Clinical Policy Title: Cervical cancer and human papillomavirus screening

Clinical Policy Number: 13.01.03

Effective Date: February 1, 2017
Initial Review Date: August 17, 2016
Most Recent Review Date: November 16, 2016
Next Review Date: November 2017

Policy contains:
- Cervical cancer.
- Cytology (Papanicolaou [Pap] test).
- Human papillomavirus (HPV).

Related policies:
None.

ABOUT THIS POLICY: AmeriHealth Caritas District of Columbia has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas District of Columbia’ clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by AmeriHealth Caritas District of Columbia when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas District of Columbia’ clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas District of Columbia’ clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas District of Columbia will update its clinical policies as necessary. AmeriHealth Caritas District of Columbia’ clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas District of Columbia considers screening for cervical cancer and HPV to be clinically proven and, therefore, medically necessary when all of the following criteria are met:

- Screening for average risk members:
  - Average risk is defined as no history of high-grade, precancerous cervical lesion (cervical intra-epithelial neoplasia [CIN] grade two or a more severe lesion) or cervical cancer; not immunocompromised (including Human Immunodeficiency Virus [HIV] infection); and no in utero exposure to diethylstilbestrol (DES) (U.S. Preventive Task Force [USPSTF], 2015).
  - Beginning at age 21 years.

- Screening intervals:
  - Age 21 to 29 years — cytology every three years.
  - Age 30 to 65 years — cytology-HPV co-testing every five years (preferred) or a Pap test alone every three years.
  - Age-specific recommendations are regardless of HPV vaccination status.
• End of screening criteria:
  – Members who are > 65 years assuming three consecutive negative results on cytology or two consecutive negative results on cytology plus HPV testing within 10 years before cessation of screening, with the most recent test performed within five years.
  – Members who had a total hysterectomy (specifically for members without a cervix and without a history of CIN 2, CIN 3, adenocarcinoma in situ, or cancer in the past 20 years).
• Screening may be needed more frequently for members with any of the following risk factors:
  – Exposure to DES before birth.
  – A weakened immune system (e.g., solid organ transplant recipients or long-term corticosteroid therapy).
  – History of treatment for CIN 2, CIN 3, or cancer.
  – HIV infection.

For Medicare members only:
• Medicare covers a SCREENING pelvic examination and Pap test for all female beneficiaries at 12 or 24 month intervals, based on specific risk factors. See 42 C.F.R. § 410.56; Medicare National Coverage Determinations Manual, § 210.2.1 Current Medicare coverage does not include the HPV testing. Pursuant to §1861(ddd) of the Social Security Act, the Secretary may add coverage of "additional preventive services" if certain statutory requirements are met.
• Effective for services performed on or after July 9, 2015, CMS has determined that the evidence is sufficient to add HPV testing once every five years as an additional preventive service benefit under the Medicare program for asymptomatic beneficiaries aged 30 to 65 years in conjunction with the Pap smear test. CMS will cover screening for cervical cancer with the appropriate U.S. Food and Drug Administration (FDA)-approved/cleared laboratory tests, used consistent with FDA-approved labeling and in compliance with the Clinical Laboratory Improvement Act regulations.

Limitations:
• All other screening for cervical cancer and HPV are not medically necessary.
• Cervical cancer screening for women under age 21 years is not medically necessary regardless of the age of sexual initiation or other risk factors, because its efficacy in this population has not been established.

Alternative covered services:
• HPV vaccination in accordance with the recommendations of the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP).

Background
Cervical cancer is one of the most common malignancies in women and remains a significant cause of morbidity and mortality worldwide. In 2016, an estimated 12,990 U.S. women will be diagnosed with cervical cancer, and 4,120 will die of the disease (National Cancer Institute, 2016). Despite decreasing mortality rates for all U.S. women, significant racial disparities in the risk of death from cervical cancer persist (Collins, 2013; Mann, 2015).

HPV infection is the most significant risk factor for pre-invasive cervical lesions and cervical cancer (American Cancer Society [ACS], 2016). Persistent high-risk HPV infection can lead to cervical precancerous lesions known as CIN, which can become invasive. The majority of cervical carcinomas are squamous cell; the remainder is adenocarcinomas, adenosquamous carcinomas, and cancers of undifferentiated cell types. However, HPV is found in many women who never develop the disease. Other risk factors for cervical carcinoma and pre-invasive cervical lesions include: early age at first intercourse; multiple sexual partners; high number of pregnancies; sexual contact with high risk partner; history of sexually transmitted disease; smoking; a personal history of HIV infection; immunosuppression; and DES exposure in utero (ACS, 2016).

Screening for cervical cancer:

Cervical cytology became the standard screening test for cervical cancer and premalignant cervical lesions with the introduction of the Pap smear in 1941. Liquid-based, thin layer preparation of cervical cytology specimens was a subsequent modification in technique. The FDA approved a HPV deoxyribonucleic acid (DNA) test as an adjunct to Pap smear screening for women age 30 and older (FDA, 2014). Other potential uses for HPV DNA testing include triage of patients with atypical squamous cells of undetermined significance (ASC-US), follow-up after treatment, follow-up for patients with abnormal cytology, and resolution of discrepancies in colposcopy or histology findings.

HPV vaccination:

The FDA has approved a bivalent (2vHPV), quadrivalent (4vHPV), and most recently, a 9-valent (9vHPV) recombinant HPV vaccine for protection against some of the more common HPV infections (FDA, 2016). 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 CDC ACIP issued the following recommendations for HPV vaccination (CDC, 2015). The ACIP updates HPV dosages and schedules periodically, and the HPV vaccine dosage is one of the changes ACIP is anticipated to include in the 2017 Immunization Schedules.

- Begin HPV vaccination for girls and boys at 11 or 12 years, but children as young as nine years can start receiving the three-dose vaccine series.
- Vaccinate children age 9–10 years at high-risk in this age group, including children with a history of sexual abuse.
- Fully vaccinate young women between 13 and 26 years and young men between 13 and 21 who have never been vaccinated against HPV or have not had all three doses.
- Vaccinate teens older than 11 or 12 who have not been fully vaccinated against HPV as soon as possible.
• Advise adults between 22 and 26 who were not vaccinated against HPV that vaccination against the virus at older ages is less effective in reducing the risk for cancer. CDC does not recommend routine HPV vaccination for people in this age group.
  – Exception: vaccinate through age 26 years men who have sex with men and immunocompromised persons (including those with HIV infection) if not vaccinated previously.

HPV vaccines are contraindicated for persons with a history of immediate hypersensitivity to any vaccine component. 4vHPV and 9vHPV are contraindicated for persons with a history of immediate hypersensitivity to yeast. 2vHPV should not be used in persons with anaphylactic latex allergy. HPV vaccines are not recommended for use in pregnant women.

**Searches**

AmeriHealth Caritas District of Columbia searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s (AHRQ’s) National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on December 19, 2016. Search terms were: “cervical cancer,” “cancer prevention,” “cervical screening,” and “HPV testing.”

We included:
- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

Evidence from observational and case-controlled studies strongly suggests that the Pap smear has significantly reduced the mortality rate from invasive cervical cancer. Identification and treatment of CIN 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 (Peirson, 2013).
Both conventional and liquid-based techniques for Pap smears are acceptable for screening. Conventional cytology is less costly than the liquid-based; however, the liquid-based technique is able to screen for HPV and other infections. The evidence suggests a role for HPV-cytology co-testing as an initial screening strategy in average-risk women age 30 to 65 years, but the evidence for use of HPV alone as an initial testing strategy or as triage for abnormal cytology results is inconclusive (Bouchard-Fortier, 2014; Nahvijou, 2014).

The potential harms associated with cervical screening with cytology or HPV testing are both physical and emotional (Vesco, 2011; USPSTF, 2015). 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 Pap smear results may occur as a result of many factors such as slide preparation, laboratory, and reporting inaccuracies.

There are potential harms associated with diagnostic and treatment procedures for cervical cancer (Vesco, 2011). Adverse effects associated with the diagnostic procedure include vaginal bleeding, pain, infection, and failure to diagnose (due to inadequate sampling). Potential harms associated with the treatment procedure (such as cold-knife conization and loop excision) include adverse pregnancy outcomes. The potential for over-diagnosis may result from identification and treatment of either precancerous cervical lesions that will regress or slow-growing lesions that will not become clinically important over a woman's lifetime. It is difficult to estimate the precise magnitude of over-diagnosis associated with any screening or treatment strategy, but it is of concern as it confers no benefit and can lead to unnecessary surveillance, diagnostic tests, and treatments with the associated harms (USPSTF, 2015).

Recent evidence-based guidelines for screening have refined the approach in an effort to minimize harms and maximize benefits. In general, the approach has focused on increasing the age at which to begin screening, lengthening the screening interval, incorporating HPV testing, and discontinuing screening in women at low risk for future cervical cancer. In 2012, the USPSTF, the American College of Obstetricians and Gynecologists (ACOG), and the ACS, in collaboration with the American Society for Colposcopy and Cervical Pathology (ASCCP) and the American Society for Clinical Pathology (ASCP), released revised recommendations for cervical cancer screening (Saslow, 2012). Guidelines by the American Association of Family Physicians (AAFP) follow USPSTF recommendations (AAFP, 2016). 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 HPV vaccination on the need for screening with cytology alone or in combination with HPV testing is not established. Given these uncertainties, women who have been vaccinated should continue to be screened (USPSTF, 2015). The following recommendations apply to women of average-risk with a cervix, regardless of HPV 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 DES, or women who are immunocompromised (e.g., HIV positive):

- Begin screening with cytology beginning at the age of 21, regardless of the onset of sexual activity, and continuing every three years until the age of 29.
- From age 30 to 65, HPV-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 age ≥ 65 years, many women still are being screened who will not benefit from it (CDC, 2013). Specific recommendations for these women are as follows:

- For women age > 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 HPV results within 10 years before cessation of screening, with the most recent test occurring within five years. Women with a history of CIN 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, and without a history of CIN 2 or a more severe diagnosis in the past 20 years or cervical cancer ever.

**Policy updates:**

None.

**Summary of clinical evidence:**

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<th>Content, Methods, Recommendations</th>
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| Sawaya (2015) for the ACP | **Key points:**  
- No screening of average-risk women younger than 21 years.  
- Start screening average-risk women at age 21 years once every three years with cytology (without HPV tests).  
- No screening of average-risk women with cytology > once every three years.  
- May use a combination of cytology and HPV testing once every five years in average-risk women age ≥ 30 years who prefer screening less often than every three years.  
- No HPV testing in average-risk women age < 30 years.  
- Stop screening average-risk women age > 65 years if they have had three consecutive negative cytology results or two consecutive negative cytology plus HPV test results within 10 years, with the most recent test performed within five years.  
- No screening of average-risk women of any age if they have had a hysterectomy with removal of the cervix. |
| Bouchard-Fortier (2014) | **Key points:**  
- Meta-analysis of four randomized controlled trials (RCTs).  
- Co-testing increases detection of CIN 2+ lesions at baseline, and produces a statistically significant 23% reduction in the detection of CIN2+ lesions and a 32% reduction in the detection of CIN 3+ lesions at subsequent screening. |
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| Nahvijou (2014) | - Results suggest that co-testing is effective for earlier detection of precancerous lesions, which may lead to further intervention and decreased rates of detection of high-grade CIN lesions at subsequent screening.  
- Results of co-testing favor longer cervical cancer screening intervals, but the ideal screening interval is unclear and further studies are needed. |
| CDC (2013) | - Analysis of biennial cross-sectional data from the Behavioral Risk Factor Surveillance System on women aged ≥30 years stratified by hysterectomy status and by age (30-64 years and ≥65 years).  
- The proportion of women reporting having had a hysterectomy who reported a recent (within three years) Pap test declined from 73.3% in 2000 to 58.7% in 2010.  
- Significant declines among women with hysterectomy age 30-64 years (from 81.0% in 2000 to 68.5% in 2010) and age ≥ 65 years (from 62.0% to 45.0%).  
- Among women aged ≥ 65 years with no hysterectomy, recent Pap testing also declined significantly (from 73.5% to 64.5%).  
- Although recommendations have resulted in reductions in screening post-hysterectomy and of those aged ≥ 65 years, many women still are being screened who will not benefit from it. |
| Peirson (2013) for the Canadian Task Force on Preventive Health Care | - Systematic review and meta-analysis of one RCT, two cohort studies, and eight case-control studies of women aged 15 to 70 years who were screened using conventional cytology, liquid-based cytology or HPV DNA tests. Also included five older studies from a USPSTF review.  
- Overall quality: low to moderate.  
- Compared to no screening, screening with either HPV or cytology testing is associated with a reduction in the incidence and subsequent mortality from invasive cervical cancer.  
- Cytology screening has a significant protective effect (odds ratio 0.35; 95% confidence interval 0.30, 0.41; 12 studies).  
- No conclusive evidence for establishing optimal ages to start and stop cervical screening, or to determine how often to screen; but data suggest substantial protective effects for screening women 30 years and older and for intervals of up to five years. |
| Saslow (2012) for the ACS-ASCCP-ASCP Cervical Cancer Guideline Committee | - Aged <21 y: No screening. HPV testing should not be used for screening or management of ASC-US in this age group.  
- Aged 21-29 y: Cytology alone every three y. HPV testing should not be used for screening in this age group.  
- Aged 30-65 y: HPV–cytology ‘co-testing’ every five y (preferred) or cytology alone |
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| every 3 y (acceptable). Screening by HPV testing alone is not recommended for most clinical settings.  
- Aged >65 y: No screening following adequate negative prior screening. Women with a history of CIN 2 or a more severe diagnosis should continue routine screening for at least 20 y.  
- After hysterectomy: No screening. Applies to women without a cervix and without a history of CIN 2 or a more severe diagnosis in the past 20 y or cervical cancer ever.  
- HPV vaccinated: Follow age-specific recommendations (same as unvaccinated women). |
| Vesco (2011) for AHRQ in concert with USPSTF | Key points: |
| Screening for cervical cancer |  
- Systematic review of 35 studies reported in 66 articles.  
- The best studied test for any HPV-enhanced screening program is Hybrid Capture 2 (HC2) using positive threshold of one pg/ml, and to a lesser extent, polymerase chain reaction GP5+/6+.  
- A reasonable age to initiate cervical cancer screening in women is age 21 years (five studies).  
- For cytology-based screening, no difference in diagnostic performance of liquid-based cytology (LBC) versus conventional cytology (CC), but may yield a lower proportion of unsatisfactory slides (four studies).  
- A primary screening strategy using HPV test (with or without cytology triage) appears promising in women aged 30 years and older, but net impact of such a program is undetermined (12 studies).  
- Inconclusive benefit of a primary screening strategy using HPV-cytology co-testing over cytology alone, except for a subgroup of women who are negative on both tests and can be referred to a program of less-intensive screening (four studies).  
- Inconclusive benefit of combined cytology and HPV triage over HPV triage alone; combined strategy is associated with more false positives (one study).  
- Inconclusive benefit of HPV testing over repeat cytology for triage of ASC-US or low-grade squamous intraepithelial lesions on Pap smears (six studies).  
- Harms of HPV testing: Psychological impact with increased levels of immediate anxiety and distress in HPV positive women versus HPV negative women, but differences resolved at six-month follow-up (four studies). |

**References**

**Professional society guidelines/other:**


American College of Obstetricians and Gynecologists (ACOG):


Peer-reviewed references:


**CMS National Coverage Determinations (NCDs):**

210.2.1 National Coverage Determination (NCD) for Screening for Cervical Cancer with Human Papillomavirus (HPV). Effective Date of this Version 7/9/2015. Implementation Date 3/7/2016. CMS website. [https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=365&ndcvrver=1&SearchType=Advanced&CoverageSelection=Both&NCSelection=NCA%7cCAL%7cNCD%7cMEDCAC%7cTA%7cMCD&ArticleType=SAD%7cEd&PolicyType=Both&s=All&KeyWord=Screeening+for+Cervical+Cancer+with+Human+Papillomavirus+(HPV)&KeyWordLookUp=Title&KeyWordSearchType=Exact&kq=true&bc=IAAAAACAAAAAAA%3d%3d&](https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=365&ndcvrver=1&SearchType=Advanced&CoverageSelection=Both&NCSelection=NCA%7cCAL%7cNCD%7cMEDCAC%7cTA%7cMCD&ArticleType=SAD%7cEd&PolicyType=Both&s=All&KeyWord=Screeening+for+Cervical+Cancer+with+Human+Papillomavirus+(HPV)&KeyWordLookUp=Title&KeyWordSearchType=Exact&kq=true&bc=IAAAAACAAAAAAA%3d%3d&). Accessed December 5, 2016.

**Local Coverage Determinations (LCDs):**
https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34089&ver=5&SearchType=Advanced&CoverageSelection=Both&NCSelection=NCA%7cCAL%7cNCD%7cMEDCAC%7cTA%7cMCD&ArticleType=SAD%7cEd&PolicyType=Both&s=All&KeyWord=Human+Papillomavirus+(HPV)+Testing&KeyWordLookUp=Title&KeyWordSearchType=Exact&kq=true&bc=IAAAACAAAAAAA%3d%3d&. December 5, 2016.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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