



COLLEGE of AMERICAN PATHOLOGISTS

October 9, 2017

David C. Grossman, M.D., M.P.H.
Chairperson
U.S. Preventive Services Task Force
5600 Fishers Lane
Mail Stop 06E53A
Rockville, MD 20857

Re: USPSTF Draft Recommendation Statements for Cervical Cancer Screening

Dear Dr. Grossman:

The College of American Pathologists appreciates the opportunity to comment on the U.S. Preventive Services Task Force (USPSTF) draft recommendation statements for cervical cancer screening. As the world's largest organization of board-certified pathologists and leading provider of laboratory accreditation and proficiency testing programs, the CAP serves patients, pathologists, and the public by fostering and advocating excellence in the practice of pathology and laboratory medicine worldwide. Pathologists are physicians whose diagnoses drive care decisions made by patients, primary care physicians, and surgeons. When other physicians need more information about a patient's disease, they often turn to pathologists who provide specific diagnoses for each patient. The pathologist's diagnosis and value is recognized throughout the care continuum and many patient encounters.

Participation in regular screening has a far greater effect on cervical cancer morbidity and mortality than which of the two recommended screening methods is chosen. Implementation should therefore focus on ensuring that women receive adequate screening, regardless of which method is used. Therefore the CAP applauds continued efforts by the USPSTF to improve cervical cancer screening practices. Given the health benefit, we believe the USPSTF should retain the co-testing and cytology screening options for screening in women ages 30 to 65 years. We also agree with your statement in the draft report that, *clinicians and individuals use the annual Papanicolaou (Pap) smear screening visit as an opportunity to discuss other health problems and preventive measures.*

USPSTF Recommendations

The recommendation to permit cervical cytology screening alone every 3 years for women ages 21-65 is acceptable and consistent with current practices and guidelines of other major societies.^{1,2} However, the USPSTF draft guidelines have removed the option for cytology and HPV co-testing, and this is different than the current guidelines of the American Cancer Society, ACOG and other professional organizations which have tremendous experience with cancer screening methods.^{1,2} These organizations state



that co-testing is the preferred screening method. Most laboratories in the U.S. are receiving cytology and HPV co-testing orders for the majority of their patient population 30 years and older. A recommendation omitting cytology and HPV co-testing is against current standard practice and preferences for both physicians and patients in this country and is based mainly on international studies which may not apply to U.S. screening practices.³ We respectfully disagree with the USPSTF statement that “Both clinical trial evidence and modeling suggest that cotesting increases the number of followup tests by as much as twofold and does not lead to increased detection of CIN3+ (CIN3 and all invasive cancers) or cervical cancer compared with screening with hrHPV testing alone” and the data used to support it.

The USPSTF guidelines include an option for primary HPV testing every 5 years. The only HPV testing method approved by the FDA for a primary screening indication is the Roche cobas method.⁴ The ATHENA clinical trial on which this approval was based had only three years of follow-up data. The interim clinical guidance document from the ASCCP and SGO published shortly after FDA approval of Roche cobas⁴ recommended that HPV primary screening be done no less frequently than every 3 years. A longer interval of 5 years was not recommended because of insufficient prospective and long-term follow-up data and insufficient data comparing co-testing to HPV primary screening in U.S. populations. These studies were from national programs with follow-up and different from US population. Finally, that ASCCP/SGO guidance document specifically states that co-testing and cytology screening remain options for screening and does not recommend a preference for primary HPV screening.

The USPSTF draft guideline cites many international studies as a basis for the recommendation to move to HPV primary screening every 5 years. While HPV primary screening has been initiated in certain parts of the world, these countries generally have organized screening programs. Screening in the U.S. is opportunistic and many women do not receive sufficient screening. Studies from the CDC⁵ show that only 83% of women reported being current with cervical cancer screening, which is considerably below the Healthy People 2020 target of 93%. Less educated women are at higher risk of not being screened as well as several minority groups including Hispanic women, American Indians, and Alaskan natives. When these women can be screened, offering a highly sensitive co-testing screening strategy has many advantages and no additional patient harms. When standard co-testing management guidelines (as recommended by ASCCP and ACOG) are followed in women age 30 and older, there is no evidence that colposcopy procedures will increase in women ages 30 and older who receive co-testing instead of primary screening.⁶ Furthermore, many women reject arguments made by organizations that resources and money saved by deleting cytology screening are better spent elsewhere; women in general are not interested in assuming more cancer risk. Many women and their doctors prefer 3-year testing strategies over 5-year intervals.³ A



3-year co-testing interval has been shown to be optimal as evidenced by several large studies conducted in the United States.^{7, 8}

While it is most advantageous to detect precancers to prevent invasive cancer, some women in the U.S. will not present for evaluation until they have an invasive cancer, and many of these are women with insufficient prior screening. Several studies performed in the U.S. have found that up to 18.6% of invasive cancers will test negative for HPV by commercial tests.⁹⁻¹¹ Studies performed in U.S. population's show that the addition of cytology screening will add screening sensitivity in many of these women.¹²

The USPSTF guidelines are silent as to the HPV testing method and even state that a variety of platforms can be used for HPV testing. Pathologists and laboratory professionals recommend that only methods approved by the FDA or validated for a primary screening indication be used. Laboratory quality control and ongoing proficiency testing evaluation are extremely important. Several HPV testing modalities do not provide an internal specimen adequacy control to ensure that cervical epithelial cells have been sampled. There is very little data regarding interfering substances. When co-testing is utilized, the laboratory is able to provide a visual evaluation of specimen adequacy and ensure that sufficient squamous cells are present.

RECOMMENDATIONS

In summary, the CAP recommends that cytology and HPV co-testing be included as a screening strategy for women ages 30-65; we also recommend that primary HPV screening use only a test platform validated for that purpose and that any HPV primary screening method be applied every three years until there is more longitudinal data applicable to U.S. screening populations.

The remaining recommendations for women younger than age 21, older than age 65, and women who have had a hysterectomy are worded appropriately and are consistent with consensus guidelines published by other major organizations.

The CAP greatly appreciates the opportunity to advance medical advancements through innovative research methods; however, we support a process that improves cervical screening, especially in US populations that are in most need. Please contact Helena Duncan, CAP Assistant Director, Economic and Regulatory Affairs at hduncan@cap.org if you have any questions on these comments.

Sincerely,

Richard C. Friedberg, MD, PhD, FCAP
President



REFERENCES

1. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology Screening Guidelines for the Prevention and Early Detection of Cervical Cancer. *CA Cancer J Clin* 2012.
2. American College of Obstetricians and Gynecologists Practice Bulletin Number 157. Cervical Cancer Screening and Prevention. *Obstet Gynecol* 2016 (Jan)
3. Kinney WK, Hug WK. Protection against cervical cancer versus decreasing harms from screening—What would U.S. patients and clinicians prefer, and do their preferences matter? *Preventive Medicine* 2017;98:31-32.
4. Huh WK, Ault K, Chelmow D, Davey DD, et al. Use of primary high risk papillomavirus testing for cervical cancer screening: interim clinical guidance. *Gynecol Oncol* 2015; 136:178-182 (Feb) (PMID 25579107).
5. White A, Thompson TD, White MC, et al. Cancer screening test use—United States, 2015. Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report. 2017; 66 (No. 8, March 3): 201.
6. Wright TC, Stoler MH, Behrens CM, Sharma A, Zhang G, Wright TL. Primary cervical cancer screening with human papillomavirus: end of study results from the ATHENA study using HPV as the first-line screening test. *Gynecol Oncol*. 2015;136:189-197.
7. Kinney, W, Wright TC, Dinkelspeil HE, DeFrancesco M, Thomas Cox J, Huh W. Increased cervical cancer risk associated with screening at longer intervals. *Obstet Gynecol*.2015;125:311-315.
8. Kulasingam SL, Havrilesky LJ, Ghebre T, Myers ER. Screening for cervical cancer: A modeling study for the US Preventive Services Task Force. *J Lower Genit Tract Dis*. 2013;17:193-202.
9. Blatt AJ, Kennedy R, Luff RD, Austin RM, Rabin DS. Comparison of cervical cancer screening results among 256,648 women in multiple clinical practices. *Cancer Cytopathol*. 2015;123:282-288.
10. Mbatani N, Adams T, Wijk Lv, Behrens C, Tam T, Wright T Jr, Stoler M, Denny L. Performance of an Human Papillomavirus Test in Samples From Women With Histopathologically Confirmed Invasive Cervical Cancer. *J Low Genit Tract Dis*. 2016 Apr;20(2): 151-3.
11. Can NT, Tesic V, Antic T. Human papillomavirus testing in patients with invasive cervical carcinoma: An institutional experience *JASC* 2014;3(3):126-30.
12. Katki HA, Kinney WK, Fetterman B, et al. Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: a population-based study in routine clinical practice. *Lancet Oncol* 2011;12(7):663-72.