Why Use Primary HPV Testing: A Resource for Providers

This resource was developed by the Provider Needs 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.

What is primary HPV testing?

Primary HPV screening is screening for cervical cancer using an HPV test by itself. Prior strategies for cervical cancer screening included cytology alone (Pap test) and co-testing (cytology + HPV testing). The sample for the primary HPV test is collected as you would perform these other strategies, using a plastic broom or brush to collect the sample during a internal pelvic exam.

Why use a primary HPV test for screening?

The primary HPV test is more sensitive than cytology, leading to greater detection of cervical abnormalities, and is also more cost-effective than co-testing since it does not add more unnecessary tests.

Who recommends a primary HPV test for screening?

In the United States, three organizations recommend primary HPV testing for cervical cancer screening. The primary HPV test is the "preferred" method of screening for cervical cancer per ACS, while cytology and co-testing are "acceptable" alternatives. The American College of Obstetrics and Gynecology (ACOG) and the United States Preventive Services Task Force (USPSTF) include primary HPV testing as an "acceptable" method along with cytology and/or co-testing for screening.

Can we use any type of HPV test for screening?

While there are several HPV tests approved for use in co-testing, there are currently only three FDA-approved tests for primary HPV screening. Primary HPV screening should only be performed with these testing systems:

- cobas® HPV Test (Roche)
- Onclarity™ HPV Assay (BD)
- Alinity m (Abbott)

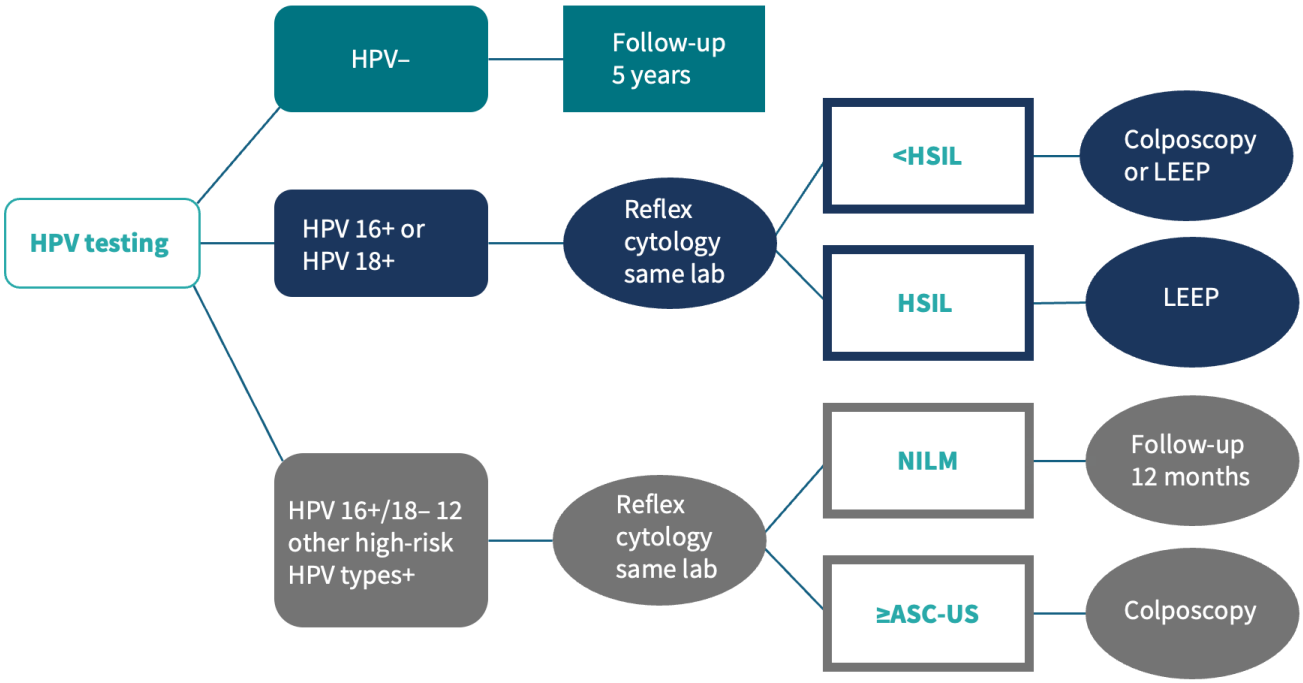
What do we do with the results of a primary HPV test?

Similar to cytology or co-testing results, primary HPV test results should follow recommendations of the 2019 American Society for Colposcopy and Cervical Pathology (ASCCP) Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors. (See example below).

HPV type and cytology results determine clinical action and may include recommendation for follow-up in 12 months, colposcopy, or loop electrosurgical excision procedure/treatment per the 2019 ASCCP risk-based consensus guidelines. A negative/normal primary HPV screening test result should follow up in five years, among low-risk patients with all normal prior screening tests results. A positive/abnormal primary HPV screening test result requires a reflex cytology test to be completed. This may require an additional sample to be collected or, if available at the lab, the test may be performed from the same specimen.

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(2):102-131. doi: 10.1097/LGT.0000000000000525

Algorithm for Primary HPV Screening



ACS-US, atypical squamous cells of undetermined significance; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LEEP, loop electrosurgical excision procedure; NILM, negative for intraepithelial lesion or malignancy.

Huh WK, Ault KA, Chelmow D, et al. Use of primary high-risk human papillomavirus testing for cervical cancer screening: interim clinical guidance. *Gynecol Oncol*. 2015;136(2):178-182. doi:10.1016/j.ygyno.2014.12.022

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(2):102-131. doi:10.1097/LGT.0000000000000525

What about risks associated with HPV-negative/high-grade squamous intraepithelial lesion or worse (HSIL+)?

Persistent HPV infection with high-risk HPV types, most commonly genotypes 16 and 18 but inclusive of 14 high-risk types, is necessary for the development of cervical pre-cancer and cancer. This understanding has provided a basis for HPV testing, including primary HPV testing, as a key component of cervical cancer screening.

Extensive studies confirm that a negative HPV testing result is associated with a very low risk of cervical pre-cancer and cancer. An analysis of the Kaiser Permanente of Northern California/National Cancer Institute Guidelines Cohort of 1,546,462 screened women has shown that the number of people receiving this combination of results (HPV-negative HSIL+) was 183 (0.01%) with unknown prior results, of which 43 received a diagnosis of cervical intraepithelial neoplasia grade 3 (CIN3), adenocarcinoma in-situ (AIS), or cancer (defined subsequently as CIN3+).

Of 819,533 screened women with a prior negative HPV result, 64 (0.01%) had an HPV-negative HSIL result, of which 8 had CIN3+. Of 44,391 screened women with a prior HPV-positive/negative for intraepithelial lesion or malignancy (NILM) result, 9 (0.02%) had HPV-negative HSIL+, of which 4 were diagnosed with CIN3+. These numbers demonstrate that this combination of results is rare, affecting 0.02% or less of all people screened.

Unfortunately, absolute cervical cancer prevention is not a realistic or achievable goal. Therefore, screening guidelines based on population health maximize benefits of screening for cancer prevention while minimizing harms of overtesting and overtreatment.

Gage JC, Schiffman M, Katki HA, et al. Reassurance against future risk of precancer and cancer conferred by a negative human papillomavirus test. *J Natl Cancer Inst*. 2014;106(8):dju153. doi:10.1093/jnci/dju153

Huh WK, Ault KA, Chelmow D, et al. Use of primary high-risk human papillomavirus testing for cervical cancer screening: interim clinical guidance. *Gynecol Oncol*. 2015;136(2):178-182. doi:10.1016/j.ygyno.2014.12.022

Fontham ETH, Wolf AMD, Church TR, et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. *CA Cancer J Clin*. 2020:70: 321 346. doi:10.3322/caac.21628

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(2):132-143. doi: 10.1097/LGT.0000000000000529

Why does the American Cancer Society recommend screening starting at age 25?

Women and people with a cervix younger than age 25 represent an age group with consistently low cervical cancer incidence (0.8% of all new cases diagnosed). We know from the natural history of HPV infection that while the HPV prevalence is high in the group younger than age 25, rates of persistence and progression of HPV infection are low when compared with older age groups. The rates of regression of precursor abnormalities are also comparatively high in this age group. That is, the infection usually clears before progressing to pre-cancer or cancer. However, treatment of lesions that are likely to regress is associated with increased risk of harm, including potential adverse obstetrical outcomes as well as psychological and sexual effects. Additionally, observational studies have shown little benefit with screening and reduction of incidence of invasive disease for those younger than age 25.

This evidence demonstrates a favorable benefit-to-harm balance and so supports the recommendation of cervical cancer screening initiation at age 25, preferably with primary HPV testing.

Fontham ETH, Wolf AMD, Church TR, et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. *CA Cancer J Clin*. 2020: 70: 321- 346. doi:10.3322/caac.21628

How can I encourage adoption of primary HPV testing for screening?

The widespread rollout of primary HPV testing will require a collaboration between clinicians ordering and performing the test, the laboratory running the test, and other health care and IT personnel involved in the clinical workflows for laboratory testing.

Your workplace may already have the equipment needed for primary HPV testing. Many labs and institutions have testing systems that can run both COVID-19 and primary HPV assays. Ask your lab if an FDA-approved testing platform is available for doing primary HPV testing, and request this cervical cancer screening practice for your patients.

Visit the ACS NRTCC Resource Center for more information about primary HPV screening.