Cervical cancer and human papillomavirus screening

Clinical Policy ID: CCP.1280

Recent review date: 11/2025

Next review date: 3/2027

Policy contains: Cervical cancer; cytology (Papanicolaou test); high-risk human papillomavirus test.

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Coverage policy

Screening for cervical cancer and human papillomavirus using clinician-collected samples is clinically proven and, therefore, may be medically necessary when all of the following criteria are met (National Institutes of Health, 2019; American College of Obstetricians and Gynecologists, 2019; U.S. Preventive Services Task Force, 2018):

- All female members ages 21 to 65 years with a cervix without signs or symptoms of cervical cancer, regardless of their sexual history or human papillomavirus vaccination status, and not at high risk[1] for cervical cancer.
- Screening intervals:
- Age 21 to 29 years — Pap cytology alone every three years.
- Age 30 to 65 years — Pap cytology combined with high-risk human papillomavirus co-testing every five years, high-risk human papillomavirus testing alone every five years, or Pap cytology alone every three years.

[1] Factors associated with increased risk of cervical cancer include a compromised immune system, in utero exposure to diethylstilbestrol, and previous treatment of a high-grade precancerous lesion or cervical cancer.

- Routine screening should continue for at least 20 years after spontaneous regression or appropriate management of a high-grade precancerous lesion, even if this extends screening past age 65 years.
- Age > 65 years who have not been adequately screened or are otherwise at high risk.
- End of screening criteria:
- Age > 65 years assuming three consecutive negative results on cytology or two consecutive negative results on co-testing within 10 years before cessation of screening, with the most recent test performed within five years.
- Total hysterectomy (specifically for members without a cervix and without a history of cervical intra-epithelial neoplasia 2, cervical intra-epithelial neoplasia 3, adenocarcinoma *in situ*, or cancer in the past 20 years).
- Once screening has stopped, it should not resume in women ages 65 years or older, even if they report having a new sexual partner.
- Members at high risk for cervical cancer should receive individualized follow-up.

Limitations

All other screening tests for cervical cancer and human papillomavirus are not medically necessary, including high risk human papillomavirus testing using vaginal deoxyribonucleic acid or Papanicolaou liquid-based cytology using self-sampling devices (American College of Obstetricians and Gynecologists, 2019; Arbyn, 2018).

Cervical cancer screening is not medically necessary for members (American College of Obstetricians and Gynecologists, 2016, 2019; U.S. Preventive Services Task Force, 2018):

- Younger than 21 years.
- Older than 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer.
- Who have had a hysterectomy with removal of the cervix and do not have a history of a high-grade precancerous lesion or cervical cancer.

There is no role for testing for low-risk genotypes, and tests for low-risk human papillomavirus should not be performed (American College of Obstetricians and Gynecologists, 2019; U.S. Preventive Services Task Force, 2018).

Alternative covered services

Human papillomavirus vaccination in accordance with the recommendations of the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices listed in the appendix.

Background

Cervical cancer is one of the most common malignancies in women and remains a significant cause of morbidity and mortality worldwide. Despite decreasing mortality rates for all U.S. women, significant racial disparities in the risk of death from cervical cancer persist (National Cancer Institute, 2023a).

Human papillomavirus infection is the most significant risk factor for pre-invasive cervical lesions and cervical cancer, as human papillomavirus infection of epithelial cells can induce malignant growth in humans (American Cancer Society, 2020). Most human papillomavirus infections resolve spontaneously, but persistent high-risk human papillomavirus infection can lead to precancerous cervical intra-epithelial neoplasia, which can become invasive. The majority of cervical carcinomas are squamous cell; the remainder are adenocarcinomas, adenosquamous carcinomas, and cancers of undifferentiated cell types. However, human papillomavirus is found in many women who never develop the disease.

Screening for cervical cancer

Identification and treatment of cervical lesions through screening reduces cervical cancer incidence, morbidity, and mortality. Detection of early-stage asymptomatic cancer also contributes to decreased morbidity by making women eligible for treatments with lower morbidity (National Cancer Institute, 2023b). Cervical cytology with liquid-based, thin layer preparation, *in situ* hybridization, polymerase chain reaction, and hybrid capture technology are available to test for human papillomavirus strains.

The U.S. Food and Drug Administration (2023) has approved several human papillomavirus deoxyribonucleic acid and ribonucleic acid tests as adjuncts to cytology screening for women ages 30 and older, including one (Cobas® HPV Test, Roche Molecular Systems Inc., Pleasanton, California) that received specific approval as a primary screening test for women ages 25 years and older to detect high-risk human papillomavirus types 16 and 18 — the two types that cause 70% of cervical cancers. In 2018, the BD Onclarity HPV Assay (Becton, Dickinson, and Company, Sparks, Maryland) received regulatory approval as a primary screening test in women 25 years and older. Other potential uses for human papillomavirus deoxyribonucleic testing include triage of patients with atypical squamous cells of undetermined significance, follow-up after treatment, follow-up for patients with abnormal cytology, and resolution of discrepancies in colposcopy or histology findings.

Human papillomavirus vaccination

The U.S. Food and Drug Administration has approved a bivalent, quadrivalent, and most recently, a 9-valent recombinant human papillomavirus vaccine for protection against some of the more common human papillomavirus infections (U.S. Food and Drug Administration, 2018). Immunizing women and men prior to infection can reduce the risk for cervical cancer, although the effectiveness and duration of the vaccine continues to be evaluated.

The Centers for Disease Control and Prevention Advisory Committee on Immunization Practices issued new recommendations for a two-dose schedule for human papillomavirus vaccination (Gardisil) of girls and boys who initiate it at ages nine through 14 years of age (Meites, 2016). The change was based on available immunogenicity evidence that showed equivalent efficacy of a two-dose schedule (zero, six to 12 months) to a three-dose schedule (zero, one to two, six months) if the human papillomavirus vaccination series is initiated before the 15th birthday.

At its June 2019 meeting, the Committee updated recommendations for catch-up vaccination for all individuals through age 26 who are not adequately vaccinated and based on shared clinical decision making also for individuals aged 27 through 45 years who are not adequately vaccinated (Meites, 2019). Human papillomavirus vaccines are not licensed for use in adults older than age 45 years. Dosing schedules, intervals, and definitions of persons considered adequately vaccinated have not changed. The updated recommendations are detailed in the appendix.

Findings

Both conventional and liquid-based techniques for Papanicolaou tests are acceptable for screening. Conventional cytology is less costly than the liquid-based; however, the liquid-based technique is able to screen for human papillomavirus and other infections. The evidence suggests a role for human papillomavirus-cytology co-testing as an initial screening strategy in average-risk women ages 30 to 65 years, but the evidence for use of human papillomavirus alone as an initial testing strategy or as triage for abnormal cytology results is inconclusive (Bouchard-Fortier, 2014).

The potential harms associated with cervical screening with cytology or human papillomavirus testing are both physical and emotional (Sroczynski, 2020). Abnormal test results can lead to more frequent testing and invasive diagnostic procedures, such as colposcopy and cervical biopsy, and increased anxiety and distress. False-

negative Papanicolaou test results may occur as a result of many factors such as slide preparation, laboratory, and reporting inaccuracies. The potential for over-diagnosis in the absence of benefit can lead to unnecessary surveillance, diagnostic tests, and treatments with associated harms.

In 2012, the U.S. Preventive Services Task Force, American College of Obstetricians and Gynecologists, and American Cancer Society, in collaboration with the American Society for Colposcopy and Cervical Pathology and the American Society for Clinical Pathology, released revised recommendations for cervical cancer screening (Saslow, 2012). Guidelines by the American Academy of Family Physicians (2020) and the American College of Physicians (Sawaya, 2015) follow U.S. Preventive Services Task Force recommendations. For the first time, these guidelines agreed on the populations to whom the recommendations apply, the ages at which to begin and end screening, the appropriate screening intervals, and the appropriate tests to be used.

The effect of human papillomavirus vaccination on the need for screening with cytology alone or in combination with human papillomavirus testing is not established. Given these uncertainties, women who have been vaccinated should continue to be screened (U.S. Preventive Services Task Force, 2016). The following recommendations apply to women of average risk with a cervix, regardless of human papillomavirus vaccination status and sexual history. These recommendations do not apply to women who have received a diagnosis of a high-grade precancerous cervical lesion or cervical cancer, women with in utero exposure to diethylstilbestrol, or women who are immunocompromised (e.g., human immunodeficiency virus positive):

- Begin screening with cytology at the age of 21, regardless of the onset of sexual activity, and continue every three years until the age of 29.
- From ages 30 to 65, human papillomavirus-cytology co-testing every five years is preferred; cytology alone every three years is also acceptable.

Although recommendations have resulted in reductions in screening post-hysterectomy and of those ages ≥ 65 years, many women still are being screened who will not benefit from it (Centers for Disease Control and Prevention, 2013, 2015). Specific recommendations for these women are as follows:

- For women ages > 65 years, no screening is recommended following adequate negative prior screening. Adequate prior screening is defined as three consecutive negative cytology results or two consecutive negative human papillomavirus results within 10 years before cessation of screening, with the most recent test occurring within five years. Women with a history of cervical intra-epithelial neoplasia 2 or a more severe diagnosis should continue routine screening for at least 20 years after spontaneous regression or appropriate management of a high-grade precancerous lesion, even if this extends screening past age 65 years. Screening should not resume after cessation in women older than age 65 years, even if a woman reports having a new sexual partner.
- No screening is recommended for women without a cervix, without a history of cervical intra-epithelial neoplasia 2 or a more severe diagnosis in the past 20 years, or cervical cancer ever.

Abnormal results are interpreted commonly using two systems - the Cervical intraepithelial neoplasia system (CIN 1-CIN3) and the Bethesda system.

In 2020, the American Cancer Society made updates to its earlier guideline, for average-risk women. These updates include primary human papillomavirus testing should occur every five years; testing should start at age 25, not 21; and cytology screening should be phased out when full access to human papillomavirus testing becomes available (Fontham, 2020).

A Cochrane review of randomized controlled trials found primary high-risk human papillomavirus screening is at least as effective as cytology alone at the same screening intervals (Koliopoulos, 2017). Human papillomavirus tests are less likely to miss cases of cervical intra-epithelial neoplasia 2+ and cervical intra-epithelial neoplasia

3+, but may lead to more false positives and unnecessary referrals. On the other hand, cytology has a greater chance of being falsely negative, which could delay appropriate treatment.

In 2018, the U.S. Preventive Services Task Force finalized recommendations for cervical cancer screening to include three screening strategies for average-risk women ages 30 to 65 years: high-risk human papillomavirus testing alone every five years; cervical cytology alone every three years or cytology; and high-risk human papillomavirus co-testing testing every five years. All three screening strategies offer a reasonable balance between benefits and harms in this cohort. The American College of Obstetricians and Gynecologists (2020, 2021) is reviewing these new recommendations and, in the interim, affirms its current cervical cancer screening guidelines that encompass all three cervical cancer screening options for women at average risk of cervical cancer. The recommendations of both organizations for the other age groups have not changed. The policy was changed to include high-risk human papillomavirus testing alone every five years as a screening strategy in this cohort of women. The policy ID was changed from CP# 13.01.03 to CCP.1280.

The American College of Obstetricians and Gynecologists (2016) recommends human papillomavirus testing as an acceptable alternative cervical cancer screening methodology in low-resource settings where cytology-based screening is not feasible or practical, e.g., in the U.S. Affiliated Pacific Islands. The optimal screening strategy incorporating self-samples requires further study, particularly in areas with more organized screening programs (American College of Obstetricians and Gynecologists, 2016; U.S. Preventive Services Task Force, 2018). We added a statement about self-samples to the limitations section and clarified that samples be collected by the clinician in the coverage section.

In 2019, we added a meta-analysis (Arbyn, 2018) of 56 accuracy studies and 25 participation trials found that, compared to clinician samples, self-samples using high-risk human papillomavirus assays based on polymerase chain reaction showed comparable sensitivity for detecting cervical intra-epithelial neoplasia 2+ or cervical intra-epithelial neoplasia 3+ (pooled ratio 0.99, 95%t confidence interval 0.97 to 1.02), whereas those assays based on signal amplification were less sensitive (pooled ratio 0.85, 95% confidence interval 0.80 to 0.89). The specificity of self-samples to exclude cervical intra-epithelial neoplasia 2+ with high-risk human papillomavirus assays based on either polymerase chain reaction or signal amplification was 2% and 4% lower than that of clinician samples, respectively.

In 2020 and 2021, we updated American College of Obstetricians and Gynecologists guidance on human papillomavirus vaccination (2021, update of 2017). We added four systematic reviews (Biddell, 2020; Caleia, 2020; Connolly, 2020; Malone, 2020) that provide limited evidence suggesting a patient preference for human papillomavirus self-sampling over traditional Papanicolaou screening, which may overcome some of the barriers to screening, particularly among medically underserved populations. However, the evidence of clinical utility and cost-effectiveness is insufficient to support widespread use of human papillomavirus self-sampling as a screening test. No policy changes are warranted.

In 2022, we added several new meta-analyses, including:

- Five studies (n = 2,778) found sensitivity and specificity of 86% and 79% for cervical cancer after ThinPrep cytology and human papillomavirus deoxyribonucleic acid tests (Li, 2022).
- Twenty-six (26) studies (n = 10,071) determined high agreement rates of self-collected and clinician-collected human papillomavirus tests (positive = 84.6%, negative = 91.7%) (Arbyn, 2022).
- Twenty-one (21) studies (n = 21,933) showed self-collected urine papillomavirus tests had a significantly low (84%) sensitivity compared with clinician-collected samples (Cho, 2022).

In 2023, we updated references, and added a systematic review of five studies showing accuracy of using menstrual blood in cervical cancer screening ranged from 82.8% to 97.7% (sensitivity) and 50.0% to 98.0% (specificity), supporting use as a screening tool in low- and middle-income nations (Chakravarti, 2022).

We also added an American College of Obstetricians and Gynecologists recommendation that supports Centers for Disease Control recommendations to vaccinate individuals age 9-26; and to consider adjuvant vaccination for immunocompetent previously unvaccinated persons 27-45 undergoing treatment for cervical intraepithelial neoplasia 2+ (American College of Obstetricians and Gynecologists, 2023).

In 2025, we updated references and found no new relevant literature. No policy changes warranted.

References

On October 20, 2025, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “cervical intraepithelial neoplasia” (MeSH), “uterine cervical dysplasia” (MeSH), “early detection of cancer” (MeSH), “human papillomavirus screening, “cervical cancer screening” and “human papillomavirus vaccines” (MeSH). We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

11/2016: initial review date and clinical policy effective date: 2/2017

8/2017: Policy references updated.

11/2018: Policy references updated. Changes to coverage and policy number.

11/2019: Policy references updated. Changes to coverage and limitations.

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Appendix

Use of a 2- or 3-Dose Schedule for Human Papillomavirus Vaccination — Updated Recommendations of the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices

Routine and catch-up vaccination age groups:

- Routine human papillomavirus vaccination for all adolescents starting at age 11 or 12 years, but can be started at age 9 years, and through age 18 years if not previously adequately vaccinated.
- Catch-up vaccination for all individuals through age 26 years who were not adequately vaccinated previously.
- Catch-up vaccination for individuals aged 27 through 45 years who are not adequately vaccinated based on shared clinical decision making.
- Human papillomavirus vaccines are not licensed for use in adults older than age 45 years.
- No pre-vaccination testing is recommended to establish the appropriateness of human papillomavirus vaccination.

Two- or 3-dose series depending on age at initial vaccination:

- Age 9 through 14 years at initial vaccination: 2-dose series at 0, 6 to 12 months (minimum interval: 5 months; repeat dose if administered too soon).
- Age 15 years or older at initial vaccination: 3-dose series at 0, 1 to 2 months, 6 months (minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 12 weeks / dose 1 to dose 3: 5 months; repeat dose if administered too soon).

Special situations:

- Immunocompromising conditions, including human immunodeficiency virus infection: 3-dose series as above. This recommendation does not apply to children ages < 15 years with asplenia; asthma; chronic granulomatous disease; chronic liver disease; chronic lung disease; chronic renal disease; central nervous system anatomic barrier defects (e.g., cochlear implant); complement deficiency; diabetes; heart disease; or sickle cell disease.
- History of sexual abuse or assault: Start at age 9 years.
- Pregnancy: Human papillomavirus vaccination not recommended until after pregnancy; no intervention needed if vaccinated while pregnant; pregnancy testing not needed before vaccination. Individuals who are breastfeeding or lactating can receive human papillomavirus vaccine.

Persons vaccinated previously are considered adequately vaccinated:

- If initially vaccinated with 9-valent, quadrivalent, or bivalent before their 15th birthday, and received two doses of any human papillomavirus vaccine at the recommended dosing schedule (0, six to 12 months),

or three doses of any human papillomavirus vaccine at the recommended dosing schedule (0, one to two, six months).

- If initially vaccinated with 9-valent, quadrivalent, or bivalent on or after their 15th birthday, and received three doses of any human papillomavirus vaccine at the recommended dosing schedule.
- 9-valent may be used to continue or complete a vaccination series started with quadrivalent or bivalent.
- For persons who have been adequately vaccinated with bivalent or quadrivalent, there is no Advisory Committee on Immunization Practices recommendation regarding additional vaccination with 9-valent.
- If the vaccination schedule is interrupted, the series does not need to be restarted. The number of recommended doses is based on the age at the administration of the first dose.

Contraindications and precautions:

- Persons with a history of immediate hypersensitivity to any vaccine component.
- Quadrivalent and 9-valent are contraindicated for persons with a history of immediate hypersensitivity to yeast.
- Bivalent should not be used in persons with anaphylactic latex allergy.
- Adverse events occurring after administration of any vaccine should be reported to the Vaccine Adverse Event Reporting System (VAERS). Reports can be submitted to VAERS online, by fax, or by mail. Additional information about VAERS is available by phone (**800-822-7967**) or online (https://vaers.hhs.gov).

Source: Meites (2016, 2019).