FAQs for Transitioning to Primary HPV Testing for Cervical Cancer Screening: Moving from Cytology Alone

This resource was developed by the Moving from Cytology Alone Workgroup as a part of the American Cancer Society National Roundtable on Cervical Cancer (ACS NRTCC) Primary HPV Screening Initiative, which aims to support the transition and implementation of the primary HPV test for cervical cancer screening across the United States. To learn more about the transition to primary HPV test for screening, and this initiative, please visit our webpage.

Why is primary HPV testing better than cytology alone?

- Screening with primary HPV testing in combination with cytology triage of those who test positive for hrHPV infection has been shown to best balance the detection of pre-cancer while minimizing the number of tests and colposcopies that need to be performed (Kim JJ, *JAMA* 2018). In contrast, cytology alone every three years detected fewer cases of pre-cancer and cancer and resulted in more testing. Compared to primary HPV testing, the addition of cytology to the HPV test (i.e., co-testing) increases the number of tests performed without an increase in the number of cases of pre-cancer or cancer detected (Melnikow et al., *JAMA* 2018; Liang et al., *CEBP* 2021, Gage et al., *JNCI* 2014).
    - Co-testing at five-year intervals beginning at age 30 was associated with 60% more lifetime total tests and 12% more colposcopies with similar number of cases detected compared with primary HPV screening and cytology triage. There was no difference in the number of cervical cancer–related deaths between the two strategies (Kim JJ, *JAMA* 2018).
- Primary HPV testing detects more glandular cervical cancer lesions than Pap cytology testing (Castle et al., *Gynecol Oncol* 2017).

How is the primary HPV testing data applicable to individual patient populations? Is primary HPV testing safe for diverse populations?

- Data demonstrating the safety and efficacy of cervical cancer screening using primary HPV tests are available from randomized trials conducted in many different countries, including several in Europe, India, Hong Kong, Canada, Australia, and Mexico, and have been summarized in systematic reviews and meta-analyses.
    - These data demonstrate the superiority of primary HPV testing strategies across diverse populations regardless of race/ethnicity, socioeconomic background, or geography.
    - These studies show that HPV screening is more sensitive than Pap cytology for detecting cervical precancer and cancer (CIN2+) and is associated with less detection of CIN2+ in subsequent screening rounds.
    - A pooled analysis from 5 trials (Ronco et al., *Lancet* 2014) demonstrated that screening with the primary HPV test led to a greater reduction in the incidence of cervical cancer compared with cytology (cumulative detection of invasive cervical cancer of 46.7 per 100,000 among women screened with the HPV test, compared with 93.6 per 100,000 women in the cytology groups).
    - Some studies based on retrospective analyses of large laboratory data have challenged the use of the primary HPV test for cervical cancer screening, arguing that it may miss a subset of cervical cancers that are cytology positive/HPV negative (Blatt et al., *Cancer Cytopathol* 2015; Kaufman et al., *AJCP* 2021). Methodologic design flaws in these studies have been addressed elsewhere (Rossi et al., *Cancer Cytopathol* 2016; Wentzensen and Arbyn, *Prev Med* 2017; Schiffman and Wentzensen, *AJCP* 2021).

Nevertheless, large studies of HPV testing for cervical cancer screening have identified a subset of cancers testing HPV negative but positive for cytology. Explanations for these findings include the possibility of a very rare subset of cervical cancer that is not caused by HPV, misclassified cancers from other sites, and/or the inclusion of rare cancers that are caused by HPV types that are not included in a typical panel of high-risk HPV types. Finally, HPV results may be negative when advanced cancers are detected by microscopic signs of necrosis; however, many cancers detected at this stage are already symptomatic.

Which primary HPV screening test should I use? Where can I find recommendations for HPV-based screening and management?

There are several HPV tests on the market, but not all have FDA approval for primary screening. There are currently two FDA-approved tests for primary HPV screening that may be used alone as primary HPV screening or in conjunction with cytology. Current tests approved for primary HPV screening are DNA-based assays with a built-in internal control as a check of sample adequacy. Further, HPV tests can either provide partial HPV genotyping results (two individual HPV genotypes plus pooled results) or extended HPV genotyping (at least five individual HPV genotype results plus pooled results).

Recommendations for HPV-based screening can be found through ACS, the United States Preventive Services Task Force (USPSTF), and the American College of Obstetricians and Gynecologists (ACOG). Risk-based management guidelines can be found through the American Society for Colposcopy and Cervical Pathology (ASCCP).

Do I need special collection materials or other supplies to implement screening with primary HPV testing?

Cervical specimens are collected in the same manner as cytology collection (endocervical broom or brush/spatula combination). The provider then places a laboratory order for a primary HPV test (if the HPV test has FDA approval for use as a primary HPV test), which initiates reflex cytology if positive.

Will my patient need a Pap test anyway? What is the role of cytology?

According to current ASCCP screening guidelines, if a patient tests positive for HPV, then they should have additional reflex cytology performed, regardless of the HPV genotype. This reflex cytology result will dictate follow-up to either co-testing in 12 months, colposcopy, or expedited treatment. For example, those with high-grade squamous intraepithelial lesion cytology and HPV-16 positivity have high enough risk that qualifies them for expedited treatment.

What is the out-of-pocket cost of primary HPV testing for the patient?

This is likely to vary state by state, type of insurance payer, and the laboratories where the test is being performed. Laboratory charges may vary based on contracting by payers.

Does the National Breast and Cervical Early Detection Program cover primary HPV testing for patients? Is the primary HPV test covered by most insurance plans?

The National Breast and Cervical Cancer Early Detection Program does cover primary HPV testing for patients as it is a recommended strategy included in the USPSTF recommendation for cervical cancer screening.

Primary HPV testing for screening is also covered by most insurance plans because it is included in the USPSTF recommendation.

How can I best discuss this transition with patients? How do I best explain what the results mean?

The provider has a key role to play in discussing the primary HPV test and the move away from cytology alone with patients. The ACS NRTCC Primary HPV Screening Initiative has developed resources for providers, including a provider script on how to talk to patients about this transition, a patient-communication dialogue tool, and other provider education resources available in the ACS NRTCC Resource Center.

How can I discuss this transition with my institution? What are the key points to emphasize why we should be transitioning to primary HPV testing from over doing cytology alone?

See our accompanying resource, "Primary HPV Screening Initiative Available Resources" and supporting slide deck. The key point to emphasize is that the primary HPV test is overwhelmingly superior to cytology alone and is just as good as co-testing. Additionally, primary HPV testing helps reduce disparities by offering longer screening intervals, benefiting those with limited access to care.