HUMAN PAPILLOMAVIRUS TESTING

Policy Number: PDS - 016
Effective Date: October 1, 2018

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INSTRUCTIONS FOR USE

Physician Decision Support (PDS) is a lab ordering tool operated by BeaconLBS. This Clinical Guideline supports the Questions and Answers that appear in PDS for tests referenced in this document. UnitedHealthcare reserves the right, in its sole discretion, to modify its Clinical Guidelines as necessary. This Clinical Guideline is provided for informational purposes. It does not constitute a Medical Policy or medical advice.

GUIDELINES

BeaconLBS recommends Human Papillomavirus (HPV) testing for the following screening and management purposes:

Screening Recommendations:

- HPV testing may be used as co-testing with cytology in women between the ages of 30 to 64. A negative HPV test with normal cytology results may allow for a decreased frequency of surveillance.

Management Recommendations:

- HPV testing in women >21 years of age can be used to stratify risk in conjunction with a cytology result of ASCUS.
- It may also be used in women >65 years of age in conjunction with a cytology result of LSIL.

BeaconLBS does not recommend that Human Papillomavirus (HPV) testing be undertaken in women < 21 years of age.
These recommendations are consistent with current 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).

**BACKGROUND**

*Note: For additional background on cervical cancer and the Gynecologic Pap Test see Clinical Policy number PDS – 015.

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%).\(^1\)

HPV, a sexually transmitted infection, has been strongly linked to cervical cancer. It has been stated that the demonstration that cervical cancer is caused by the persistent infection by certain genotypes of HPV is one of the most important discoveries in the investigation of cancer etiology over the past 25 years.\(^2\)

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.\(^3\)\(^-\)\(^6\)

Sometimes, however, in a small fraction of women the infection persists and becomes chronic.\(^4\) It is this small group of women, chronic carriers of certain HPV genotypes, who have a high risk of disease progression and development of neoplastic lesions of the anogenital tract.\(^2\)\(^,\)\(^7\)

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.\(^1\) 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.\(^1\)\(^,\)\(^3\)\(^,\)\(^8\)\(^,\)\(^9\)

**HPV DNA testing**

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. The Food and Drug Administration (FDA) approved the first test for HPV in 2000. Since then, there are multiple tests available for use with cervical samples. These HPV tests are molecular based and detect HPV DNA or RNA.
Even though the Pap test has saved countless lives, it is not a perfect test. The Pap test sensitivity for the detection of high-grade CIN is in the range of 70-80%. This has led to the development of additional tests aimed at increasing the sensitivity for detection of high grade cervical disease.

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. Furthermore, high sensitivity has been repeatedly demonstrated.

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.” HPV testing has the ability to detect 25-50% of lesions missed by a single cytology screen.

Another feature of HPV tests is the possibility to increase the time between screenings. The combination of cytology and high risk HPV testing may significantly improve the rate of detection of cervical cancer precursors and facilitate the safe lengthening of the screening interval.

**HPV Testing**

Until recently in the US, the use of HPV testing as a primary screening method for cervical cancer was not approved by the FDA. In April 2014, the FDA approved the first HPV DNA test for women 25 and older that can be used alone as primary screening for cervical cancer. The test can be used to determine if women need to undergo additional diagnostic testing for cervical cancer or be used to determine the woman's risk for future development of cervical cancer. The cobas HPV Test detects DNA from 14 high-risk HPV types (including HPV 16 and 18) using a sample of cervical cells. The FDA states in the press release that "Health care professionals should use the cobas HPV Test results together with other information, such as the patient screening history and risk factors, and current professional guidelines." 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.

Currently, there is interest in using the HPV test as a triage test to stratify risk of women age 21 and older with ASC-US cytology and post-menopausal women with LSIL cytology. Additionally, concurrent testing for HPV and cervical cytology (co-testing) is an approved alternative to cytology alone in women 30+ years.

**Using HPV Testing for Triage of Abnormal Cytology Results**

HPV DNA testing in women over the age of 21 is an effective way to triage ASCUS cytology. HPV DNA testing should not be used for women under the age of 21 due to the high proportion of women with transient HPV infections and a positive result may lead to potentially harmful and costly overtreatment.

Arbyn et al completed a 20 study meta-analysis to determine the efficacy of HPV DNA testing for use in ASCUS triage. 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%.
Performing HPV DNA testing as a reflex for high grade squamous intraepithelial lesion (HSIL) has little clinical utility as more than likely the results will be positive. Additionally, HPV DNA results are often positive in women with LSIL, thereby making the use of HPV DNA testing as a triage for LSIL cytology difficult. An exception to this is in post-menopausal women with LSIL cytology results where HPV DNA testing is recommended.

Co-testing: Cervical Cytology and HPV Testing

Concurrent testing for HPV and cervical cytology (co-testing) is an acceptable alternative to cytology alone in women 30+ years. 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.

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. For comparison, pooled sensitivity and specificity of cytology at a threshold of ASCUS 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%.

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 in the US. 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. 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+. Similar results have been reported in women aged 30 years or older in Portland, OR.

Guidelines and Recommendations

American Society for Colposcopy and Cervical Pathology (ASCCP), American Cancer Society (ACS), American Society of Clinical Pathology (ASCP)

These following are current 2012 and 2013 evidence-based guidelines from the American Society for Colposcopy and Cervical Pathology (ASCCP), American Cancer Society (ACS), American Society of Clinical Pathology (ASCP), and Preventive Services Task Force (USPSTF), and are supported by the American College of Obstetrics and Gynecologists (ACOG).

Screening

- Co-testing with cytology is the preferred screening strategy for women aged 30-64 years (see Figure 3) http://www.asccp.org/asccp-guidelines
- 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
* In 2017, the USPSTF drafted new recommendation to exclude co-testing as a screening option for women aged 30-65.\textsuperscript{35}

**Management**

- For women aged 25 and above with ASC-US cytology, reflex HPV testing is preferred (see Figure 4 [http://www.asccp.org/asccp-guidelines\textsuperscript{35}])

- For women aged 21-24 years with ASC-US, reflex HPV testing is acceptable (see Figure 5 [http://www.asccp.org/asccp-guidelines\textsuperscript{35}])

Acceptable options for the management of postmenopausal women with LSIL and no HPV test include obtaining HPV testing

**US FOOD AND DRUG ADMINISTRATION (US FDA)**

The US FDA is involved in multiple aspects of the gynecologic Pap test including approval of new screening methods.

**CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)**

For Medicare populations, CMS does not pay for screening procedures (tests) performed in the absence of signs or symptoms. (Section 1862(a)(7) of the Social Security Act)

Medicare does not have a National Coverage Determination (NCD) for Human Papillomavirus (HPV) Testing. CPTs 87623, 87624, 87625 are addressed in the Local Coverage Determination (LCD) for Human Papillomavirus (HPV) Testing and compliance with these policies is required where applicable. (Accessed December 30, 2013)

**APPLICABLE CODING**

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<td>87624</td>
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REFERENCES


2. Castellsague X. Natural history and epidemiology of HPV infection and cervical cancer. Gyn Oncol. 2008;S4-S7.


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<td>10/06/2016</td>
<td>Annual Policy Review Completed – changes made: Clinical Evidence Section and HPV subsection: Modified the following statement to reflect that the clinical guidance has been published: &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. References Section: Updated ACOG reference from practice bulletin No. 131 version 2012 to practice bulletin No. 157 version 2016.</td>
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<td>12/03/2015</td>
<td>Annual Policy Review Completed – changes made: Added reference: Huh, 2015. Added sentence in 'Recommendations' section, under 'Screening Recommendations': &quot;Primary hrHPV screening may be undertaken....and Society for Gynecologist Oncologists (SGO),&quot; based on the Huh, 2015 reference. Added paragraph in 'Clinical Evidence' section, under 'HPV Testing': &quot;The SGO and the ASCCP....test that is positive for HPV types other than 16 or 18 should be followed with cytology testing.&quot; based on the Huh, 2015 reference.</td>
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<td>10/01/2015</td>
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<td>10/23/2014</td>
<td>Reference added in reference section: FDA News Release. FDA approves first human papillomavirus test for primary cervical cancer screening. Available at: <a href="http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm394773.htm">http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm394773.htm</a>. (Accessed: October 10, 2014). Within the body of the policy, in the &quot;Clinical Evidence&quot; - &quot;HPV Testing&quot;, the following was added: &quot;Until recently in the US, the use of HPV testing as a primary screening method for cervical cancer was not approved by the FDA.1-3 In April 2014, the FDA approved the first HPV DNA test for women 25 and older that can be used alone as primary screening for cervical cancer.21 The test can be used to determine if women need to undergo additional diagnostic testing for cervical cancer or can be used to determine the woman's risk for future development of cervical cancer. The cobas HPV Test detects DNA from 14 high-risk HPV types (including HPV 16 and 18) using a sample of cervical cells. The FDA states in the press release that &quot;Health care professionals should use the cobas HPV Test results together with other information, such as the patient screening history and risk factors, and current professional guidelines.&quot;21 A task force appointed by the Society of Gynecologic Oncology (SGO) and the American Society of Colposcopy and Cervical Pathology (ASCCP) are preparing an interim clinical guidance document for HPV primary screening in the United States which is expected to be published in the next few months.&quot; &quot;Currently, there is interest in using the HPV test as a triage test to stratify risk of women age 21 and older with ASC-US cytology and post-menopausal women with LSIL cytology.18-19 Additionally, concurrent testing for HPV and cervical cytology (co-testing) is an approved alternative to cytology alone in women 30+ years.18-19&quot;</td>
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