Clinical Policy Title: Cervical cancer and human papillomavirus screening

Clinical Policy Number: CCP.1280

Effective Date: February 1, 2017
Initial Review Date: August 17, 2016
Most Recent Review Date: November 6, 2018
Next Review Date: November 2019

Related policies:
None.

ABOUT THIS POLICY: Prestige Health Choice has developed clinical policies to assist with making coverage determinations. Prestige Health Choice’s 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 Prestige Health Choice 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. Prestige Health Choice’s 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. Prestige Health Choice’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Prestige Health Choice will update its clinical policies as necessary. Prestige Health Choice’s clinical policies are not guarantees of payment.

Coverage policy

Prestige Health Choice considers screening for cervical cancer and human papillomavirus to be clinically proven and, therefore, medically necessary when all of the following criteria are met (American College of Obstetricians and Gynecologists, 2018; 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 risk1 for cervical cancer.
- Screening intervals:
  - Age 21 to 29 years — cytology alone every three years.

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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.
- Age 30 to 65 years — cytology for high-risk human papillomavirus co-testing every five years, high-risk human papillomavirus testing every five years, or cytology alone every three years.
  ▪ 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.

**For Medicare members only:**

- Medicare covers a screening pelvic examination and Papanicolaou 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 human papillomavirus 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, human papillomavirus testing can be added once every five years as an additional preventive service benefit under the Medicare program for asymptomatic beneficiaries ages 30 to 65 years in conjunction with the Papanicolaou smear test. The Centers for Medicare & Medicaid Services will cover screening for cervical cancer with the appropriate U.S. Food and Drug Administration-approved/cleared laboratory tests, used consistent with U.S. Food and Drug Administration-approved labeling and in compliance with the Clinical Laboratory Improvement Act regulations (National Coverage Determination 210.2.1).

**Limitations:**

Coverage determinations are subject to benefit limitations and exclusions as delineated by the state Medicaid authority. The Florida Medicaid website may be accessed at [http://ahca.myflorida.com/Medicaid/](http://ahca.myflorida.com/Medicaid/).

All other screening tests for cervical cancer and human papillomavirus are not medically necessary.
Cervical cancer screening is not medically necessary for members (American College of Obstetricians and Gynecologists, 2018; 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, 2018; 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 (Mann, 2015; Collins, 2013).

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, 2016). 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 intra-epithelial neoplasia 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). 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 (2017) has approved five 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 percent of cervical cancers. 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, 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 Centers for Disease Control and Prevention Advisory Committee on Immunization Practices issued new recommendations for a two-dose schedule for human papillomavirus vaccination of girls and boys who initiate the vaccination series at ages 9 through 14 years (Meites, 2016). The change was based on available immunogenicity evidence that showed equivalent efficacy of a two-dose schedule (0, six to 12 months) to a three-dose schedule (0, one to two, six months) if the human papillomavirus vaccination series is initiated before the 15th birthday. The new recommendations are detailed in the appendix.

**Searches**

Prestige Health Choice searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services.

We conducted searches on September 4, 2018. Search terms were: “cervical intraepithelial neoplasia” (MeSH), “uterine cervical dysplasia” (MeSH), “atypical squamous cells of the cervix” (MeSH), “squamous intraepithelial lesions of the cervix” (MeSH), and “early detection of cancer” (MeSH).

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**

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 (Vesco, 2011). 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.

Recent evidence-based guidelines for screening have refined the approach 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 human papillomavirus testing, and discontinuing screening in women at low risk for future cervical cancer. 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 (2016) 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). 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, and without a history of cervical intra-epithelial neoplasia 2 or a more severe diagnosis in the past 20 years or cervical cancer ever.

Policy updates:

A new 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.

The U.S. Preventive Services Task Force (2016) now recommends primary high-risk human papillomavirus testing in their draft screening algorithm for average-risk women ages 30 – 65 years as an alternative to cytology screening alone; co-testing is no longer recommended in this age group. The American College of Obstetricians and Gynecologists (2016) continues to recommend cytology alone every three years or co-testing at five-year intervals. The recommendations of both organizations for routine cervical cancer screening in women younger than 21 years, for women ages 21 – 29 years, and for women older than 65 years who have been adequately screened previously have not changed.

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 – 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 (2018) 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 has 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.
Policy ID changed from CP# 13.01.03 to CCP.1280.

Summary of clinical evidence:

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<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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| Curry (2018) for the U.S. Preventive Services Task Force Screening for cervical cancer | **Key points:**  
  - Screening with cervical cytology alone, primary high-risk human papillomavirus testing alone, or co-testing can detect high-grade precancerous cervical lesions and cervical cancer, and reduces cervical cancer incidence and mortality.  
  - In women ages 21 to 29 years: every three years with cervical cytology alone (A recommendation).  
  - In women ages 30 to 65 years: every three years with cervical cytology alone; every five years with high-risk human papillomavirus testing alone; or every five years with high-risk human papillomavirus testing in combination with cytology (co-testing) (A recommendation).  
  - Recommendations against screening:  
    - Women younger than 21 years (D recommendation).  
    - Women older than 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer (D recommendation).  
    - Women 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 (D recommendation). |
| Koliopoulos (2017) Cochrane review Cytology versus high-risk human papillomavirus testing for cervical cancer screening in the general population | **Key points:**  
  - Systematic review and meta-analysis of 40 studies with more than 140,000 women ages 20 to 70 years.  
  - Overall quality: moderate for sensitivity estimates and high for specificity estimates.  
  - High-risk human papillomavirus testing has sensitivity sufficiently high for primary screening.  
  - Human papillomavirus tests — Hybrid Capture 2 (Qiagen, Gaithersburg, Maryland) and polymerase chain reaction (for more than 12 human papillomavirus types) — have higher sensitivity than cytology even at the lowest cytological positivity threshold of atypical squamous cells of undetermined significance (i.e., are less likely to miss cervical intra-epithelial neoplasia 2+, and also cervical intra-epithelial neoplasia 3+, than cytological tests).  
  - Cytology has higher specificity at the threshold of low-grade squamous intraepithelial lesion than either Hybrid Capture 2 or polymerase chain reaction.  
  - Human papillomavirus tests are associated with more unnecessary referrals (for false positives) than cytological tests.  
  - Improved cross-sectional accuracy does not guarantee a better performance in reduction on the incidence of cervical cancer if the human papillomavirus test is implemented in primary screening. |
| American College of Obstetricians and Gynecologists (2016) | **Key points:**  
  - Based on data from European screening randomized controlled trials and the U.S.-based data from the prospective trial “Addressing the Need for Advanced Human
Citation bulletin number 168: cervical cancer screening

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<th>Citation</th>
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<tbody>
<tr>
<td>Papillomavirus Diagnostics” (ATHENA; Wright, 2015), primary high-risk human papillomavirus screening is at least as effective as cytology at the same screening intervals.</td>
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<td>Because of equivalent or superior effectiveness, primary high-risk human papillomavirus screening can be considered as an alternative to current U.S. cytology-based cervical cancer screening.</td>
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<td>Rescreening after a negative primary high-risk human papillomavirus screen should occur no sooner than every three years.</td>
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<td>Primary high-risk human papillomavirus screening should not be initiated prior to 25 years of age.</td>
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<td>Clinicians should not use an U.S. Food and Drug Administration-approved test without a specific primary high-risk human papillomavirus screening indication.</td>
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<td>Cytology alone and co-testing remain the screening options specifically recommended.</td>
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References

Professional society guidelines/other:


American College of Obstetricians and Gynecologists:


Centers for Disease Control and Prevention:


**Peer-reviewed references:**


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<td>Cytopathology, cervical or vaginal (any reporting system), collected in preservation fluid, automated thin layer preparation; with screening by automated system and manual rescreening or review, under physician supervision</td>
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Appendix

Use of a 2-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 age groups:
- Routine human papillomavirus vaccination starting at age 11 or 12 years, but can be started at age 9 years.
- All females through age 26 years and males through age 21 years who were not adequately vaccinated previously.
- Males ages 22 through 26 years may be vaccinated.

Recommended dosing schedules:
- For persons initiating vaccination before their 15th birthday — two doses of human papillomavirus vaccine. The second dose should be administered six – 12 months after the first dose (0, six- to 12-month schedule). The minimum interval between the first and second doses is five months. If the second dose is administered after a shorter interval, a third dose should be administered a minimum of 12 weeks after the second dose and a minimum of five months after the first dose.
- For persons initiating vaccination on or after their 15th birthday — three doses. The second dose should be administered one to two months after the first dose, and the third dose should be administered six months after the first dose (0, one to two, six-month schedule). In a three-dose schedule of human papillomavirus vaccine, the minimum intervals are four weeks between the first and second doses, 12 weeks between the second and third doses, and five months between the first and third doses. If a vaccine dose is administered after a shorter
interval, it should be re-administered after another minimum interval has elapsed since the most recent dose.

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 – 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.

Special populations:

- For men who have sex with men, including men who either identify as gay or bisexual or who intend to have sex with men, routine human papillomavirus vaccination schedule as for all males, and vaccination through age 26 years for those who were not adequately vaccinated previously.
- For transgender persons, routine human papillomavirus vaccination schedule as for all adolescents, and vaccination through age 26 years for those who were not adequately vaccinated previously.
- A three-dose human papillomavirus vaccine (0, one to two, six months) for females and males ages 9 through 26 years with primary or secondary immunocompromising conditions that might reduce cell-mediated or humoral immunity, such as B lymphocyte antibody deficiencies, T lymphocyte complete or partial defects, human immunodeficiency virus infection, malignant neoplasms, transplantation, autoimmune disease, or immunosuppressive therapy, because immune response to vaccination might be attenuated. 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.

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.
• Human papillomavirus vaccines are not recommended for use in pregnant women.
• 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).