



## CYTOPATHOLOGY EDUCATION AND TECHNOLOGY CONSORTIUM

October 2<sup>nd</sup>, 2017

**TO: United States Preventive Service Task Force**

**FROM: Cytopathology Education and Technology Consortium (CETC)\***

*\*The CETC is an independent consortium of professional organizations involved in diagnostic cytopathology. The member organizations are the American Society of Cytopathology (ASC), the American Society for Clinical Pathology (ASCP), the American Society for Cytotechnology (ASCT), the College of American Pathologists (CAP), the International Academy of Cytology (IAC) and the Papanicolaou Society of Cytopathology (PSC). The representatives from each of the organizations are nationally recognized members of the cytopathology community.*

**RE: Response to New USPSTF Draft Guidelines for Cervical Cancer Screening**

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We are writing to express concern regarding the draft recommendations for women ages 30 to 65 years as stated below:

*“The USPSTF recommends either screening every 3 years with cervical cytology alone or every 5 years with high-risk human papillomavirus (hrHPV) testing alone in women ages 30-65 years”*

The recommendation to permit cervical cytology screening alone every 3 years for women ages 21-65 years is acceptable and consistent with current practices and guidelines of major professional societies.<sup>(1,2)</sup> However, the USPSTF draft guidelines do not include an option for cytology and HPV co-testing for women 30-65 years, and this differs from the current guidelines of the American Cancer Society, the American Society for Colposcopy and Cervical Pathology, the American Congress of Obstetricians and Gynecologists, and other professional organizations which have guided cervical cancer screening practice in the USA.<sup>(1,2)</sup> The guidelines from these organizations state that co-testing is the “preferred” screening method in women 30-65 years and that primary HPV screening at 3 year intervals is one of three options for women 25-65 years.<sup>(3)</sup> The remaining USPSTF 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 Cytopathology Education and Technology Consortium (CETC) recommends that:**

- 1. Cytology and high risk HPV co-testing be retained as a screening strategy for women aged 30-65 years.**
- 2. Primary HPV only screening should be utilized only with testing platform(s) validated for that purpose and approved by the FDA.**
- 3. Any Primary HPV screening method should be applied every three years until there is more longitudinal data applicable to the U.S. screening population.**

**The CETC is concerned that if Primary HPV screening every 5 years is endorsed by the USPSTF, without co-testing as a screening option, this change may potentially impact safety and efficacy for cervical cancer prevention in the United States.**

**The justifications for our concern and recommendations are summarized below along with selected, pertinent references:**

### **1. Issues Regarding Supporting Data for Primary HPV Screening and Specific Considerations for Cervical Cancer Prevention in the United States**

The USPSTF draft guideline cites a number of 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 with follow up/recall for non-compliant women and high rates of HPV vaccination. In contrast, screening in the USA is opportunistic and many women do not receive sufficient screening. Furthermore, HPV vaccination uptake in the USA has lagged significantly behind that in other developed countries. *Thus women in the USA have less primary and secondary prevention of cervical cancer than countries with organized preventive services.*

Studies from the CDC<sup>(4)</sup> show that only 83% of women reported being current with cervical cancer screening, which is considerably below the Healthy People 2020 target of 93% and that screening compliance has decreased in the past few years. Women of lower socioeconomic status are at higher risk of not having screening along with several minority groups including Hispanic women, American Indians, and Alaskan natives. *If cervical cytology is no longer covered by insurers, the existing disparities in preventive services for women are likely to increase.*

When currently recommended co-testing management guidelines are followed in women age 30 and older, sensitivity is maximized and there is no evidence that colposcopy procedures will increase for those who receive co-testing when compared to primary HPV screening.

### **2. Availability of FDA Approved HPV Testing Methodology and False Negative Results**

The USPSTF draft guidelines do not specify that the HPV testing method should be FDA approved if HPV testing alone is used for primary screening; in fact they state that a variety of platforms can be used for HPV testing. As pathologists and laboratory professionals, we strongly recommend that only methods approved by the FDA or vigorously validated for a primary screening indication be used. Laboratory quality control and ongoing proficiency testing are extremely important. Several current HPV testing modalities do not provide an internal specimen adequacy control to ensure that cervical epithelial cells have been sampled. 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. *In our opinion, there is a risk of false negative HPV results without the added morphologic control offered by co-testing because testing platforms lack a control mechanism that specifically identifies the DNA of epithelial cells as opposed to other contaminating cells.* Similarly RNA based tests currently on the market lack an internal control. There is also very little data regarding interfering substances such as lubricants and blood.

*At present, there is only one HPV test approved by the FDA for Primary HPV screening that is only available in a limited number of laboratories.* Before considering the option of primary HPV only screening, clinicians should be advised to inquire which HPV testing platform(s) are offered by their respective laboratories.

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### 3. HPV Negative Cervical Cancer

The prevalence of HR-HPV types varies with demographic populations and the current U.S. population is very diverse, in contrast to the patient populations in the prior European trials. As with any laboratory test, the sensitivity of high risk HPV testing is not 100%. A subset of carcinomas, both squamous and glandular, as well as other tumor types may not be detected by HPV testing alone. A United States cancer registry study showed that 9.4% of cervical cancers were HPV negative and an additional 3.2% contained rare HPV subtypes.<sup>(5)</sup> The incidence of cervical adenocarcinoma has increased significantly and these tumors have a higher rate of testing HPV negative.<sup>(6)</sup>

The majority of the European trials in the literature used precancer (CIN2/3), not invasive cancer as an end point. *A number of studies performed in the U.S. and other countries have found that about 9-10% of invasive cancers will test negative for HPV by commercially available tests.*<sup>(7-9)</sup> Studies performed in U.S. population show that the addition of cytology screening will add sensitivity in many of these women. Data from one study cited below suggests that cytology and HR-HPV testing miss different sub-sets of invasive cancer, hence the higher sensitivity of co-testing.<sup>(9)</sup> As with most cancer, clinical outcomes are better when cervical tumors are detected at a lower stage, and we are concerned about delayed diagnoses resulting in higher stage tumors due to longer screening intervals, such as the USPSTF recommended 5 years, after negative HPV results.

Due to the documentation of HPV-negative squamous cell carcinoma and adenocarcinoma, women should have a morphological examination (Pap test) in their screening history and should not be screened solely with HPV tests.

### 4. Follow Up of Women with Primary HPV only Results

*Before primary HPV screening for cervical cancer is widely adopted, there should be clear evidence-based algorithms for the follow up of both positive and negative tests to prevent loss of women to appropriate management and the resulting potential increases in cervical cancer incidence.* The ATHENA trial, upon which the U.S. FDA approval of Primary HPV screening was based, had only 3 years of longitudinal follow up data. There is minimal evidence in clinical practice as to the optimal method of follow up for HPV negative women. Additionally, if clinicians triage all HPV positive results to colposcopy, rather than the suggested follow-up of Non 16/18 HPV genotypes to reflex cytology, colposcopy services could potentially be overwhelmed, with associated increased costs and harms.

### 5. Physician and Patient Compliance

Furthermore, women in the USA are unwilling to give up the use of cervical cytology or extend screening intervals to 5 years in spite of arguments made by organizations that resources saved by deleting cytology screening are better spent elsewhere. Women in general are not interested in assuming more cancer risk. Similarly, physicians seem to prefer 3-year testing strategies over 5-year screening intervals. In fact, clinicians have shown resistance to the 5-year co-testing interval recommendation within the 2012 screening guidelines since it permits higher cancer risks after a single negative co-test than 3-year co-testing.<sup>(11-13)</sup> *It is highly unlikely that either physicians or patients will be compliant with HPV only screening every 5 years.*

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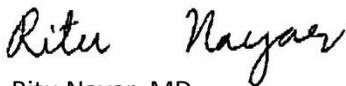
*To avoid an increase in cervical cancer cases, regular screening is required, with methodologies that provide an optimal balance between sensitivity and specificity and remain readily accessible and affordable for all women. The U.S. should focus efforts on increasing primary prevention by vaccination, better organization/availability and follow up in preventive services before assuming greater risk by endorsing secondary prevention/screening strategies that are not currently ready for successful implementation.*

**In conclusion, the CETC organizations listed below recommend that:**

- 1. Cytology and high risk HPV co-testing be retained as a screening strategy for women aged 30-65 years.**
- 2. Primary HPV only screening should be utilized only with testing platform(s) validated for that purpose and approved by the FDA.**
- 3. Any Primary HPV screening method should be applied every three years until there is more longitudinal data applicable to the U.S. screening population.**

Thank you for your consideration.

Sincerely,



Ritu Nayar, MD

Co-Chair, On behalf of The Cytopathology Educational and Technology Consortium



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## 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. 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).
  4. 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.
  5. Hopenhayn C, Christian A, Christian WJ, et al. Prevalence of human papillomavirus types in invasive cervical cancers from 7 US cancer registries before vaccine introduction. *J Low Genit Tract Dis*. 2014;18:182e189.
  6. Pirog EC, Loveras B, Moljin A, et al, for the RIS HPV TT Study Group. HPV relevance and genotypes in different histologic subtypes of cervical adenocarcinoma, a worldwide analysis of 780 cases. *Mod Pathol*. 2014;27:1559e1567.
  7. Zhao C, Li Z, Nayar R, et al. Prior High-risk human papillomavirus testing and Papanicolaou test results of 70 invasive cervical carcinomas diagnosed in 2012: results of a retrospective multicenter study. *Arch Pathol Lab Med*. 2015;139:184e188.
  8. Blatt AJ, Kennedy R, Luff R, Austin RM, Rabin DS. Comparison of cervical screening results among 256,648 women in multiple clinical practices. *Cancer Cytopathol*. 2015;123:282e288.
  9. Zheng B, Li Z, Griffith CC, Yan S, Chen C, Ding X, Liang X, Yang H, Zhao C. Prior high-risk HPV testing and Pap test results for 427 invasive cervical cancers in China's largest CAP-certified laboratory. *Cancer Cytopathol*. 2015;123:428–34.
  10. Kinney W, Wright TC, Dinkelspiel HE, DeFrancesco M, Thomas Cox J, Huh W. Increased cervical cancer risk associated with screening at longer intervals. *Obstet Gynecol*. 2015;125:311e315.
  11. Kinney WK, Huh 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.
  12. J.C. Gage, M. Schiffman, H.A. Katki, P.E. Castle, B. Fetterman, N. Wentzensen, N.E. Poitras, T. Lorey, L.C. Cheung, W.K. Kinney. Reassurance against future risk of precancer and cancer conferred by a negative human papillomavirus test. *J. Natl. Cancer Inst.*, 18 (2014 Jul), p. 106
  13. Silver, M. Schiffman, B. Fetterman, N.E. Poitras, J.C. Gage, N. Wentzensen, T. Lorey, W.K. Kinney, P.E. Castle The population impact of human papillomavirus/cytology cervical cotesting at 3-year intervals: reduced cervical cancer risk and decreased yield of precancer per screen. *Cancer*, 122 (23) (2016 Dec 1), pp. 3682-3686
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