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An Introduction to the 2019 ASCCP Risk-Based Management Consensus Guidelines

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The 2019 revision of the ASCCP Risk-Based Management Consensus Guidelines expands upon the "risk-based" approach introduced in 2012. It addresses the need for simplicity and stability in clinical guidelines while anticipating continued technologic advances in cervical screening methods. This introduction explains why the 2019 revision was needed, describes the general approach of the new guidelines, and outlines briefly how the new approach will work in practice.

WHY THE 2019 REVISION WAS NEEDED

The revision was motivated by the complexity of the 2012 guidelines and the queue of soon-to-be available new tests. It gradually became clear that there were too many acceptable choices in use, or in final development, to continue as before. In a departure from previous versions, the 2019 guidelines therefore do not present separate algorithm figures for most screening and triage combinations. For example, there are no algorithm figures entitled "Triage of ASC-US" or "Follow-up of HPV-Positive Results." Dozens of algorithm diagrams would have been required to cover the many test combinations now in use or proposed to be introduced soon (such as extended genotyping or dual-stain cytology), along with the influence of past screening history on the meaning of current abnormal test results.

The National Cancer Institute (NCI) and ASCCP agreed formally in 2017 through a Memorandum of Understanding to embark on a new set of guidelines.[1] Three times before, in 2001,[2,3] 2006,[4,5] and 2012,[6] the NCI and ASCCP had collaborated in a formal consensus guidelines process and also helped produce several other related guidances.

The role of NCI epidemiologists and statisticians who specialize in cervical screening has been to provide state-of-the-art epidemiologic evidence regarding test performance based on NCI and other research. The role of ASCCP has been to convene and conduct a consensus process bringing together US clinical organizations and other important "stakeholders" to create the guidelines. The objective of the new agreement was to produce clear and simple consensus recommendations based on risk, to achieve a "long shelf-life" for this version of the 2019 guidelines before another guidelines conference is needed, despite the abundance of competing tests and strategies.

THE GENERAL APPROACH TAKEN TO CREATE THE NEW GUIDELINES

The ASCCP and NCI cooperatively planned and supported the consensus process, with administrative support provided by the ASCCP. The convening of the consensus group is described in the main guidelines article. Once convened, the major task of the participating representatives was to decide on durable clinical action thresholds, striving to represent US consensus as to what clinical actions are recommended for increasing severity of cervical screening abnormalities. The following axiomatic principles were followed: the main purpose of cervical screening in the United States is to find precancerous lesions ("precancer") that can be treated easily to prevent invasive cervical cancer. Putting aside temporarily whether precancer is best defined as cervical intraepithelial neoplasia (CIN) 2/CIN 3/AIS, or CIN 3/adenocarcinoma in situ (AIS), or histologic high-grade squamous intraepithelial lesion/AIS, there are a limited number of clinical actions available to clinicians and patients when faced with a cervical screening abnormality. Logically, a patient known to be at very high risk of having precancer has the greatest need of preventive treatment; at the highest risk, expedited treatment might be preferred without need for colposcopic biopsy. At somewhat lower but still high risk, colposcopic biopsies are recommended to find or rule out precancer requiring treatment. At lower but nonnegligible risk, colposcopy is not needed, but surveillance at shortened intervals is prudent (1 and 3 years were maintained as the 2 levels of concern/attention) to reduce the risk of "interval cancers" occurring before the next testing visit. Women at very low risk provided by a negative human papillomavirus (HPV) test (or HPV and cytology cotest) are recommended to continue screening at the 5-year interval.

Deciding on the clinical action thresholds for each management option (treatment preferred, treatment or colposcopic biopsy, colposcopic biopsy, surveillance retesting at 1 year, surveillance retesting at 3 years, return at regular screening interval of 5 years) required an 18-month collective effort involving the volunteering cervical health professionals and patient advocates and including a period for public input. These societal decisions were acknowledged to be part of the larger subjective question of "How safe is safe enough? What risk levels in our society warrant escalating to the next, more aggressive clinical actions?"

The clinical action thresholds adopted by consensus voting in October 2019 after substantial study and discussion are intended to endure, providing stability to the US cervical screening effort, even as screening test methods and strategies evolve. When a new test is approved by the Food and Drug Administration that test can be considered for inclusion in the consensus guidelines as soon as sufficient data are available to know what risk of precancer is predicted by a positive result versus a negative result. Adequate prospective data will be necessary before a test can be

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recommended as the basis for surveillance at 1- or 3-year intervals or return to routine screening at 5-year intervals. Cross-sectional data will be needed to supply the immediate risk estimates that support recommendations for treatment or referral to colposcopy. To give an example, the new consensus is that the clinical action threshold for referral to colposcopy and biopsies (and possibly treatment) is a 4.0% immediate risk of CIN 3+. Patients with an underlying immediate risk of CIN 3+ of 4.0% or more are recommended to have colposcopy whether that risk is due to HPV-positive ASC-US, HPV-positive low-grade squamous intraepithelial lesion or greater, HPV 16–positive NILM, a posttreatment positive HPV test, or any other set of results predicting equally high risk. If a positive result from a new triage test for HPV-positive patients is convincingly shown to convey a CIN 3+ risk greater than or equal to 4.0% upon immediate referral to colposcopy, there would be no need for a new consensus conference to determine how to use that test in clinical practice: the management of a positive result would be to refer to colposcopy (with optional or even preferred, expedited treatment if risk is sufficiently high). By the guiding principle of "Equal Management of Equal Risk," the guideline would be evident and easily settled.

At the same time that the clinical action thresholds were being considered, the large remaining task was to estimate the risks themselves, for the cervical screening test combinations that a clinician and patient might encounter together at a management visit after abnormal screening. In the development of the new guidelines, it was the responsibility of NCI HPV epidemiologists and statisticians to estimate the risks of precancer predicted by the large number of combinations of HPV tests and cytology, and past screening test and colposcopic biopsy results, and other possibly important factors. The main source of the risk estimates was the unique clinical database from Kaiser Permanente Northern California (KPNC), which instituted HPV/cytology cervical cotesting at 3-year intervals in their very large membership in 2003. The KPNC has uniquely detailed data and follow-up, permitting us to observe the risk of CIN 2, CIN 3, AIS, and cancer after even unusual combinations of screening test results.

The generalizability ("portability") of the estimates from the KPNC to other US populations at known higher risk of cervical cancer than KPNC was addressed by research in 4 diverse screening programs and trials. A systematic review covering items too uncommon or otherwise not addressed adequately by risk estimation was also performed.[7,8]

Of note, CIN 3+ (including CIN 3 and AIS) was chosen as the working definition of precancer. Rare cancers found within a screening program were included as screening targets, recognizing however that detection of precancers is the dominant goal of screening in the United States. Cervical intraepithelial neoplasia 2 was considered too variable to serve as a surrogate end point of cancer risk. The Lower Anogenital Squamous Terminology category of histologic high-grade squamous intraepithelial lesion could not be highlighted because of lack of prospective studies using that terminology.

Clinical action thresholds were based on estimated risk of CIN 3+ at the time of the abnormal screening results ("immediate" risk) for treatment and referral to colposcopic biopsies. For surveillance thresholds, risks at 5 years were emphasized.

HOW THE NEW APPROACH WILL WORK IN PRACTICE

Clinicians are likely to consult guidelines in 5 different clinical situations: consideration of a new abnormal screening result; management of a follow-up test result at a 1- or 3-year surveillance return visit; interpretation of colposcopic biopsy diagnosis; follow-up of postcolposcopy surveillance of patients not initially found to need treatment (e.g., a biopsy <CIN 2); and posttreatment follow-up. An individual patient under management would likely attend more than one of these visits.

It is important to realize that most clinical visits devoted to management of abnormal cervical cancer screening results will involve common and ultimately benign HPV infections and minor cytologic abnormalities. For example, roughly 20% of individuals participating in cotesting for 7 years at KPNC had at least 1 abnormal result (HPV and/or cytology). The 2019 guidelines address as many abnormal result combinations as possible, using 2 different approaches. The common initial visits that are mainly minor abnormalities are handled in the 2019 guidelines by use of risk tables and clinical action thresholds.[9] At the KPNC, colposcopy referrals leading to postcolposcopy management decisions are about half as frequent as initial management visits; these are addressed by both risk tables[9] and, for uncommon or especially high-risk situations, management algorithm figures.[10] Treatment and posttreatment visits are uncommon (approximately 1/10th as frequent as initial management visits in the KPNC data set), but are especially important to preventing cancer, and are addressed using a series of management algorithm figures.[10]

At each management visit after an abnormal screening result, the current test results under consideration, including both screening and triage tests, colposcopic biopsy results, recent past screening history, etc depending on the decision point will be used to find the estimated risk of CIN 3+. Current HPV test results, as the most important prediction factor, is necessary for "precision management." However, some other missing data are expected for the risk estimations and were accommodated in the risk tables. Increased precision of management guidance will be possible if information is complete, but risk estimates and resultant management recommendations can be based on whatever test results in addition to HPV result are available.

The predicted risk of CIN 3+ is determined by referencing an extensive risk table compiled by the NCI and accessible on an NIH Web site. A comparison of the risk, found for the given patient in the risk database, to the Clinical Action Thresholds will yield the recommended course of action. Navigation of the guidelines can be facilitated by applications on platforms such as smartphones or websites, or eventually integrated into lab reports or the electronic medical record. Of note, risk is not calculated at the time of use; the precalculated risk for the combination of current test results, past screening history, and other factors is found in the tables either manually or by a software application. Health decision aids are increasingly familiar in US medical practice. Well-known examples include the FRAX fracture risk assessment tool as well as the Breast Cancer Risk Assessment Tool of Gail et al.[11,12]

The risk database will be kept current, to permit updates of the guidelines as new methods and prospective follow-up data emerge. The risks predicted by the new tests can be added to the database, and clinicians can access updates without waiting for a new guidelines meeting. Under the principle of "Equal Management of Equal Risk," management recommendations are made regardless of which test results and screening history led to that risk level.

CONCLUDING DESCRIPTION OF THE GUIDELINES ARTICLES

This introduction is followed by a statistical method paper,[13] which describes how NCI statisticians developed new methods and applied them to analyze available data to produce the risk table. The main guideline paper[10] had input from many sources; the risk-based approach proved adequate for most visits, but some special populations and topics are best handled at this time by using management algorithms of the conventional kind, guided by expert opinion. The risk table manuscript,[9] mainly derived from

KPNC, gives the risk estimation data permitting management of most patients. Use of genotyping is addressed separately.[14] A literature review led by the new technologies working group[8] is followed by an article addressing how quality assessment was used in the literature review.[7] Finally, there is a description[15] of the broader US public input received in the formulation of the guidelines.

We conclude this introduction with the express hope that the revised guidelines improve and simplify the management of cervical cancer screening abnormalities in the United States. We welcome suggestions from any reader as to how further improvements could be made.

REFERENCES

1. Schiffman M, Wentzensen N, Khan MJ, et al. Preparing for the next round of ASCCP-sponsored cervical screening and management guidelines. *J Low Genit Tract Dis* 2017;21:87–90.
2. Wright TC Jr., Cox JT, Massad LS, et al, 2001 ASCCP-sponsored Consensus Conference. 2001 Consensus Guidelines for the Management of Women with Cervical Cytological Abnormalities. *J Low Genit Tract Dis* 2002;6:127–43.
3. Wright TC Jr., Cox JT, Massad LS, et al. 2001 consensus guidelines for the management of women with cervical intraepithelial neoplasia. *Am J Obstet Gynecol* 2003;189:295–304.
4. Wright TC Jr., Massad LS, Dunton CJ, et al. 2006 consensus guidelines for the management of women with abnormal cervical screening tests. *J Low Genit Tract Dis* 2007;11:201–22.
5. Wright TC Jr., Massad LS, Dunton CJ, et al, 2006 American Society for Colposcopy and Cervical Pathology-sponsored Consensus Conference. 2006 consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarcinoma in situ. *J Low Genit Tract Dis* 2007;11:223–39.
6. Massad LS, Einstein MH, Huh WK, et al, 2012 ASCCP Consensus Guidelines Conference. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. *J Low Genit Tract Dis* 2013;17(5 suppl 1):S1–27.
7. Clarke M, Unger ER, Zuna R, et al. A systematic review of tests for post-colposcopy and post-treatment surveillance. *J Low Genit Tract Dis* 2020;24:148–56.
8. Clarke M, Darragh TM, Nelson E, et al. Reporting and assessing the quality of diagnostic accuracy studies for cervical cancer screening and management. *J Low Genit Tract Dis* 2020;24:157–66.
9. Egemen D, Cheung LC, Chen X, et al. Risk estimates supporting the 2019 ASCCP Risk-Based Management Consensus Guidelines. *J Low Genit Tract Dis* 2020;24:132–43.
10. Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP Risk-Based Management Consensus Guidelines for abnormal cervical cancer screening tests and cancer precursors. *J Low Genit Tract Dis* 2020;24:102–31.
11. Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst* 1989;81:1879–86.
12. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. *World Health Organ Tech Rep Ser* 1994;843:1–129.
13. Cheung LC, Egemen D, Chen X, et al. 2019 ASCCP risk-based management consensus guidelines: methods for risk estimation, recommended management, & validation. *J Low Genit Tract Dis* 2020;24:90–101.
14. Demarco M, Egemen D, Raine-Bennett TR, et al. A study of partial human papillomavirus genotyping in support of the 2019 ASCCP Risk-Based Management Consensus Guidelines. *J Low Genit Tract Dis* 2020;24:144–7.
15. Perkins RB, Fuzzell LN, Lake P, et al. Incorporating stakeholder feedback in guidelines development for the management of abnormal cervical cancer screening tests. *J Low Genit Tract Dis* 2020;24:167–77.