a transforming infection (precancer). The knowledge of the biology of HPV carcinogenesis was leveraged for the development of HPV vaccines as well as the development of HPV tests to aid in screening, and triage/management of abnormal test results to prevent the development of invasive cervical cancer by detecting/treating precancerous lesions.

2. Impact of HPV Vaccination on Secondary Prevention of Cervical Cancer

Primary prevention by HPV vaccination has been available since 2006 and the current second generation of prophylactic vaccines can prevent up to 87% of cervical cancer [2]. Furthermore, it has been determined that currently two doses, and in the future, perhaps even one dose (personal communication), in individuals between 9 and 15 years, will provide sufficient immunity [3]. HPV vaccine uptake varies significantly across the world due to several factors, including vaccine availability, cost, methods of administration (school based or not), health care provider recommendation, parental and patient attitudes/consent, and antivaccine campaigns. In spite of this, even in regions where cancer prevention is opportunistic and uptake limited, vaccination has significantly decreased the prevalence of HPV types contained in the vaccines as well as the prevalence of precancers [4]. The positive predictive value of current screening tests, both cytology and HPV will continue to decrease in vaccinated cohorts [5]. It has been suggested that HPV screening tests in the postvaccination era might perform better if restricted to the HPV types 16, 18, 45, 31, 33, and 52 since screening for all 14 high-risk types may result in a suboptimal balance of harms and benefits [6].

3. HPV Testing: Platforms and Incorporation into Screening and Management Guidelines

The value of HPV-based testing for screening, triage, and follow-up is based on some key attributes, including (1) increased sensitivity, compared to cytology, which has been shown in many studies around the world. It is, however, acknowledged as being less specific than cytology. HPV testing is also more reproducible and can overcome to a large extent, the interobserver and interlaboratory variability and ambiguity associated with atypical cytologic interpretations [7]; (2) the high negative predictive value of a negative HPV test allows for safe lengthening of screening intervals; (3) the ability to further stratify the risk associated with a positive test, by performing genotyping allows identification of the highest risk types. Partial genotyping for HPV 16/18 was FDA approved in the US in 2006; it was not until 2020 that extended genotyping was approved [8]. Research and data from clinical trials have shown genotype-related risk bands, which can be very useful for both triage of abnormal screen results as well as post colposcopic/post-treatment follow-up. In the Onclarity trial, in patients with NILM cytology, HPV 16 and 31 carried the highest risk for CIN2/3. Among the other 12 genotypes, HPV 18, 33/58, and 52 comprised an intermediate risk band and genotypes 45, 51, 35/39/68, and 56/59/66 constituted the lowest risk bands for CIN2/3. [9] It has been emphasized that genotype distribution differs between precancer (CIN2/3) and invasive cervical cancer (ICC). HPV 16/18/45 have a high risk of ICC and 18/45 related ICC is more often adenocarcinoma and tends to occur in younger women [10]. In vaccinated cohorts, extended genotyping is expected to assume more importance, as genotypes targeted by vaccines will become less common.

The goal of secondary cervical cancer prevention (screening and management) is the detection of high-risk HPV infections that may progress to precancer or cancer; therefore, only testing platforms that detect high-risk (oncogenic) HPV types should be used. Low-risk HPV types are rarely if ever linked to cervical cancer or high-grade precursor lesions. HPV testing entered the gamut of options for cervical cancer screening and management in the United States in the mid-1990s and was slowly but surely included in options for screening, triage, and surveillance. Currently, there are five HPV tests approved by the US Food and Drug Administration (FDA): Qiagen Hybrid Capture (Gaithersburg, MD, USA), Hologic Cervista and Hologic Aptima (Marlborough, MA, USA), Roche Cobas (Indianapolis, IN, USA), and Becton Dickinson Onclarity (Franklin Lakes, NJ, USA). Four

of these tests utilize DNA hybridization and amplification; only Aptima is based on RNA amplification, making it slightly more specific for the detection of high-grade lesions [11]. Aside from Hybrid Capture, others have an internal control; although it is not specific for the detection of epithelial cells. As of 2021, only the Roche Cobas and BD Onclarity platforms are approved for primary HPV screening in the US. Arbyn et al. have published a systematic review of HPV tests available in 2020 that were suitable for primary screening using Meijer criteria [12].

As of 2021, cytology, cotesting, and primary HPV testing are all options for cervical cancer screening in the US. In July 2020, the American Cancer Society (ACS) issued new screening guidelines that recommend the use of primary HPV as the preferred testing option, beginning at age 25 years, and also emphasized that future guidelines will not include cytology-based screening [13]. Since 2014, when primary screening was approved in the US, the Cytopathology Education and Technology Consortium (CETC) has shared concerns regarding the implementation of primary HPV screening as the preferred or only screening strategy in the current US opportunistic screening program [14–16]. The American College of Gynecologists and Obstetricians (ACOG) 2021 screening guidelines, which followed the ACS update, retain all three testing options and do not have a preferred screening strategy at this time [17]. As of 2021, the ACS has ongoing efforts to determine what infrastructural changes may be needed for a successful transition to primary screening in the US.

4. United States Management Guidelines for Abnormal Screen Results

Following the 2001 Bethesda cervical cytology reporting workshop, the ASCCP aligned management guidelines with Bethesda terminology; these guidelines subsequently underwent updates in 2006 and 2012. With the shift to HPV-based screening and cotesting being the preferred US *Screen.* option until 2020, several possible combinations of cytology and HPV test results were possible. This made management options very complex, in spite of the 2012 ASCCP guidelines having facilitated implementation and use of the guidelines with decision aides, including algorithms and an App. Therefore, in 2017, the ASCCP in collaboration with the National Cancer Institute (NCI) experts in this area, undertook a consensus effort to update the US management guidelines. A total of 19 stakeholder organizations participated, with significant involvement of pathology and cytopathologists [18].

The goal of the 2019 ASCCP guidelines effort was to personalize and maximize the prevention of cervical cancer while minimizing the harms from overtesting and overtreating by managing patients according to their current and future risk of CIN3+ [18]. The updated Risk-Based ASCCP Management Consensus Guidelines were published in April 2020 along with several supporting articles [18–21]. They are based on an individual patients' risk of CIN3+. The guidelines recommend that testing should be HPV based; either primary HPV testing alone or HPV testing in conjunction with cervical cytology (cotesting). HPV testing forms the basis for risk estimation [18]. Unlike in prior guidelines, management is based on the combination of current results and past history. Unknown history is accounted for as a risk factor; at this time, HPV vaccination status has not been included but will be evaluated as further risk data on patients who received on-time vaccines accumulates.

In the general asymptomatic, screened population, the risk of cervical cancer and CIN3 is low. Results of screening tests such as cytology or HPV can help to differentiate between higher-risk (test positive) and lower-risk (test negative) patients. When we examine all our management options, at each stage of them, we can employ triage tests, the results of which are only useful if they can move a patient from one risk strata to another that needs a different management strategy. For example, HPV testing in ASCUS changes management; on the other hand, HPV testing is not worth performing for HSIL because irrespective of the result, colposcopy is indicated. The 2019 ASCCP guidelines aim to decrease complexity for the provider by having an easier interface. This is achieved by using a so-called black box, which is essentially a complex risk matrix in which tables of risk estimates from all

meaningful combinations of current screening test results and screening history (including unknown history) have been generated using data from high-quality observation studies, clinical trials, and long-term observational screening and management data using cytology and HPV testing [18–20].

Management recommendations use thresholds of risk and decisions are based on immediate risk and 5-year risk estimates. The lower threshold of each risk stratum, called the clinical action threshold (CAT), defines the level at which the treatment recommendation changes. The CATs were determined through the consensus process and link each risk level to corresponding management recommendations of *surveillance, colposcopy, or treatment*. The CAT for referral to colposcopy was determined to be 4% (approximates the risk for a patient after an HPV-positive ASC-US or LSIL screening result in the general population, for whom colposcopy was recommended in the 2012 guidelines.) The first step for the follow-up recommendation is based on the immediate risk of CIN3+. If it is above 4%, the next step is based on a specific risk threshold to determine if colposcopy/biopsy or expedited treatment is preferred. In these guidelines, expedited treatment has been emphasized for the highest risk women (>60% immediate risk of CIN3+).

If the immediate risk of CIN3+ is below 4%, then the type of follow-up/surveillance (which includes 1-year, 3-year, and 5-year retesting intervals) is based on 5-year risk estimates of CIN3+. A 5-year return approximates the risk for a patient after a negative screening test using HPV testing or cotesting in the general population, for whom retesting in 5 years is recommended by national screening guidelines. A 3-year return approximates the risk for a patient after a negative cervical cytology screen in the general population, for whom retesting in 3 years is recommended by national screening guidelines. A 1-year return is recommended for patients with risks above the 3-year threshold but below the CAT for colposcopy [18].

In the ASCCP risk-based guidelines, the CAT remains constant; therefore, new data can be added to the risk calculations, making these guidelines enduring. Thus, new tests in development or recently approved can be assessed by the guidelines new technology workgroup and incorporated into the guidelines if approved by a consensus vote by the enduring guidelines workgroup. Examples of new tests approved by the US FDA after the publication of the 2019 ASCCP guidelines include dual stain and extended genotyping [9,22]. This enduring design makes management decision-making seamless for the provider and avoids confusion caused by frequently changing guidelines.

In prior results-based guidelines, patients with atypical squamous cells of undetermined significance (ASC-US) cytology and positive HPV and those with a low-grade squamous intraepithelial lesion (LSIL) cytology were managed similarly, by referral to colposcopy. In the 2019 ASCCP risk-based guidelines, management recommendations for the same test results may vary in different patients, since their prior history and HPV status will determine their individual risk threshold [18]. As an example, a patient with a current cotesting result of ASC-US/HPV positive and either unknown prior history or prior negative cytology/HPV+ will have a 4.5% or 5.4% immediate risk of CIN3+ respectively, both of which exceed the 4% colposcopy threshold. If a patient with the same test result, ASC-US/HPV+, had a previous negative cotest or HPV primary screen, the immediate risk of CIN3+ will drop to 2%, resulting in follow-up with HPV-based testing in 1 year instead of colposcopy [18–20].

As of 2021, HPV genotyping and p16/Ki-67 dual-stained cytology are available methods that can provide specificity to complement the analytical sensitivity of HPV testing, so as to focus management resources to follow up only women with the highest risk of underlying CIN3+. Routine use of partial and extended HPV genotyping is still variable in the United States due to the use of different testing platforms; however, when available, this information further stratifies CIN3+ risk when using the ASCCP risk-based guidelines [18,21]. Data analysis performed for the guidelines highlighted that HPV 16 positivity is very high risk and hence should be managed more aggressively. HPV 18, on the other hand, carries a disproportionately higher risk of association with invasive cancer [21].

The 2019 ASCCP guidelines recommend that all positive primary HPV screening tests, irrespective of genotype, should have additional reflex triage, since the findings may inform the management decision. For example, in a patient with HPV 16+, a cytology result of HSIL would reach the CAT for expedited treatment (>60% immediate risk of CIN3+), bypassing the need for colposcopic biopsy confirmation of HSIL. Currently, triage of HPV+ results in most US laboratories is by reflex cytology; however, the dual stain and extended genotyping were FDA approved in 2020 and will undergo evaluation by the enduring guidelines workgroup. The 2019 ASCCP guidelines also emphasize that even if reflex cytology is negative in HPV 16 and 18 positive cases, referral to colposcopy with biopsy is recommended to exclude a high-grade lesion/occult invasive cancer. As with the US screening guidelines, it is underscored that only FDA-approved high-risk HPV tests should be used for follow-up, and in a manner consistent with their regulatory approval in the United States. Cytology follow-up is not a preferred option due to lower sensitivity and lower negative predictive value, compared to HPV testing; it is, therefore, less reliable for long-term risk prediction. If cytology is used alone, shorter follow-up intervals are suggested.

Stakeholder feedback was incorporated into the development of the 2019 ASCCP Guidelines [23]. The ASCCP has developed a number of tools for clinical providers to facilitate the understanding and implementation of these risk-based guidelines. They include an updated App and a freely accessible web-based decision aid, and the main guidelines paper/accompanying articles are freely available [24]. In the US, there is high uptake of ASCCP guidelines by clinical providers, and the ASCCP App is rated very highly among medical Apps. Implications of the 2019 ASCCP management guidelines for laboratories and pathologists have been summarized in a publication by the pathologists involved in their development [25].

Cervical cancer can occur due to failure at multiple points in the prevention process. With the aim of decreasing some of these, there are ongoing efforts to assess the use of molecular-based methods for self-sampling for women who do not come in for screening, and "test and treat" using point-of-care HPV tests (versus "see and treat") to prevent loss to follow-up [26]. A world without cervical cancer is now within reach [27]. In 2020, the WHO adopted the global strategy for elimination of cervical cancer, defined as an incidence of <4 cases/100,000, and has suggested targets of 90%–70%–90% for vaccination, screening, and treatment that every country should reach by 2030 to proceed toward the goal of elimination by the next century (2120) [28]. While there have been significant advances in the primary and secondary prevention of cervical cancer, decisions on which screening and management approach to use in a particular country or health care facility should be based on specific local considerations, and any screening is better than no screening. Emphasis on primary prevention by HPV vaccination is key to the elimination of cervical cancer. Even though the nonavalent HPV vaccine is highly effective, at this time, vaccinated women should continue to be screened [29,30].

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