Cervical Cancer Screening

Policy Number: AHS – G2002 – Cervical Cancer Screening	Prior Policy Name and Number, as applicable:
Effective Date 10/01/2022	

I. Policy Description

Cervical cancer screening detects cervical precancerous lesions and cancer through cytology, human papillomavirus (HPV) testing, and if needed, colposcopy (Feldman, Goodman, & Peipert, 2021). The principal screening test to detect cancer in asymptomatic women is the Papanicolaou (Pap) smear. It involves cells being scraped from the cervix during a pelvic examination and spread onto a slide. The slide is then sent to an accredited laboratory to be stained, observed, and interpreted (Feldman & Crum, 2021).

Human papilloma virus (HPV) has been associated with development of cervical intraepithelial neoplasia, and FDA approved HPV tests detecting the presence of viral DNA from high risk strains have been developed and validated as an adjunct primary cancer screening method (Feldman & Crum, 2019).

For more information specifically regarding HPV, please refer to AHS-G2157 Diagnostic Testing of STIs.

II. Related Policies

Policy Number	Policy Title
AHS-G2157	Diagnostic Testing of Common Sexually Transmitted Infections

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Medical Policy Statements do not ensure an authorization or payment of services. Please refer to the plan contract (often referred to as the Evidence of Coverage) for the service(s) referenced in the Medical Policy Statement. If there is a conflict between the Medical Policy Statement and the plan contract (i.e., Evidence of Coverage), then the plan contract (i.e., Evidence of Coverage) will be the controlling document used to make the determination.

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. If there is a conflict between this Policy and any relevant, applicable government policy [e.g. National Coverage Determinations (NCDs) for Medicare] for a particular member, then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quicksearch.aspx?from2=search1.asp& or the manual website.

The criteria below are based on recommendations by the U.S. Preventive Services Task Force, The National Cancer Institute, NCCN, The American Society for Colposcopy and Cervical Pathology, The American Cancer Society, The American Society for Clinical Pathology, and the American College of Obstetricians and Gynecologists.

1. Women under 21 years of age **DO NOT MEET COVERAGE CRITERIA** for cervical cancer screening unless one of the following criteria are met:
    a. History of HIV and/or other Non-HIV immunocompromised conditions
    b. Previous diagnosis of cervical cancer
    c. Previous diagnosis of cervical dysplasia
    d. History of an organ transplant
2. Cervical cancer screening **MEETS COVERAGE CRITERIA** in immunosuppressed women without an HIV infection in the following situations:
    a. Annual cytology testing for individuals 30 years or younger
    b. Every 3 years co-testing (cytology and HPV) for individuals 30 years or older
3. For women 21 - 29 years of age, cervical cancer screening using conventional or liquid based Papanicolaou (Pap) smears **MEETS COVERAGE CRITERIA** at a frequency of every 3 years.
4. For women 30 - 65 years of age, cervical cancer screening using conventional or liquid based Pap smear at a frequency of every 3 years, or cervical cancer screening using the high-risk HPV test alone at a frequency of every 5 years, or co-testing (cytology with concurrent high-risk HPV testing) at a frequency of every 5 years, **MEETS COVERAGE CRITERIA**.
5. Testing for high-risk strains HPV-16 and HPV-18 **MEETS COVERAGE CRITERIA** if BOTH of the following co-testing criteria are present:
    a. Cytology negative AND
    b. HPV positive
6. Cervical cancer screening **MEETS COVERAGE CRITERIA** for women >65 years of age who are considered high-risk (women with a high-grade precancerous lesion or cervical cancer, women with in utero exposure to diethylstilbestrol, or women who are immunocompromised).
7. Routine cervical cancer screening **DOES NOT MEET COVERAGE CRITERIA** in women >65 years of age who are not considered high-risk and have an adequate screening history:

a. Three consecutive negative Pap smears, or

b. Two consecutive negative HPV tests within 10 years before cessation of screening, with the most recent test occurring within 5 years

8. Repeat cervical cancer screening by Pap smear or HPV testing in one year **MEETS COVERAGE CRITERIA** if a previous cervical cancer screen had an abnormal cytology result and/or was positive for HPV, or if the woman is at high risk for cervical cancer (organ transplant, exposure to the drug DES, immunocompromised women).

9. Cervical cancer screening (at any age) **DOES NOT MEET COVERAGE CRITERIA** for women who have undergone surgical removal of uterus and cervix and have no history of cervical cancer or pre-cancer.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient's illness.

10. The following **DO NOT MEET COVERAGE CRITERIA**:

a. Inclusion of low-risk strains of HPV in co-testing, as the clinical utility has not been established.

b. Other technologies for cervical cancer screening because of insufficient evidence of clinical utility.

IV. Scientific Background

The American Cancer Society estimates that 14,480 new cases of cervical cancer will be diagnosed in 2021 and approximately 4,290 women will die from the disease (ACS, 2021). To screen for cervical cancer, a Papanicolaou (Pap) test or human papillomavirus (HPV) test is performed. Co-testing with both is also a common clinical practice. To obtain the cell sample for cytology, cells are scraped from both the ectocervix (external surface) and endocervix (cervical canal) during a speculum exam to evaluate the squamocolumnar junction where most neoplasia occur. Cytological examination can be performed as either a traditional Pap smear where the swab is rolled directly on the slide for observation or as a liquid-based thin layer cytology examination where the swab is swirled in a liquid solution so that the free cells can be trapped and plated as a monolayer on the glass slide. One advantage of the liquid cytology assay is that the same sample can be used for HPV testing whereas a traditional Pap smear requires a second sample to be taken. HPV testing is typically a nucleic acid-based assay that checks for the presence of high-risk types of HPV, especially types 16 and 18. HPV testing can be performed on samples obtained during a cervical exam; furthermore, testing on samples obtained from vaginal swabs, tampons, and urine samples have been reported (Feldman & Crum, 2019).

Analytical Validity

A study by Marchand, Mundt, Klein, and Agarwal (2005) explored the optimal collection technique for Pap testing. Their study consisted of two different cytology labs and 128 clinicians over the course of

one year. They discovered that in conventional Pap testing the sequence of collection—the cytobrush for the endocervix and the spatula for the ectocervix—had no effect on the quality of the assay. Further, 47% of the clinicians who had high levels of absent endocervical cells on their samples used the cytobrush method alone. The authors conclude, "The combination of the Cytobrush (endocervix) and spatula (ectocervix) is superior for a quality Pap smear. The sequence of collection was not important in conventional Pap smears. The broom alone performs poorly (Marchand et al., 2005)."

Urine-based HPV DNA testing as a screening tool would be a less invasive method than cervical examinations and swabs. A study by Mendez et al. (2014) using both urine samples and cervical swabs from 52 female patients, however, showed that there was only 76% agreement between the two methodologies. The urine testing correctly identified 100% of the uninfected individuals but only 65% of the infected as compared to the cervical swab controls (Mendez et al., 2014). An extensive meta-analysis of 14 different studies using urinary testing, on the other hand, reported an 87% sensitivity and 94% specificity of the urine-based methodology for all strains of HPV, but the sensitivity for high-risk strains alone was only 77%. The specificity for the high-risk strains alone was reported to be higher at 98%. "The major limitations of this review are the lack of a strictly uniform method for the detection of HPV in urine and the variation in accuracy between individual studies. Testing urine for HPV seems to have good accuracy for the detection of cervical HPV, and testing first void urine samples is more accurate than random or midstream sampling. When cervical HPV detection is considered difficult in particular subgroups, urine testing should be regarded as an acceptable alternative" (Pathak, Dodds, Zamora, & Khan, 2014).

Clinical Validity and Utility

The National Cancer Institute (NCI) reports that "Regular Pap screening decreases cervix cancer incidence and mortality by at least 80%" (NCI, 2021). They also note that Pap testing can result in the possibility of additional diagnostic testing, especially in younger women, when unwarranted, especially in cases of possible low-grade squamous intraepithelial lesions (LSILs); however, even though 50% of women undergoing Pap testing required additional, follow-up diagnostic procedures, only 5% were treated for LSILs. The NCI also reports that "HPV-based screening provides 60% to 70% greater protection against invasive cervical carcinoma, compared with cytology" (NCI, 2021).

A study by Sabeena et al. (2019) measured the utility of urine-based sampling for cervical cancer screening in low-resource settings. The researchers compared 114 samples to determine the accuracy of HPV detection (by polymerase chain reaction (PCR)) in paired cervical and urine samples. Samples were taken from patients previously diagnosed with cervical cancer through histological methods. Of the 114 samples, "HPV DNA was tested positive in cervical samples of 89 (78.1%) and urine samples of 55 (48.2%) patients. The agreement between the two sampling methods was 66.7%" (Sabeena et al., 2019). HPV detection in urine samples had a sensitivity of 59.6% and a specificity of 92%. The authors concluded, "Even though not acceptable as an HPV DNA screening tool due to low sensitivity, the urine sampling method is inexpensive and more socially acceptable for large epidemiological surveys in developing countries to estimate the burden" (Sabeena et al., 2019).

Cervical cancer guidelines published by the National Comprehensive Cancer Network (NCCN) (NCCN, 2020) state that, although the rates of both incidence and mortality of squamous cell carcinoma of the cervix has been declining over the last thirty years, "adenocarcinoma of the cervix has increased over the past 3 decades, probably because cervical cytologic screening methods are less effective for adenocarcinoma." A study in the United Kingdom supports this because the risk-reduction associated with 3-yearly screening was reduced by 75% for squamous carcinoma and 83% for adenosquamous

carcinoma, but adenocarcinoma was reduced only by 43% (Sasieni, Castanon, & Cuzick, 2009). Another extensive study of more than 900,000 women in Sweden showed that PCR-based HPV testing for the high-risk types 16 and 18 is better at predicting the risk of both in situ and invasive adenocarcinoma. The authors conclude, "infections with HPV 16 and 18 are detectable up to at least 14 years before diagnosis of cervical adenocarcinoma. Our data provide prospective evidence that the association of HPV 16/18 with cervical adenocarcinoma is strong and causal (Dahlstrom et al., 2010)."

A report by Chen et al. (2011) reviewed HPV testing and the risk of the development of cervical cancer. Of the 11,923 women participating in the study, 86% of the women who tested positive for HPV did not develop cervical cancer with ten years. The authors concluded, "HPV negativity was associated with a very low long-term risk of cervical cancer. Persistent detection of HPV among cytologically normal women greatly increased risk. Thus, it is useful to perform repeated HPV testing following an initial positive test" (Chen et al., 2011).

In 2018, the results of the multi-year HPV for cervical cancer screening trial (FOCAL) randomized clinical trial testing of the use of HPV testing alone for detection of cervical intraepithelial neoplasia (CIN) grade 3 or worse (CIN3+) were published. More than 19,000 women participated in the study split between the intervention group (HPV testing alone) and the control group (liquid-based cytology). "Baseline HPV-negative women had a significantly lower cumulative incidence of CIN3+ at 48 months than cytology-negative women (CIN3+ incidence rate, 1.4/1000 [95% CI, 0.8-2.4]; CIN3+ risk ratio, 0.25 [95% CI, 0.13-0.48]). Among women undergoing cervical cancer screening, the use of primary HPV testing compared with cytology testing resulted in a significantly lower likelihood of CIN3+ at 48 months. Further research is needed to understand long-term clinical outcomes as well as cost-effectiveness (Ogilvie et al., 2018)." In a commentary concerning the findings of this trial, the author notes that "multiple randomized trials have shown that primary HPV screening linked to subsequent identification and treatment of cervical precancer is more effective than Pap testing in reducing the incidence of cervical cancer and precancer, at the cost of lower specificity and more false-negative subsequent colposcopic assessments (Massad, 2018)." The author does address the limitations of the FOCAL study, including that the study concluded prior to seeing what effects, if any, women vaccinated against HPV 16 and HPV 18 would have since the adolescents vaccinated upon FDA approval of the vaccine would not have necessarily been included within the study. They also state that a limitation of the FOCAL trial is "the use of a pooled HPV test for screening, incorporating all carcinogenic HPV types in a single positive or negative result" (Massad, 2018).

Melnikow et al. (2018) performed a review for the USPSTF regarding cervical cancer screening through high-risk (hr) HPV testing. The authors reviewed the following studies: "8 randomized clinical trials (n = 410556), 5 cohort studies (n = 402615), and 1 individual participant data (IPD) meta-analysis (n = 176464)." Primary hr-HPV testing was found to detect cervical intraepithelial neoplasia (CIN) 3+ at an increased rate (relative risk rate ranging from 1.61 to 7.46) in round 1 screening. False positive rates for primary hr-HPV testing ranged from 6.6% to 7.4%, compared with 2.6% to 6.5% for cytology, whereas in cotesting, false-positives ranged from 5.8% to 19.9% in the first round of screening, compared with 2.6% to 10.9% for cytology. Overall, the authors concluded that "primary hrHPV screening detected higher rates of CIN 3+ at first-round screening compared with cytology. Cotesting trials did not show initial increased CIN 3+ detection" (Melnikow et al., 2018).

Bonde, Sandri, Gary, and Andrews (2020) performed a systematic review on the clinical utility of HPV genotyping as a form of cervical cancer screening. Through 16 studies, the researchers concluded that "HPV genotyping can refine clinical management for women screened through the primary HPV

paradigm and the co-testing paradigm by stratifying genotype-specific results and thereby assign women at highest risk for cervical disease to further testing (i.e., colposcopy) or treatment, while designating those with lowest risk to retesting at a shortened interval." After deeming low risk of bias, the review also stated "the overall quality of evidence for CIN 3 or worse risk with negative for intraepithelial lesions or malignancies or low-grade squamous intraepithelial cytology was assessed as moderate; that with atypical squamous cells-undetermined significance and "all cytology" was assessed as high… Human papillomavirus genotyping discriminated risk of CIN 3 or worse to a clinically significant degree, regardless of cytology result" (Bonde et al., 2020).

V. Guidelines and Recommendations

U.S. Preventive Services Task Force (USPSTF) (Bibbins-Domingo et al., 2017; USPSTF, 2018a)

The USPSTF updated their recommendations in 2018. The recommendations are outlined in the table below. The USPSTF did change the recommendation concerning women aged 30-65 to now include the possibility of high-risk HPV testing alone once every 5 years as a screening. They still allow the possibility of co-testing every 5 years or for Pap testing alone every 3 years.

The USPSTF notes certain risk factors that may increase the risk of cervical cancer, such as "HIV infection, a compromised immune system, in utero exposure to diethylstilbestrol, and previous treatment of a high-grade precancerous lesion or cervical cancer." Cytology, primary testing for high-risk HPV alone, or both methods simultaneously may detect the high-risk lesions that are precursors to cervical cancer (USPSTF, 2018b).

USPSTF Summary of Recommendations and Evidence (USPSTF, 2018b)

Population	Recommendation	Grade
Women 21 to 29	Screen for cervical cancer every 3 years with cytology alone. For women 30-65 years, screen for cervical cancer every 3 years with cytology alone, every 5 years with high-risk (hr) HPV testing alone, or every 5 years with co-testing.	The USPSTF recommends the service. There is high certainty that the net benefit is substantial. Offer or provide this service. Grade A
Women younger than 21, older than 65, who have had adequate prior screening, or who have had had a hysterectomy	Do not screen for cervical cancer.	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits. Discourage the use of this service. Grade D

In 2017, "The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of performing screening pelvic examinations in asymptomatic, nonpregnant adult women. (I statement) This statement does not apply to specific disorders for which the USPSTF

already recommends screening (ie, screening for cervical cancer with a Papanicolaou smear, screening for gonorrhea and chlamydia)."

National Comprehensive Cancer Network (NCCN) (NCCN, 2020)

Concerning cervical cancer, the NCCN states, "Persistent human papillomavirus (HPV) infection is the most important factor in the development of cervical cancer. The incidence of cervical cancer appears to be related to the prevalence of HPV in the population…. Screening methods using HPV testing may increase detection of adenocarcinoma" (NCCN, 2020). The NCCN lists chronic, persistent HPV infection along with persistently abnormal Pap smear tests as criteria to be considered for women contemplating hysterectomy. Further, the NCCN also states that "In developed countries, the substantial decline in incidence and mortality of squamous cell carcinoma of the cervix is presumed to be the result of effective screening, although racial, ethnic, and geographic disparities exist" (NCCN, 2020).

National Cancer Institute (NCI) (NCI, 2021)

Concerning the use of Pap testing in screening, the NCI recommends: "Based on solid evidence, regular screening for cervical cancer with the Pap test in an appropriate population of women reduces mortality from cervical cancer. The benefits of screening women younger than 21 years are small because of the low prevalence of lesions that will progress to invasive cancer. Screening is not beneficial in women older than 65 years if they have had a recent history of negative test results… Based on solid evidence, regular screening with the Pap test leads to additional diagnostic procedures (e.g., colposcopy) and treatment for low-grade squamous intraepithelial lesions (LSILs), with long-term consequences for fertility and pregnancy. These harms are greatest for younger women, who have a higher prevalence of LSILs, lesions that often regress without treatment. Harms are also increased in younger women because they have a higher rate of false-positive results" (NCI, 2021).

Concerning the use of HPV DNA testing, the NCI states: "Based on solid evidence, screening with the HPV DNA or HPV RNA test detects high-grade cervical dysplasia, a precursor lesion for cervical cancer. Additional clinical trials show that HPV testing is superior to other cervical cancer screening strategies. In April 2014, the U.S. Food and Drug Administration approved an HPV DNA test that can be used alone for the primary screening of cervical cancer risk in women aged 25 years and older… Based on solid evidence, HPV testing identifies numerous infections that will not lead to cervical dysplasia or cervical cancer. This is especially true in women younger than 30 years, in whom rates of HPV infection may be higher (NCI, 2021)."

Concerning cotesting, they recommend: "Based on solid evidence, screening every 5 years with the Pap test and the HPV DNA test (cotesting) in women aged 30 years and older is more sensitive in detecting cervical abnormalities, compared with the Pap test alone. Screening with the Pap test and HPV DNA test reduces the incidence of cervical cancer… Based on solid evidence, HPV and Pap cotesting is associated with more false-positives than is the Pap test alone. Abnormal test results can lead to more frequent testing and invasive diagnostic procedures (NCI, 2021)."

Choosing Wisely and the American Society for Colposcopy and Cervical Pathology (ASCCP) (ASCCP, 2017, 2019)

The ASCCP recommends: "Don't perform cervical cytology (Pap tests) or HPV screening in patients under age 21 who have a normal immune system. Cervical cancer is rare in adolescents and screening does not appear to lower that risk. Screening adolescents for cervical cancer exposes them to the potential harms of tests, biopsies, and procedures, without proven benefit" (ASCCP, 2019).

The ASCCP also recommends against screening for low-risk HPV types (ASCCP, 2017).

In 2019, the ASCCP also published guidelines for cervical cancer screening in immunosuppressed women without an HIV infection. The following table was provided by Moscicki et al. (2019):

Table 3. Summary of Cervical Cancer Screening Recommendations for Non-HIV Immunocompromised Women

Risk group category	Recommendation
Solid organ transplant	• Cytology is recommended if younger than 30 y • Co-testing is preferred, but cytology is acceptable if 30 y or older • If using cytology alone, perform annual cervical cytology. If results of 3 consecutive cytology results are normal, perform cytology every 3 y • If using co-testing, perform baseline co-test with cytology and HPV. If result of cytology is normal and HPV is negative, co-testing can be performed every 3 y • If transplant before the age of 21 y, begin screening within 1 y of sexual debut • Continue screening throughout lifetime (older than 65 y). Discontinue screening based on shared discussion regarding quality and duration of life rather than age
Allogeneic hematopoietic stem cell transplant	• Cytology is recommended if younger than 30 y • Co-testing is preferred, but cytology is acceptable if 30 y or older • If using cytology alone, perform annual cervical cytology. If results of 3 consecutive cytology results are normal, perform cytology every 3 y • If using co-testing, perform baseline co-test with cytology and HPV. If result of cytology is normal and HPV is negative, co-testing can be performed every 3 y • If transplant before the age of 21 y, begin screening within 1 y of sexual debut • Continue screening throughout lifetime (older than 65 y). Discontinue screening based on shared discussion regarding quality and duration of life rather than age • For HSCT patients who develop a new diagnosis of genital GVHD or chronic GVHD, resume annual cervical cytology until 3 consecutive normal results at which time perform cytology every 3 y, or perform an initial baseline co-test and, if cytology is normal and HPV is negative, perform co-testing every 3 y
Inflammatory bowel disease on immunosuppressant treatments	• Cytology is recommended if younger than 30 y • Co-testing is preferred, but cytology is acceptable if 30 y or older

	• If using cytology alone, perform annual cervical cytology. If results of 3 consecutive cytology results are normal, perform cytology every 3 y • If using co-testing, perform baseline co-test with cytology and HPV. If result of cytology is normal and HPV is negative, co-testing can be performed every 3 y • If on immunosuppressant therapy before the age of 21 y, begin screening within 1 y of sexual debut • Continue screening throughout lifetime (older than 65 y). Discontinue screening based on shared discussion regarding quality and duration of life rather than age
Inflammatory bowel disease not on immunosuppressant treatment	• Follow general population screening guidelines
Systemic lupus erythematosus and rheumatoid arthritis on immunosuppressant treatments	• Cytology is recommended if younger than 30 y • Co-testing is preferred, but cytology is acceptable if 30 y or older • If using cytology alone, perform annual cervical cytology. If results of 3 consecutive cytology results are normal, perform cytology every 3 y • If using co-testing, perform baseline co-test with cytology and HPV. If result of cytology is normal and HPV is negative, co-testing can be performed every 3 y • If on immunosuppressant therapy before the age of 21 y, begin screening within 1 y of sexual debut • Continue screening throughout lifetime (older than 65 y). Discontinue screening based on shared discussion regarding quality and duration of life rather than age
Rheumatoid arthritis not on immunosuppressive treatments	• Follow general population screening guidelines
Type 1 diabetes mellitus	• Follow general population screening guidelines

Society of Gynecologic Oncology, American Society for Colposcopy and Cervical Pathology, American College of Obstetricians and Gynecologists, American Cancer Society, American Society of Cytopathology, College of American Pathologists, and the American Society for Clinical Pathology (Huh et al., 2015)

Since the 2011 joint guidelines issued by the American Cancer Society, American Society for Colposcopy and Cervical Pathology , and American Society for Clinical Pathology Screening concerning cervical cancer screening, additional reports concerning the use of primary hrHPV testing so that representatives from the Society of Gynecologic Oncology, American Society for Colposcopy and

Cervical Pathology, American College of Obstetricians and Gynecologists, American Cancer Society, American Society of Cytopathology, College of American Pathologists, and the American Society for Clinical Pathology convened to issue interim clinical guidance in 2015. In the 2011 statement, primary hrHPV testing was not recommended. The 2015 recommendations include:

- "Because of equivalent or superior effectiveness, primary hrHPV screening can be considered as an alternative to current US cytology-based cervical cancer screening methods. Cytology alone and cotesting remain the screening options specifically recommended in major guidelines."
- "A negative hrHPV test provides greater reassurance of low CIN3+ risk than a negative cytology result."
- "Rescreening after a negative primary hrHPV screen should occur no sooner than every 3 years."
- "Primary hrHPV screening should not be initiated prior to 25 years of age."

They give the following algorithm concerning screening (Huh et al., 2015):

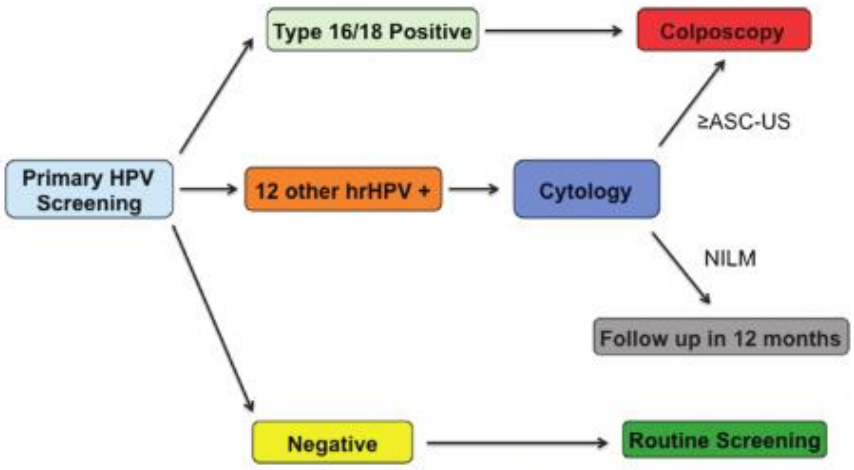

FIGURE 1. Recommended primary HPV screening algorithm. HPV, human papillomavirus; hrHPV, high-risk human papillomavirus; ASC-US, atypical squamous cells of undetermined significance; NILM, negative for intraepithelial lesion or malignancy.

American College of Obstetricians and Gynecologists (ACOG) (ACOG, 2020, 2021)

In April 2021, the ACOG released a statement withdrawing and replacing the Practice Bulletin No.168 on cervical cancer screening, stating that it will be joining the ASCCP and the SGO "in endorsing the U.S. Preventive Services Task Force (USPSTF) cervical cancer screening recommendations, which replace ACOG Practice Bulletin No.168, *Cervical Cancer Screening and Prevention,* as well as the 2012 ASCCP cervical cancer screening guidelines" (ACOG, 2021).

In October 2020, the ACOG released "Updated Guidelines for Management of Cervical Cancer Screening Abnormalities." These new consensus guidelines are based on risk to determine screening, surveillance, colposcopy, or treatment later in life (ACOG, 2020). In relation to screening, the updated management guidelines state:

1. "Recommendations are based on risk, not results.

   a. Recommendations of colposcopy, treatment, or surveillance will be based on a patient's risk of CIN 3+ determined by a combination of current results and past history (including unknown history). The same current test results may yield different management recommendations depending on the history of recent past test results.
2. Colposcopy can be deferred for certain patients.
   a. Repeat human papillomavirus (HPV) testing or cotesting at 1 year is recommended for patients with minor screening abnormalities indicating HPV infection with low risk of underlying CIN 3+ (eg, HPV-positive, low-grade cytologic abnormalities after a documented negative screening HPV test or cotest).
3. All positive primary HPV screening tests, regardless of genotype, should have additional reflex triage testing performed from the same laboratory specimen (eg, reflex cytology).
   a. Additional testing from the same laboratory specimen is recommended because the findings may inform colposcopy practice. For example, those HPV-16 positive HSIL cytology qualify for expedited treatment.
   b. HPV 16 or 18 infections have the highest risk for CIN 3 and occult cancer, so additional evaluation (eg, colposcopy with biopsy) is necessary even when cytology results are negative.
   c. If HPV 16 or 18 testing is positive, and additional laboratory testing of the same sample is not feasible, the patient should proceed directly to colposcopy.
4. Continued surveillance with HPV testing or cotesting at 3-year intervals for at least 25 years is recommended after treatment and initial posttreatment management of histologic HSIL, CIN 2, CIN 3, or AIS. Continued surveillance at 3-year intervals beyond 25 years is acceptable for as long as the patient's life expectancy and ability to be screened are not significantly compromised by serious health issues.
   a. New evidence indicates that risk remains elevated for at least 25 years, with no evidence that treated patients ever return to risk levels compatible with 5-year intervals.
5. Surveillance with cytology alone is acceptable only if testing with HPV or cotesting is not feasible. Cytology is less sensitive than HPV testing for detection of precancer and is therefore recommended more often. Cytology is recommended at 6-month intervals when HPV testing or cotesting is recommended annually. Cytology is recommended annually when 3-year intervals are recommended for HPV or cotesting.
6. Human papilloma virus assays that are Food and Drug Administration (FDA)-approved for screening should be used for management according to their regulatory approval in the United States. (Note: all HPV testing in [the guidelines] refers to testing for high-risk HPV types only).
   a. For all management indications, HPV mRNA and HPV DNA tests without FDA approval for primary screening alone should only be used as a cotest with cytology, unless sufficient, rigorous data are available to support use of these particular tests in management" (ACOG, 2020).

VI. State and Federal Regulations, as applicable

The FDA has approved the APTIMA HPV 16 18/45 Genotype Assay, a nucleic acid amplification test (NAAT), for the qualitative detection of mRNA for HPV 16, 18, and 45 from Gen-Probe Incorporated

on 10/12/2012; however, this test cannot distinguish between 18 and 45. Previously, on 10/28/2011, the FDA approved Gen-Probe Incorporated's APTIMA HPV Assay, an NAAT that tests for 14 high-risk types of HPV but is unable to distinguish between the 14 types.

Hologic, Inc. has two FDA-approved HPV NAAT tests—Cervista HPV 16/18 and Cervista HPV HR and GENFIND DNA Extraction Kit. Both were approved on 03/12/2009. The former is a fluorescent, isothermal-based reaction that detects HPV 16 and 18 whereas the latter screens for DNA from the 14 high-risk HPV strains (FDA, 2018a). A subsequent search on July 18, 2019 did not yield any new HPV-related results (FDA, 2019).

The COBAS HPV test by Roche Molecular Systems, Inc. was approved by the FDA on 04/19/2011 as a NAAT for 14 high-risk types of HPV. This test can specifically identify HPV 16 and 18 but cannot distinguish from the other 12 types of HPV. On 07/02/2018, the FDA released an approval order statement (P100020/S025) "for an expansion of the intended use for the FDA-approved cobas HPV Test to include cervical specimens collected in SurePath Preservative Fluid as a specimen type" (FDA, 2018c). This approval allows for the cobas HPV Test to be used as a first-line cervical cancer screening using the SurePath preservative, a medium often used for Pap tests (Rice, 2018). In 2020, the Cobas HPV was FDA approved for use on Cobas 6800/8800 Systems (FDA, 2020).

On February 12, 2018, the FDA approved the BD Onclarity™ HPV Assay which detects 14 high-risk HPV genotypes including high-risk strains 16 and 18. "The BD Onclarity HPV Assay is a qualitative in vitro test for the detection of Human Papillomavirus in cervical specimens collected by a clinician using an endocervical brush/spatula combination or broom and placed in BD SurePath vial" (FDA, 2018b).

For more information regarding HPV, please refer to AHS-G2157 Diagnostic testing of STIs.

Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

VII. Applicable CPT/HCPCS Procedure Codes

Code Number	Code Description
87623	Infectious agent detection by nucleic acid (DNA or RNA); Human Papillomavirus (HPV), low-risk types (eg, 6, 11, 42, 43, 44)
87624	Infectious agent detection by nucleic acid (DNA or RNA); Human Papillomavirus (HPV), high-risk types (eg, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68)
87625	Infectious agent detection by nucleic acid (DNA or RNA); Human Papillomavirus (HPV), types 16 and 18 only, includes type 45, if performed
88141	Cytopathology, cervical or vaginal (any reporting system), requiring interpretation by physician

88142	Cytopathology, cervical or vaginal (any reporting system), collected in preservative fluid, automated thin layer preparation; manual screening under physician supervision
88143	Cytopathology, cervical or vaginal (any reporting system), collected in preservative fluid, automated thin layer preparation; with manual screening and rescreening under physician supervision
88147	Cytopathology smears, cervical or vaginal; screening by automated system under physician supervision
88148	Cytopathology smears, cervical or vaginal; screening by automated system with manual rescreening under physician supervision
88150	Cytopathology, slides, cervical or vaginal; manual screening under physician supervision
88152	Cytopathology, slides, cervical or vaginal; with manual screening and computer-assisted rescreening under physician supervision
88153	Cytopathology, slides, cervical or vaginal; with manual screening and rescreening under physician supervision
88164	Cytopathology, slides, cervical or vaginal (the bethesda system); manual screening under physician supervision
88165	Cytopathology, slides, cervical or vaginal (the bethesda system); with manual screening and rescreening under physician supervision
88166	Cytopathology, slides, cervical or vaginal (the bethesda system); with manual screening and computer-assisted rescreening under physician supervision
88167	Cytopathology, slides, cervical or vaginal (the bethesda system); with manual screening and computer-assisted rescreening using cell selection and review under physician supervision
88174	Cytopathology, cervical or vaginal (any reporting system), collected in preservative fluid, automated thin layer preparation; screening by automated system, under physician supervision
88175	Cytopathology, cervical or vaginal (any reporting system), collected in preservative fluid, automated thin layer preparation; with screening by automated system and manual rescreening or review, under physician supervision
0500T	Infectious agent detection by nucleic acid (DNA or RNA), Human Papillomavirus (HPV) for five or more separately reported high-risk HPV types (eg, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) (ie, genotyping)
G0123	Screening cytopathology, cervical or vaginal (any reporting system), collected in preservative fluid, automated thin layer preparation, screening by cytotechnologist under physician supervision

G0124	Screening cytopathology, cervical or vaginal (any reporting system), collected in preservative fluid, automated thin layer preparation, requiring interpretation by physician
G0141	Screening cytopathology smears, cervical or vaginal, performed by automated system, with manual rescreening, requiring interpretation by physician
G0143	Screening cytopathology, cervical or vaginal (any reporting system), collected in preservative fluid, automated thin layer preparation, with manual screening and rescreening by cytotechnologist under physician supervision
G0144	Screening cytopathology, cervical or vaginal (any reporting system), collected in preservative fluid, automated thin layer preparation, with screening by automated system, under physician supervision
G0145	Screening cytopathology, cervical or vaginal (any reporting system), collected in preservative fluid, automated thin layer preparation, with screening by automated system and manual rescreening under physician supervision
G0147	Screening cytopathology smears, cervical or vaginal, performed by automated system under physician supervision
G0148	Screening cytopathology smears, cervical or vaginal, performed by automated system with manual rescreening
G0476	Infectious agent detection by nucleic acid (DNA or RNA); human papillomavirus (HPV), high-risk types (eg, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) for cervical cancer screening, must be performed in addition to pap test
P3000	Screening Papanicolaou smear, cervical or vaginal, up to three smears, by technician under physician supervision
P3001	Screening Papanicolaou smear, cervical or vaginal, up to three smears, requiring interpretation by physician
Q0091	Screening Papanicolaou smear; obtaining, preparing and conveyance of cervical or vaginal smear to laboratory

Procedure codes appearing in policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

VIII. Evidence-based Scientific References

ACOG. (2020, October 9). Updated Guidelines for Management of Cervical Cancer Screening Abnormalities. Retrieved from https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2020/10/updated-guidelines-for-management-of-cervical-cancer-screening-abnormalities

ACOG. (2021, April 12). Updated Cervical Cancer Screening Guidelines. Retrieved from https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2021/04/updated-cervical-cancer-screening-guidelines

ACS. (2021, January 12). Key Statistics for Cervical Cancer. Retrieved from https://www.cancer.org/cancer/cervical-cancer/about/key-statistics.html

ASCCP. (2017, February 14). Don't order screening tests for low-risk HPV types. *Five Things Physicians and Patients Should Question.* Retrieved from http://www.choosingwisely.org/clinician-lists/asccp-screening-tests-for-low-risk-hpv-types/

ASCCP. (2019, October 3). Don't perform cervical cytology (Pap tests) or HPV screening in patients under age 21 who have a normal immune system. *Five Things Physicians and Patients Should Question.* Retrieved from http://www.choosingwisely.org/clinician-lists/asccp-pap-tests-or-hpv-screening-in-women-under-21/

Bibbins-Domingo, K., Grossman, D. C., Curry, S. J., Barry, M. J., Davidson, K. W., Doubeni, C. A., . . . Tseng, C. W. (2017). Screening for Gynecologic Conditions With Pelvic Examination: US Preventive Services Task Force Recommendation Statement. *JAMA, 317*(9), 947-953. doi:10.1001/jama.2017.0807

Bonde, J. H., Sandri, M. T., Gary, D. S., & Andrews, J. C. (2020). Clinical Utility of Human Papillomavirus Genotyping in Cervical Cancer Screening: A Systematic Review. *J Low Genit Tract Dis, 24*(1), 1-13. doi:10.1097/lgt.0000000000000494

Chen, H. C., Schiffman, M., Lin, C. Y., Pan, M. H., You, S. L., Chuang, L. C., . . . Chen, C. J. (2011). Persistence of type-specific human papillomavirus infection and increased long-term risk of cervical cancer. *J Natl Cancer Inst, 103*(18), 1387-1396. doi:10.1093/jnci/djr283

Dahlstrom, L. A., Ylitalo, N., Sundstrom, K., Palmgren, J., Ploner, A., Eloranta, S., . . . Sparen, P. (2010). Prospective study of human papillomavirus and risk of cervical adenocarcinoma. *Int J Cancer, 127*(8), 1923-1930. doi:10.1002/ijc.25408

FDA. (2018a, 07/09/2018). BD ONCLARITY HPV ASSAY. *Devices@FDA.* Retrieved from https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?db=pma&id=391601

FDA. (2018b). BD ONCLARITY HPV ASSAY. Retrieved from https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?db=pma&id=391601

FDA. (2018c, 08/06/2018). PMA Monthly approvals from 7/1/2018 to 7/31/2018. Retrieved from https://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/UCM615947.pdf

FDA. (2019). Devices@FDA. *Devices@FDA.* Retrieved from https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm

FDA. (2020). Cobas HPV For Use On The Cobas 6800/8800 Systems. Retrieved from https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?db=pma&id=448383

Feldman, S., & Crum, C. (2019). Cervical cancer screening tests: Techniques for cervical cytology and human papillomavirus testing. In S. Falk & B. Goff (Eds.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/cervical-cancer-screening-tests-techniques-for-cervical-cytology-and-human-papillomavirus-testing

Feldman, S., & Crum, C. (2021, April 26). Cervical cancer screening tests: Techniques for cervical cytology and human papillomavirus testing. *UpToDate.* Retrieved from https://www.uptodate.com/contents/cervical-cancer-screening-tests-techniques-for-cervical-cytology-and-human-papillomavirus-testing

Feldman, S., Goodman, A., & Peipert, J. (2021, May 17). Screening for cervical cancer in resource-rich settings. *UpToDate.* Retrieved from https://www.uptodate.com/contents/screening-for-cervical-cancer-in-resource-rich-settings

Huh, W. K., Ault, K. A., Chelmow, D., Davey, D. D., Goulart, R. A., Garcia, F. A., . . . Einstein, M. H. (2015). Use of primary high-risk human papillomavirus testing for cervical cancer screening: interim clinical guidance. *J Low Genit Tract Dis, 19*(2), 91-96. doi:10.1097/lgt.0000000000000103

Marchand, L., Mundt, M., Klein, G., & Agarwal, S. C. (2005). Optimal collection technique and devices for a quality pap smear. *Wmj, 104*(6), 51-55.

Massad, L. S. (2018). Replacing the Pap Test With Screening Based on Human Papillomavirus Assays. *JAMA, 320*(1), 35-37. doi:10.1001/jama.2018.7911

Melnikow, J., Henderson, J. T., Burda, B. U., Senger, C. A., Durbin, S., & Weyrich, M. S. (2018). Screening for Cervical Cancer With High-Risk Human Papillomavirus Testing: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA, 320*(7), 687-705. doi:10.1001/jama.2018.10400

Mendez, K., Romaguera, J., Ortiz, A. P., Lopez, M., Steinau, M., & Unger, E. R. (2014). Urine-based human papillomavirus DNA testing as a screening tool for cervical cancer in high-risk women. *Int J Gynaecol Obstet, 124*(2), 151-155. doi:10.1016/j.ijgo.2013.07.036

Moscicki, A. B., Flowers, L., Huchko, M. J., Long, M. E., MacLaughlin, K. L., Murphy, J., . . . Gold, M. A. (2019). Guidelines for Cervical Cancer Screening in Immunosuppressed Women Without HIV Infection. *J Low Genit Tract Dis, 23*(2), 87-101. doi:10.1097/lgt.0000000000000468

NCCN. (2020, October 2). NCCN Clinical Practice Guidelines in Oncology - Cervical Cancer Version 1.2021. *NCCN Guidelines.* Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf

NCI. (2021, March 24). Cervical Cancer Screening (PDQ®)–Health Professional Version. Retrieved from https://www.cancer.gov/types/cervical/hp/cervical-screening-pdq

Ogilvie, G. S., van Niekerk, D., Krajden, M., Smith, L. W., Cook, D., Gondara, L., . . . Coldman, A. J. (2018). Effect of Screening With Primary Cervical HPV Testing vs Cytology Testing on High-grade Cervical Intraepithelial Neoplasia at 48 Months: The HPV FOCAL Randomized Clinical Trial. *JAMA, 320*(1), 43-52. doi:10.1001/jama.2018.7464

Pathak, N., Dodds, J., Zamora, J., & Khan, K. (2014). Accuracy of urinary human papillomavirus testing for presence of cervical HPV: systematic review and meta-analysis. *BMJ, 349*, g5264. doi:10.1136/bmj.g5264

Rice, S. L., Editor. (2018, August 2018). Cobas HPV test approved for first-line screening using SurePath preservative fluid. *CAP Today*.

Sabeena, S., Kuriakose, S., Binesh, D., Abdulmajeed, J., Dsouza, G., Ramachandran, A., . . . Arunkumar, G. (2019). The Utility of Urine-Based Sampling for Cervical Cancer Screening in Low-Resource Settings. *Asian Pac J Cancer Prev, 20*(8), 2409-2413. doi:10.31557/apjcp.2019.20.8.2409

Sasieni, P., Castanon, A., & Cuzick, J. (2009). Screening and adenocarcinoma of the cervix. *Int J Cancer, 125*(3), 525-529. doi:10.1002/ijc.24410

USPSTF. (2018a). Screening for cervical cancer: Us preventive services task force recommendation statement. *JAMA, 320*(7), 674-686. doi:10.1001/jama.2018.10897

USPSTF. (2018b). Screening for Cervical Cancer: US Preventive Services Task Force Recommendation StatementUSPSTF Recommendation: Screening for Cervical CancerUSPSTF Recommendation: Screening for Cervical Cancer. *JAMA, 320*(7), 674-686. doi:10.1001/jama.2018.10897

IX. Revision History

Revision Date	Summary of Changes
01/01/2022	Initial Effective Date

5/20/2022	Updated background, guidelines, and evidence-based scientific references. Literature review did not necessitate any modifications to the coverage criteria.