HUMAN PAPILLOMAVIRUS (HPV) TESTING

Policy Number: CDP - 041
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INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD)) may differ greatly. In the event of a conflict, the enrollee's specific benefit document supersedes this Medical Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Medical Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

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BACKGROUND

Cervical cancer slowly progresses as the normal cervical cells gradually develop precancerous changes, defined as cervical intraepithelial neoplasia (CIN), squamous intraepithelial lesion (SIL), or dysplasia. These precancerous changes have the potential to turn into cancer if left untreated.1 There are two main types of cervical cancer including squamous cell carcinoma (80-90%) and adenocarcinoma (10-20%).1

Human Papillomavirus (HPV), a sexually transmitted infection, has been strongly linked to cervical cancer. Infection with HPV is common and in most women the body is able to clear the infection on its own. At young ages and at the most sexually active ages, the great majority of infected women (more than 90%) have transient infections that resolve spontaneously without producing symptoms or cellular changes.2-5
Sometimes, however, in a small fraction of women the infection persists and becomes chronic.\(^3\) It is this small group of women, chronic carriers of certain HPV types, who have a high risk of disease progression and development of neoplastic lesions of the anogenital tract.\(^6\)

Overall, there are more than 100 different HPV that infect the surfaces of the skin, genitals, anus, mouth and throat.\(^1\) Many of these viruses are low risk and cause papillomas (warts), like HPV 6 or HPV 11 that cause genital warts. Some HPV genotypes are considered high-risk as they are linked to certain cancers including cancer of the cervix, vulva, and vagina in women, penile cancer in men and anal and oral cancer in both men and women.\(^3\) The most common high risk types include HPV 16, 18, 31, 33, and 45. Between 93-100% of squamous cell carcinomas contain DNA from high risk types of HPV and HPV 16 and 18 are implicated in two-thirds of all cervical cancers.\(^1, 2, 7, 8\)

HPV DNA testing is performed on residual exfoliated cervical cells from a liquid-based cytology or specimen transport medium. If the sample is not in conjunction with a Pap cytology specimen, it is collected similarly. Based on the central role of persistent, high risk HPV in cervical cancer, HPV testing has recently been introduced into cervical cancer screening algorithms. High-risk HPV testing has proven greater reproducibility and greater sensitivity for detection of cervical pre-cancer and cancer than cytology.\(^9-14\) Furthermore, high sensitivity has been repeatedly demonstrated.\(^15-18\)

While the Pap test detects cellular changes in cervical cells caused by HPV infection; the newer molecular based tests look for the infections themselves by finding DNA and RNA from HPV in the cells. According to a risk stratification article by Castle et al, “the addition of more accurate methods of screening and diagnosis such as HPV testing could increase both the sensitivity and efficiency of the cervical cancer screening process.”\(^19\) HPV testing has the ability to detect 25-50% of lesions missed by a single cytology screen.\(^20\)

**HPV Testing**

Currently in the US, the use of HPV testing as a primary screening method for cervical cancer is not approved by the FDA. However, there is interest in using the HPV test as a triage test to stratify risk of women age 21 and older with atypical squamous cells of undetermined significance (ASC-US) cytology and post-menopausal women with low grade squamous intraepithelial lesion (LSIL) cytology.\(^17, 18, 21\) Additionally, HPV testing has also become an adjunct to cytology for primary screening for certain age groups.

HPV DNA testing in women over the age of 21 is an effective way to triage ASC-US cytology.\(^10, 20, 22-26\) Arbyn et al completed a 20 study meta-analysis to determine the efficacy of HPV DNA testing for use in ASC-US triage.\(^10\) The overall results demonstrated a sensitivity of 92.5% to detect CIN2+ (high-grade CIN) with a specificity of 62.5%. Likewise, for detecting CIN3+, the sensitivity was 95.6% with a specificity of 59.2%.

Concurrent testing for HPV and cervical cytology (co-testing) is an acceptable alternative to cytology alone in women 30+ years.\(^20\) In routine clinical practice for women 30+ years of age who are negative by co-testing, Katki et al, demonstrated that 3 year screening intervals are safe because a single negative test for HPV was sufficient to reassure against cervical cancer over 5 years.\(^27\)

In screening studies in North American and Europe, the pooled sensitivity and specificity of HPV testing for the detection of CIN2+ in women 35 years and older is 95% and 93%, respectively.\(^9\) For comparison, pooled
sensitivity and specificity of cytology at a threshold of ASC-US are 60% and 97%, respectively. Sensitivity using a combination of HPV and cytology is significantly higher than that of either test alone with NPVs of 99-100%.\textsuperscript{9, 17} Recently, the ATHENA (Addressing THE Need for Advanced HPV Diagnostics) HPV study evaluated the clinical usefulness of the cobas HPV test (Roche Molecular Systems, Pleasanton, CA) for high-risk HPV testing (14 high-risk types) and individual HPV-16/HPV-18 genotyping in women undergoing routine cervical cytology screening the US.\textsuperscript{28} In over 30,000 women age 30 years or older with NILM cytology, the prevalence of high-risk HPV overall was 6.7% and this study demonstrated that high-risk HPV status is an important predictor of the current and future detection of CIN2+ in women with NILM cytology.

It has also been demonstrated in several studies that women with negative HPV and cytology results have a lower risk of developing CIN 2+ than women with only a negative cytology test.\textsuperscript{10, 16-18, 26} In a study of Danish women age 40-50 years of age with 10 years of follow up, less than 2% of cytology negative and HPV negative women developed CIN3+.\textsuperscript{29} Similar results have been reported in women aged 30 years or older in Portland, OR.\textsuperscript{30}

A task force appointed by the Society of Gynecologic Oncology (SGO) and the American Society of Colposcopy and Cervical Pathology (ASCCP) have prepared an interim clinical guidance document for HPV primary screening in the United States.\textsuperscript{31}

\textbf{Society Guidelines}

\textit{American Society for Colposcopy and Cervical Pathology (ASCCP), American Cancer Society (ACS), American Society of Clinical Pathology (ASCP)}\textsuperscript{21}

The following are current 2012 evidence-based guidelines from the American Society for Colposcopy and Cervical Pathology (ASCCP), American Cancer Society (ACS), American Society of Clinical Pathology (ASCP), and U.S. Preventive Services Task Force (USPSTF), and are supported by the American College of Obstetrics and Gynecologists (ACOG).

\textbf{Screening}

- Co-testing with cytology is the preferred screening strategy for women aged 30-64 years
- For women aged 30-64 years, with negative cytology results but with absent or insufficient transformation zone component and no or unknown HPV test results, HPV testing is preferred

\textbf{Management}

- For women aged 25 and above with ASC-US cytology, reflex HPV testing is preferred
- For women aged 21-24 years with ASC-US, reflex HPV testing is acceptable
- Acceptable options for the management of postmenopausal women with LSIL and no HPV test include obtaining HPV testing
For the following CPT code(s) in Table 1, the patient should have a diagnosis (ICD-10-CM) code(s) listed in the attached files below.

**Table 1. HCPCS Codes (Alphanumeric, CPT® AMA)**

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>87623</td>
<td>INFECTIOUS AGENT DETECTION BY NUCLEIC ACID (DNA OR RNA); HUMAN PAPILLOMAVIRUS (HPV), LOW-RISK TYPES (EG, 6, 11, 42, 43, 44)</td>
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<tr>
<td>87624</td>
<td>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)</td>
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<tr>
<td>87625</td>
<td>INFECTIOUS AGENT DETECTION BY NUCLEIC ACID (DNA OR RNA); HUMAN PAPILLOMAVIRUS (HPV), TYPES 16 AND 18 ONLY, INCLUDES TYPE 45, IF PERFORMED</td>
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**ICD-10 Diagnosis Codes (Proven)**
REFERENCES


### POLICY HISTORY/REVISION HISTORY

<table>
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<tbody>
<tr>
<td>01/21/2017</td>
<td>Updated ICD10 codes as per CMS recommendations. Removed ICD9 code file.</td>
</tr>
<tr>
<td>10/06/2016</td>
<td>Annual Policy Review Completed – changes made:</td>
</tr>
<tr>
<td></td>
<td><strong>Background Section and HPV subsection:</strong></td>
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<tr>
<td></td>
<td>Added the following statement to reflect that clinical guidance have been published by the SGO and ASCCP:</td>
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<tr>
<td></td>
<td>&quot;A task force appointed by the Society of Gynecologic Oncology (SGO) and the American Society of Colposcopy and Cervical Pathology (ASCCP) have prepared an interim clinical guidance document for HPV primary screening in the United States.&quot;</td>
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<td><strong>References Section:</strong></td>
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<td>Added Huh reference 2015 documenting the statement by SGO/ASCCP above.</td>
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<tr>
<td>10/01/2015</td>
<td>Changes made:</td>
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<tr>
<td></td>
<td>Deleted CPT 87621 and added CPTs 87623, 87624, 87625 as per AMA 2015 updates.</td>
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<tr>
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<td>Removed ICD9 code table. Replaced with embedded ICD9/ICD10 pdf files.</td>
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