

**Cervical Cancer Screening**

Policy Number: AHS – G2002 – Cervical Cancer Screening	Prior Policy Name and Number, as applicable:
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**I. Policy Description**

Cervical cancer screening detects cervical precancerous lesions and cancer through cytology, human papillomavirus (HPV) testing, and if needed, colposcopy (Feldman et al., 2024). The principal screening test to detect cancer in asymptomatic individuals with a cervix 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, 2023).

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, 2023).

For additional information on testing for HPV, please refer to AHS-G2157-Diagnostic Testing of Common Sexually Transmitted Infections.

Terms such as male and female are used when necessary to refer to sex assigned at birth.

**II. Related Policies**

Policy Number	Policy Title
AHS-G2157	Diagnostic Testing of Common Sexually Transmitted Infections
AHS-M2057	Diagnosis of Vaginitis

**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. Specifications pertaining to Medicare and Medicaid can be found in the “Applicable State and Federal Regulations” section of this policy document.

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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. Within these coverage criteria, “individual(s)” is specific to individuals with a cervix.

- 1) For immunocompromised or immunosuppressed individuals, **any one** of the following cervical cancer screening techniques **MEETS COVERAGE CRITERIA**:
  - a) Annual cervical cytology testing for individuals of all ages.
  - b) Co-testing (cervical cytology and high-risk HPV testing) once every 3 years for individuals 30 years of age or older.
- 2) For individuals of all ages, cervical cancer screening using conventional or liquid-based Papanicolaou (Pap) smears **MEETS COVERAGE CRITERIA** at a frequency of once annually.
- 3) For individuals 30 to 65 years of age, **any one** of the following cervical cancer screening techniques **MEETS COVERAGE CRITERIA**:
  - a) Conventional or liquid-based Pap smear at a frequency of once annually.
  - b) Cervical cancer screening using the high-risk HPV test alone once every 5 years.
  - c) Co-testing (cytology with concurrent high-risk HPV testing) once every 5 years.
- 4) For individuals who are over 65 years of age **and** who are considered high-risk (individuals with a high-grade precancerous lesion or cervical cancer, individuals with in utero exposure to diethylstilbestrol (DES)), cervical cancer screening at the frequency described in coverage criterion 3 **MEETS COVERAGE CRITERIA**.
- 5) For individuals who are HPV positive **and** cytology negative, nucleic acid testing for high-risk strains HPV-16 and HPV-18 **MEETS COVERAGE CRITERIA**.
- 6) For individuals 65 years of age or younger, annual cervical cancer screening by Pap smear or HPV testing **MEETS COVERAGE CRITERIA** in **any** of the following situations:
  - a) For individuals who had a previous cervical cancer screen with an abnormal cytology result and/or who was positive for HPV.
  - b) For individuals at high risk for cervical cancer (organ transplant, exposure to the drug DES).
- 7) For individuals over 65 years of age who are not considered high-risk **and** who have an adequate screening history, routine cervical cancer screening **DOES NOT MEET COVERAGE CRITERIA**. Adequate screening history is defined as either:
  - a) Having three consecutive negative Pap smears.
  - b) Having two consecutive negative HPV tests within 10 years before cessation of screening, with the most recent test occurring within 5 years.

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- 8) For individuals who have undergone surgical removal of the uterus and cervix and who have no history of cervical cancer or pre-cancer, cervical cancer screening (at any age) **DOES NOT MEET COVERAGE CRITERIA.**

*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 an individual’s illness.*

- 9) The following **DO NOT MEET COVERAGE CRITERIA:**
  - a) Inclusion of low-risk strains of HPV in co-testing.
  - b) Other technologies for cervical cancer screening.

#### IV. Table of Terminology

Term	Definition
ACOG	American College of Obstetricians and Gynecologists
ACS	American Cancer Society
AIS	Adenocarcinoma in situ
ASCCP	American Society for Colposcopy and Cervical Pathology
ASC-H	Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion
ASCO	American Society of Clinical Oncology
ASCP	American Society of Clinical pathology
ASCUS	Atypical squamous cells of undetermined significance
CIN (2, 3, 3+)	Cervical intraepithelial neoplasia (Grade 2, 3, 3+)
CLIA '88	Clinical Laboratory Improvement Amendments Of 1988
CMS	Centers For Medicare and Medicaid Services
DES	Diethylstilbestrol
DNA	Deoxyribonucleic acid
EASC	European AIDS Clinical Society
FDA	Food and Drug Administration
GvHD	Graft versus/against the host disease
HGSIL/HSIL	High-grade squamous intraepithelial lesion
HHS	Health and Human Services
HIV	Human immunodeficiency virus
HPV	Human papillomavirus infection
HSCT	Hematopoietic stem cell transplantation
IPD	Individual participant data
JAMA	Journal of the American Medical Association
LDTs	Laboratory developed tests
LEEP	Loop electrosurgical excision procedure
LGSIL/LSIL	Low-grade squamous intraepithelial lesion
mRNA	Messenger ribonucleic acid
NAAT	Nucleic acid amplification test

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NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
Pap	Papanicolaou
PCR	Polymerase chain reaction
RNA	Ribonucleic acid
SGO	Society of Gynecologic Oncology
STIs	Sexually transmitted infections
USPSTF	United States Preventive Services Task Force
VAT	Visual assessment for treatment
VIA	Visual inspection with acetic acid
VIAC	Visual inspection with acetic acid and digital cervicography

## V. Scientific Background

The American Cancer Society estimates that 13,820 new cases of cervical cancer will be diagnosed in 2024 and approximately 4,360 of these individuals will die from the disease (ACS, 2023). 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 can be performed on samples obtained from a tampon, Dacron or cotton swab, cytobrush, or cervicovaginal lavage (Feldman & Crum, 2023).

Cervical cancer screening recommendations for average-risk individuals generally fall into categories based on an individual’s age (William R Robinson, 2024b):

- Age < 21 – It is suggested to not screen for cervical cancer in asymptomatic and immunocompetent patients (as observational studies show a low incidence and benefits may outweigh the harms of false positives).
- Age 21 to 29 – In average patients that are asymptomatic and immunocompetent, the age at which to initiate screening is contested and the ideal testing method varies by guideline. Opinions for expert groups also vary. A preference for cytology (rather than HPV testing) for this subgroup is based on a meta-analysis of randomized trials that revealed higher false positive rates for HPV testing.
- Age 30 to 65 – It is recommended that cervical cancer screening continues in all immunocompetent and asymptomatic individuals with a cervix. The methods range from

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primary HPV testing every 5 years to co-testing (Pap and HPV testing) every five years; or a Pap test alone every three years.

- Age >65 years – The decision to halt cervical cancer screening in asymptomatic and immunocompetent patients can depend on factors such as prior screening results, life expectancy, and patient preference, but it is suggested to discontinue screening for this subgroup if there has been adequate prior screening.

The above recommendations do not account for special populations such as patients with HIV, immunosuppression, and in utero exposure to diethylstilbestrol (DES). These populations are at greater risk for developing cervical cancer (William R Robinson, 2024b).

The following are the initial screening recommendations for individuals with HIV (William R Robinson, 2024a):

- Initial screening for HIV should occur when HIV is first diagnosed (but at no earlier than 21 years of age).
- Age 21 to 29 – Cervical cytology is the preferred method for screening.
- Age 30 years or older – Cervical cytology or co-testing are both appropriate. However, the use of HPV testing alone (i.e., without co-testing) is NOT recommended for this subgroup.

For patients with HIV in whom initial screening is normal, subsequent screening is categorized based upon method (i.e., cervical cytology, co-testing, colposcopy)(William R Robinson, 2024a):

- Cervical cytology: Those screened with cervical cytology (patients 21 to 29 years and those 30 and older) should have cervical cytology performed every 12 months for a total of three years. If results of three consecutive cytology tests are normal, a follow-up test can occur every three years.
- Co-testing: Those screened with co-testing (30 years and older) should have this co-testing occur every three years.
- Colposcopy: Should not be performed routinely at follow-up visits.
- Screening in the HIV population should occur throughout a patient’s lifetime and should not stop at 65 years old (contrasted against the general average patient recommendations, which suggest discontinuing at 65 years old).

### ***Analytical Validity***

A study by Marchand et al. (2005) explored the optimal collection technique for Pap testing. Their study occurred in two different cytology labs and 128 clinicians participated in the study over the course of one year. The authors 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 concluded, “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 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 certain subgroups, urine testing should be regarded as an acceptable alternative” (Pathak et al., 2014).

### ***Clinical Utility and Validity***

The National Cancer Institute (NCI) reports that “Regular Pap screening decreases cervix cancer incidence and mortality by at least 80%” (NCI, 2024). They also note that Pap testing can result in the possibility of additional diagnostic testing, especially in younger individuals, when unwarranted, especially in cases of possible low-grade squamous intraepithelial lesions (LSILs); however, even though 50% of individuals 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, 2024).

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, 2024) state that, although the rates of both incidence and mortality of squamous cell carcinoma of the cervix have 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 increase in adenocarcinoma findings because the risk-reduction associated with three yearly screenings was reduced by 75% for squamous carcinoma and 83% for adenosquamous carcinoma, but adenocarcinoma was reduced only by 43% (Sasiemi et al., 2009). Another extensive study of more than 900,000 individuals in Sweden showed that PCR-based HPV testing

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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 individuals participating in the study, 86% of those who tested positive for HPV did not develop cervical cancer within 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 [individuals] 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 a multi-year cervical cancer screening trial (FOCAL) were published. This randomized clinical trial tested the use of HPV testing alone for detection of cervical intraepithelial neoplasia (CIN) grade 3 or worse (CIN3+). More than 19,000 individuals participated in the study—split between the intervention group (HPV testing alone) and the control group (liquid-based cytology). Among individuals who underwent cervical cancer screening, the use of primary HPV testing as 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 noted 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 did not address the limitations of the FOCAL study, including that the study concluded prior to seeing what effects, if any, those 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 et al. (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 individuals “screened through the primary HPV

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paradigm and the co-testing paradigm by stratifying genotype-specific results and thereby assign those 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).

Between 2010 and 2019, Pry et al. (2021) reviewed 204,225 results from 183,165 study participants across 11 government health facilities in Lusaka, Zambia, as part of the Cervical Cancer Prevention Program in Zambia (CCPPZ). By examining precancerous lesions via visual inspection with acetic acid and digital cervicography (VIAC), they were able to show that the highest odds for screening positive are among individuals aged 20–29 years and that individuals “in the 30–39 years age group had the highest proportion of positive screening results (11.3%) among those with age recorded”; interestingly, however, those “who were HIV-positive and younger than 20 years had more than three times the predictive probability (18.4, 95% CI 9.56–27.32) for being positive compared with [individuals] who were HIV-negative in the same age group (predictive probability 5.5%, 95% CI 3.2–7.8)” (Pry et al., 2021). But while the high proportion of the screen positivity in individuals younger than 20 years old may suggest that individuals “with HIV have earlier disease progression” and that these individuals “should be engaged in screening at a younger age”, these data could be the result of “some misalignment between screening test positivity and neoplastic lesions, as visually, cervicitis and other benign cervical lesions could be mistaken for pre-cancerous disease” or even simply the inherent weaknesses in the test accuracy of the VIAC method (“sensitivity from 25% (95% CI 7–59) to 82% (66–95) and specificity from 74% (64–82) to 83% (77–87)”), warranting further examination (Pry et al., 2021).

Many guidelines call for the cessation of cervical cancer screening after the age of 65; however, Dilley et al. (2021) argues for a reevaluation of recommendations of this ilk, given that 20% of new cervical cancers occur in this group. Moreover, elderly individuals with a cervix are not only more likely to be diagnosed with late-stage cancer, but also receive commensurately worse outcomes and higher mortality rates. The authors point to the use of theoretical modelling and expert opinion as leading drivers of misconceptions about cervical screening harm in older individuals, specifying that while many of the models seek to minimize the harms and costs associated with increased colposcopies, they are remiss in their consideration of the costs and benefits of “the treatment of advanced cancer, such as cold knife conization, radical hysterectomy, pelvic radiation therapy and chemotherapy” and in their interpretation of exiguous data on the benefits and harms of screening after 65. Furthermore, though the existing guidelines suggest that “the guidelines account for the importance of adequate prior screening before cessation of screening,” as the majority of cervical cancer cases are diagnosed in individuals who have not been adequately screened, the authors counter that studies have shown that only 25–50% of individuals diagnosed with cervical cancer had “adequate prior screening” before their cancer diagnosis, which will only be further exacerbated as the population continues to age (Dilley et al., 2021).

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Qin et al. (2023) studied annual trends in cervical cancer screening-associated services in average-risk women 65 years or older with adequate prior screening. The US Preventative Services Task Force recommends against cervical cancer screening for women 65 years or older with adequate prior screening. Data was collected between 1999 and 2019 from over 15 million (N=15323635) women between the ages of 65 and 114 with Medicare free-for-service coverage. “From 1999 to 2019, the percentage of women who received at least 1 cytology or HPV test decreased from 18.9% (2.9 million women) in 1999 to 8.5% (1.3 million women) in 2019, a reduction of 55.3%; use rates of colposcopy and cervical procedures decreased 43.2% and 64.4%, respectively.” Further, “the total Medicare expenditure for all services rendered in 2019 was about \$83.5 million.” The authors concluded that “while annual use of cervical cancer screening-associated services in the Medicare fee-for-service population older than 65 years has decreased during the last 2 decades, more than 1.3 million women received these services in 2019 at substantial costs” (Qin et al., 2023).

Winer et al. (2023) studied the effectiveness of direct-mail and opt-in approaches for offering HPV self-sampling kits. The kits were offered, by mail or opt-in, to females between the ages of 30 and 64 who had been previously screened, at least three months prior, and were due for their next screening. A total of 31,355 participants were included. Participants were classified in three groups: those due for screening, those overdue for screening, or individuals with unknown history of screening. Within each group, individuals were randomly assigned to receive usual care, education (usual care plus educational materials about screening), direct mail (usual care, educational materials, and a mailed self-sampling kit), or opt-in (usual care, education, and the option to request a kit). In individuals due for screening, screening completion was 14.1% higher in the direct-mail group than the education group, and 3.5% higher in the opt-in group than the education group. In individuals overdue for screening, screening completion was 16.9% higher in the direct-mail group than the education group. In individuals with unknown history, screening was 2.2% higher in the opt-in group than the education group. The authors concluded that “within a US health care system, direct-mail self-sampling increased cervical cancer screening by more than 14% in individuals who were due or overdue for cervical cancer screening” and “the opt-in approach minimally increased screening” (Winer et al., 2023).

## VI. Guidelines and Recommendations

### U.S. Preventive Services Task Force (USPSTF)

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

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The USPSTF Summary of Recommendations and Evidence (USPSTF, 2018):

Population	Recommendation	Grade
<b>Women 21 to 65 years of age</b>	For women 21 to 29 years of age, screen for cervical cancer every 3 years with cytology alone. For women 30 to 65 years of age, 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
<b>Women younger than 21, older than 65, who have had adequate prior screening, or who have had</b>	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

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 (i.e., screening for cervical cancer with a Papanicolaou smear, screening for gonorrhea and chlamydia).”

**National Comprehensive Cancer Network (NCCN)**

Regarding the diagnosis and workup for cervical cancer, the NCCN states that “The earliest stages of cervical carcinoma may be asymptomatic or associated with a watery vaginal discharge and postcoital bleeding or intermittent spotting. Often these early symptoms are not recognized by the patient. Because of the accessibility of the uterine cervix, cervical cytology or Papanicolaou (Pap) smears and cervical biopsies can usually result in an accurate diagnosis. Cone biopsy (i.e., conization) is recommended if the cervical biopsy is inadequate to define invasiveness or if accurate assessment of microinvasive disease is required... However, cervical cytologic screening methods are less useful for diagnosing adenocarcinoma, because adenocarcinoma in situ affects areas of the cervix that are harder to sample (i.e., endocervical canal)” and that “Workup for these patients with suspicious symptoms includes history and physical examination, complete blood count (CBC, including platelets), and liver and renal function tests” (NCCN, 2024).

The NCCN also remarked that “Persistent 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,” adducing that “In developed countries, the substantial decline in incidence and mortality of SCC of the cervix is presumed to be the result of effective screening and higher human papillomavirus (HPV)-vaccination coverage, although racial, ethnic, and geographic disparities exist” (NCCN, 2024). As such, the NCCN lists chronic, persistent HPV

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infection along with persistently abnormal Pap smear tests as criteria to be considered for women contemplating hysterectomy.

### **National Cancer Institute (NCI)**

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 possible overtreatment for low-grade squamous intraepithelial lesions (LSILs). 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. Excisional procedures to treat preinvasive disease has been associated with increased risk of long-term consequences for fertility and pregnancy” (NCI, 2024).

Concerning the use of HPV DNA testing, the NCI states: “Based on solid evidence, screening with an 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, 2024).

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, 2024).

Regarding screening women without a cervix, they recommend: “Based on solid evidence, screening is not helpful in women who do not have a cervix as a result of a hysterectomy for a benign condition” (NCI, 2024).

### **American Cancer Society (ACS)**

The American Cancer Society updated their guidelines for cervical cancer screening for individuals at average risk in 2020. Their recommendations are summarized below:

(Adapted from Table 2 of (Fontham et al., 2020), *Comparison of Current and Previous American Cancer Society (ACS) Guidelines for Cervical Cancer Screening*)

Population	2020 ACS Recommendation
Age 21-24	No screening
Age 25-29	HPV test every 5 years (preferred) HPV/Pap cotest every 5 years (acceptable) Pap test every 3 years (acceptable)
Age 30-65	HPV test every 5 years (preferred) HPV/Pap cotest every 5 years (acceptable) Pap test every 3 years (acceptable)
Age 65 and older	No screening if a series of prior tests were normal

(Fontham et al., 2020).

### The American Society for Colposcopy and Cervical Pathology (ASCCP)

In 2019, the ASCCP 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
<b>Solid organ transplant</b>	<ul style="list-style-type: none"> <li>• Cytology is recommended if younger than 30 y</li> <li>• Co-testing is preferred, but cytology is acceptable if 30 y or older</li> <li>• If using cytology alone, perform annual cervical cytology. If results of 3 consecutive cytology results are normal, perform cytology every 3 y</li> <li>• 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</li> <li>• If transplant before the age of 21 y, begin screening within 1 y of sexual debut</li> <li>• Continue screening throughout lifetime (older than 65 y). Discontinue screening based on shared discussion regarding quality and duration of life rather than age</li> </ul>
<b>Allogeneic hematopoietic stem cell transplant</b>	<ul style="list-style-type: none"> <li>• Cytology is recommended if younger than 30 y</li> <li>• Co-testing is preferred, but cytology is acceptable if 30 y or older</li> <li>• If using cytology alone, perform annual cervical cytology. If results of 3 consecutive cytology results are normal, perform cytology every 3 y</li> </ul>

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Risk group category	Recommendation
	<ul style="list-style-type: none"> <li>• 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</li> <li>• If transplant before the age of 21 y, begin screening within 1 y of sexual debut</li> <li>• Continue screening throughout lifetime (older than 65 y). Discontinue screening based on shared discussion regarding quality and duration of life rather than age</li> <li>• 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</li> </ul>
<b>Inflammatory bowel disease on immunosuppressant treatments</b>	<ul style="list-style-type: none"> <li>• Cytology is recommended if younger than 30 y</li> <li>• Co-testing is preferred, but cytology is acceptable if 30 y or older</li> <li>• If using cytology alone, perform annual cervical cytology. If results of 3 consecutive cytology results are normal, perform cytology every 3 y</li> <li>• 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</li> <li>• If on immunosuppressant therapy before the age of 21 y, begin screening within 1 y of sexual debut</li> <li>• Continue screening throughout lifetime (older than 65 y). Discontinue screening based on shared discussion regarding quality and duration of life rather than age</li> </ul>
<b>Inflammatory bowel disease not on immunosuppressant treatment</b>	<ul style="list-style-type: none"> <li>• Follow general population screening guidelines</li> </ul>
<b>Systemic lupus erythematosus and rheumatoid arthritis on immunosuppressant treatments</b>	<ul style="list-style-type: none"> <li>• Cytology is recommended if younger than 30 y</li> <li>• Co-testing is preferred, but cytology is acceptable if 30 y or older</li> <li>• If using cytology alone, perform annual cervical cytology. If results of 3 consecutive cytology results are normal, perform cytology every 3 y</li> <li>• 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</li> <li>• If on immunosuppressant therapy before the age of 21 y, begin screening within 1 y of sexual debut</li> </ul>

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Risk group category	Recommendation
	<ul style="list-style-type: none"> <li>Continue screening throughout lifetime (older than 65 y). Discontinue screening based on shared discussion regarding quality and duration of life rather than age</li> </ul>
<b>Rheumatoid arthritis not on immunosuppressive treatments</b>	<ul style="list-style-type: none"> <li>Follow general population screening guidelines</li> </ul>
<b>Type 1 diabetes mellitus</b>	<ul style="list-style-type: none"> <li>Follow general population screening guidelines</li> </ul>

**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**

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 regarding 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.”

Moreover, they give the following screening algorithm (Huh et al., 2015):

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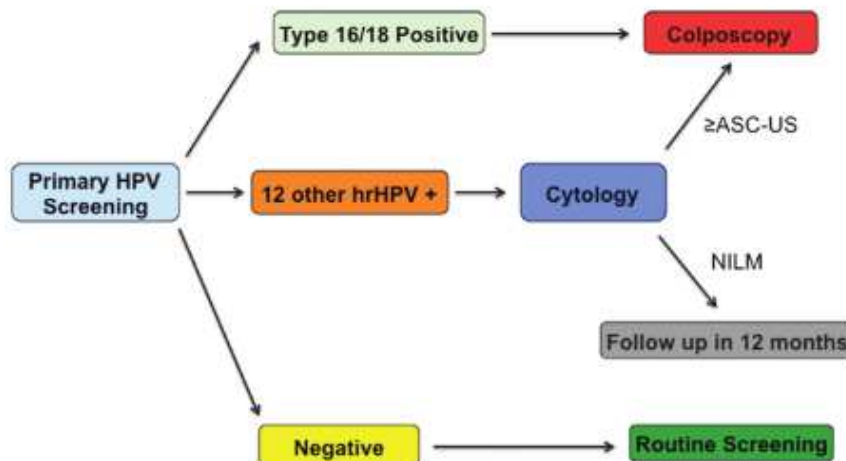


FIGURE 1. Recommended primary HPV screening algorithm. HPV, human papillomavirus; hrHPV, high-risk human papillomavirus; ASC-US, atypical squamous cells of undetermined significance; NILM, negative for intraepithelial lesion or malignancy.

### American College of Obstetricians and Gynecologists (ACOG)

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.” This was reaffirmed in 2023 (ACOG, 2021).

In October 2020, the ACOG released “Updated Guidelines for Management of Cervical Cancer Screening Abnormalities.” These 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+ (e.g., 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.

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- b. HPV 16 or 18 infections have the highest risk for CIN 3 and occult cancer, so additional evaluation (e.g., 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).

### **European AIDS Clinical Society (EASC)**

The EASC recommends cervical cancer screening (PAP smear or liquid based cervical cytology test) for women over 21 years of age every one to three years. Additionally, the EASC notes “HPV genotype testing may aid PAP/liquid based cervical screening” (EASC, 2023).

### **United States Department of Health and Human Services (HHS)**

The US HHS guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV recommend the following cervical cancer screening:

- “Women with HIV Aged <30 Years:
  - WWH aged 21 to 29 years should have a Pap test following initial diagnosis of HIV.
  - Pap test should be done at baseline and every 12 months (BII).
  - If the results of three consecutive Pap tests are normal, follow-up Pap tests can be performed every 3 years (BII).
  - Co-testing (Pap test and HPV test) is not recommended for women younger than 30 years.

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- Women with HIV Aged  $\geq 30$  Years:
  - Pap Testing Only
    - Pap test should be done at baseline and every 12 months (BII).
    - If results of 3 consecutive Pap tests are normal, follow-up Pap tests can be performed every 3 years (BII). *Or*
  - Pap Test and HPV Co-Testing
    - Pap test and HPV co-testing should be done at baseline (BII).
    - If result of the Pap test is normal and HPV co-testing is negative, follow up Pap test and HPV co-testing can be performed every 3 years (BII).
    - If the result of the Pap test is normal but HPV co-testing is positive: *Either:*
      - Follow up test with Pap test and HPV co-testing should be performed in 1 year.
      - If the 1-year follow-up Pap test is abnormal, or HPV co-testing is positive, referral to colposcopy is recommended. *Or:*
      - Perform HPV genotyping.
      - If positive for HPV-16 or HPV-18, colposcopy is recommended.
      - If negative for HPV-16 and HPV-18, repeat co-test in 1 year is recommended. If the follow-up HPV test is positive or Pap test is abnormal, colposcopy is recommended: *Or:*
  - Pap Test and HPV16 or HPV16/18 Specified in Co-Testing
    - Pap test and HPV 16 or 16/18 co-testing should be done at baseline (BII).
    - If result of the Pap test is normal, and HPV 16 or 16/18 co-testing is negative, follow-up Pap test and HPV co-testing can be performed every 3 years (BII).
    - If initial test or follow-up test is positive for HPV 16 or 16/18, referral to colposcopy is recommended (BII).
- Primary HPV testing is not recommended (CIII)” (HHS, 2024).

### American Society for Clinical Oncology (ASCO)

Resource-stratified recommendations were released in 2022 from the American Society for Clinical Oncology.

For maximal-based resource settings:

- “1.1. In maximal-resource settings, cervical cancer screening with HPV DNA testing should be offered every 5 years from age 25 to 65 years (either self- or clinician-collected). On an individual basis, women may elect to receive screening until age 70 years.
- 1.2. Women who are  $\geq 65$  years of age who have had consistently negative screening results during past  $\geq 15$  years may cease screening. Women who are 65 years of age and have a positive result after age 60 should be reinvited to undergo screening 2, 5, and 10 years after the last positive result. If women have received no or irregular screening, they should undergo screening once at 65 years of age, and if the result is negative, exit screening.
- 1.3. If the results of the HPV DNA test are positive, clinicians should then perform triage with reflex genotyping for HPV 16/18 (with or without HPV 45) and/or cytology as soon as HPV test results are known.

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- 1.4. If triage results are abnormal (ie,  $\geq$  ASC-US or positive for HPV 16/18 [with or without HPV 45]), women should be referred to colposcopy, during which biopsies of any acetowhite (or suggestive of cancer) areas should be taken, even if the acetowhite lesion might appear insignificant. If triage results are negative (e.g., primary HPV positive and cytology triage negative), then repeat HPV testing at the 12-month follow-up.
- 1.5. If HPV test results are positive at the repeat 12-month follow-up, refer women to colposcopy. If HPV test results are negative at the 12- and 24-month follow-up or negative at any consecutive HPV test 12 months apart, then women should return to routine screening.
- 1.6. Women who have received HPV and cytology co-testing triage and have HPV-positive results and abnormal cytology should be referred for colposcopy and biopsy. If results are HPV positive and cytology normal, repeat co-testing at 12 months. If at repeat testing HPV is still positive, patients should be referred for colposcopy and biopsy, regardless of cytology results.
- 1.7. If the results of the biopsy indicate that women have precursor lesions (CIN2+), then clinicians should offer loop electrosurgical excision procedure (LEEP; if there is a high level of quality assurance [QA]) or, where LEEP is contraindicated, ablative treatments may be offered.
- 1.8. After women receive treatment for precursor lesions, follow-up should consist of HPV DNA testing at 12 months. If 12-month results are positive, continue annual screening; if not, return to routine screening” (ASCO, 2022).

In enhanced-resource settings:

- “2.1. In enhanced-resource settings, cervical cancer screening with HPV DNA testing should be offered to women age 30-65 years, every 5 years (i.e., second screen 5 years from the first) (either self- or clinician-collected).
- 2.2. If there are two consecutive negative screening test results, subsequent screening should be extended to every 10 years.
- 2.3. Women who are  $\geq$  65 years of age who have had consistently negative screening results during past  $\geq$  15 years may cease screening. Women who are 65 years of age and have a positive result after age 60 should be reinvited to undergo screening 2, 5, and 10 years after the last positive result. If women have received no or irregular screening, they should undergo screening once at 65 years of age, and if the result is negative, exit screening.
- 2.4. If the results of the HPV DNA test are positive, clinicians should then perform triage with HPV genotyping for HPV 16/18 (with or without HPV 45) and/or reflex cytology.
- 2.5. If triage results are abnormal (ie,  $\geq$ ASC-US or positive for HPV 16/18 [with or without HPV 45]), women should be referred to colposcopy, during which biopsies of any acetowhite (or suggestive of cancer) areas should be taken, even if the acetowhite lesion might appear insignificant. If triage results are negative (e.g., primary HPV positive and cytology triage negative), then repeat HPV testing at the 12 month follow-up.
- 2.6. If HPV test results are positive at the repeat 12-month follow-up, refer women to colposcopy. If HPV test results are negative at the 12- and 24-month follow-up or negative

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at any consecutive HPV test 12 months apart, then women should return to routine screening.

- 2.7. If the results of colposcopy and biopsy indicate that women have precursor lesions (CIN2+), then clinicians should offer LEEP (if there is a high level of QA) or, where LEEP is contradicted, ablative treatments may be offered.
- 2.8. After women receive treatment for precursor lesions, follow-up should consist of HPV DNA testing at 12 months. If 12-month results are positive, continue annual screening; if not, return to routine screening” (ASCO, 2022).

In limited settings:

- “3.1. In limited settings, cervical cancer screening with HPV DNA testing should be offered to women 30 to 49 years of age every 10 years, corresponding to 2 to 3 times per lifetime (either self- or clinician-collected).
- 3.2. If the results of the HPV DNA test are positive, clinicians should then perform triage with reflex cytology (quality assured) and/or HPV genotyping for HPV 16/18 (with or without HPV 45) or with VIA. If institutions are currently using reflex cytology, they should transition from cytology to HPV genotyping.
- 3.3. If cytology triage results are abnormal (i.e.  $\geq$  atypical squamous cells of undetermined significance [ASC-US]), women should be referred to quality assured colposcopy (the first choice, if available and accessible for women who are ineligible for thermal ablation), during which biopsies of any acetowhite (or suggestive of cancer) areas should be taken, even if the acetowhite lesion might appear insignificant. If colposcopy is not available, then perform VAT.
- 3.4. If HPV genotyping or VIA or VAT triage results are positive, then women should be treated. If the results from these forms of triage are negative, then repeat HPV testing at the 12-month follow-up.
- 3.5. If test results are positive at the repeat 12-month follow-up, then women should be treated.
- 3.6. For treatment, clinicians should offer ablation if the criteria are satisfied; if not and resources available, then offer LEEP.
- 3.7. After women receive treatment for precursor lesions, follow-up should consist of the same testing at 12 months” (ASCO, 2022).

Finally, in basic settings:

- “4.1. Health systems in basic settings should move to population-based screening with HPV testing at the earliest opportunity (either self- or clinician-collected). If HPV DNA testing for cervical cancer screening is not available, then VIA should be offered with the goal of developing health systems. Screening should be offered to women 30 to 49 years of age, at least every 10 years (increasing the frequency to every 5 years, resources permitting).

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- 4.2. If the results of available HPV testing are positive, clinicians should then perform VAT followed by treatment with thermal ablation and/or LEEP, depending on the size and location of the lesion.
- 4.3. If primary screening is VIA and results are positive, then treatment should be offered with thermal ablation and/or LEEP, depending on the size and location of the lesion.
- 4.4. After women receive treatment for precursor lesions, then follow up with the available test at 12 months. If the result is negative, then women return to routine screening” (ASCO, 2022).

## VII. Applicable State and Federal Regulations

**DISCLAIMER:** If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: <https://www.cms.gov/medicare-coverage-database/search.aspx>. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

### Food and Drug Administration (FDA)

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 October 12, 2012; however, this test cannot distinguish between 18 and 45. Previously, on October 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 March 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, 2023a).

The COBAS HPV test by Roche Molecular Systems, Inc. was approved by the FDA on April 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 July 2, 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, 2023c). 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, 2023b).

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

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by a clinician using an endocervical brush/spatula combination or broom and placed in BD SurePath vial” (FDA, 2018).

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

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). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

### VIII. Applicable CPT/HCPCS Procedure Codes

CPT	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

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CPT	Code Description
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)
0502U	Human papillomavirus (HPV), E6/E7 markers for high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), cervical cells, branched-chain capture hybridization, reported as negative or positive for high risk for HPV Proprietary test: QuantiVirus™ HPV E6/E7 mRNA Test for Cervical Cancer Lab/Manufacturer: DiaCarta, Inc
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

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CPT	Code Description
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

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

## IX. Evidence-based Scientific References

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

Effective Date	Summary
01/01/2025	<p>Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review necessitated the following changes to coverage criteria:</p> <p>CC1 edited to include immunocompromised, now reads: “1) For immunocompromised or immunosuppressed individuals, any one of the following cervical cancer screening techniques MEETS COVERAGE CRITERIA:”</p> <p>Results in removal of “immunocompromised individuals” from CC4 and CC6.b., as it conflicts with the updated societal recommendations outlined in CC1.</p> <p>CC1.a. changed from individuals under 30 to individuals of all ages. Previously read: “a) Annual cervical cytology testing for individuals less than 30 years of age.” Now reads: “a) Annual cervical cytology testing for individuals of all ages.”</p> <p>Added “high-risk” to CC1.b. for clarity of appropriate testing, now reads: “b) Co-testing (cervical cytology and high-risk HPV) once every 3 years for individuals 30 years of age or older.”</p> <p>Added “(DES)” to CC4 to define the initialism that is repeated later in CC6b.</p> <p>For clarity on allowed test type for high-risk HPV, “nucleic acid” added to CC5. Now reads: “5) For individuals who are HPV positive and cytology negative, nucleic acid testing for high-risk strains HPV-16 and HPV-18 MEETS COVERAGE CRITERIA.”</p> <p>Added “For individuals 65 years of age or younger,” to CC6. Now reads: “6) For individuals 65 years of age or younger, annual cervical cancer screening by Pap smear or HPV testing MEETS COVERAGE CRITERIA in any of the following situations:”</p> <p>Added CPT code 0502U (effective date 10/1/2024)</p>
05/01/2024	<p>Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review necessitated the following changes to coverage criteria:</p> <p>Removal of CC1 “1) In individuals who are under 21 years of age, cervical cancer screening MEETS COVERAGE CRITERIA only when one of the following criteria are met:</p> <ul style="list-style-type: none"> <li>a) There is a history of HIV and/or other non-HIV immunocompromised conditions.</li> <li>b) There is a previous diagnosis of cervical cancer.</li> <li>c) There is a previous diagnosis of cervical dysplasia.</li> <li>d) There is a history of an organ transplant.”</li> </ul> <p>Switched the order of CC4 and CC5 such that testing for high-risk individuals over 65 immediately follows frequency testing for those 30-65.</p>

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	<p>Now CC4 edited for clarity on frequency of testing allowed in high-risk individuals over 65.</p> <p>All CC except CC9 edited for clarity and consistency. Changed “women” to “individuals” in CC6.</p> <p>Client Requested Variance: CC2 changed to read, "For individuals of all ages, cervical cancer screening using conventional or liquid -based Papanicolaou (Pap) smears MEETS COVERAGE CRITERIA at a frequency of once annually." CC3a changed to read, "Conventional or liquid-based Pap smear at a frequency of once annually." CC7 removed, "7) For all situations not addressed above, cervical cancer screening (cervical cytology, HPV testing) for individuals less than 21 years of age DOES NOT MEET COVERAGE CRITERIA."</p>
<p>03/10/2023</p>	<p>Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. The following edits were made for clarity:</p> <p>“Women” changed to “individuals” throughout coverage criteria. A note was wadded before CC to indicate “Within these coverage criteria, “individual” is specific to individuals with a cervix.” The portion before CC now reads: “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. Within these coverage criteria, “individual” is specific to individuals with a cervix.”</p> <p>CC2, CC6, CC8, CC9 edited for clarity and consistency.</p> <p>CC1 language changed from “DNMCC except” to “MCC only when” to match the overall formatting of the rest of our CC.</p> <p>CC4 previously formatted as a single sentence, now formatted with subcriteria for better clarity. Now reads: “For individuals 30 - 65 years of age, any one of the following cervical cancer screening techniques MEETS COVERAGE CRITERIA:</p> <ul style="list-style-type: none"> <li>a) Conventional or liquid-based Pap smear at a frequency of every 3 years.</li> <li>b) Cervical cancer screening using the high-risk HPV test alone at a frequency of every 5 years.</li> <li>c) Co-testing (cytology with concurrent high-risk HPV testing) at a frequency of every 5 years.”</li> </ul> <p>CC5 previously formatted with subcriteria, now reads as a single main criteria: “For individuals who are HPV positive and cytology negative, testing for high-risk strains HPV-16 and HPV-18 MEETS COVERAGE CRITERIA.”</p>

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	<p>Former CC8 moved to CC7 so that all MCC come before all DNMCC. Previously, formatted as a single sentence. Now formatted with subcriteria for better clarity. Now reads: “Repeat cervical cancer screening by Pap smear or HPV testing in one year MEETS COVERAGE CRITERIA in the following individuals:</p> <ul style="list-style-type: none"> <li>a) For individuals who had a previous cervical cancer screen with an abnormal cytology result and/or who was positive for HPV.</li> <li>b) For individuals at high risk for cervical cancer (organ transplant, exposure to the drug DES, immunocompromised individuals).”</li> </ul>
08/16/2022	<p>Revision clarifies intent of CC#3 for Papanicolaou (Pap) smear to MEET COVERAGE CRITERIA annually. Updated CC#4 for clarity to read: For women age 30 and up, 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.</p>
05/15/2022	<p>Initial Policy Implementation</p>

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