Testing for human papillomavirus (HPV) can assist with prevention of cervical cancer. This testing is covered as routine screening for women age thirty or over, and is covered as part of the medical benefit in women with certain types of abnormal Papanicolaou tests.

Medical Policy Statement:

HPV DNA testing is considered medically necessary and is covered for women 30 years of age or older as an adjunct to a screening cervical Pap smear for women with the Wellness Benefit.

HPV DNA testing is considered medically necessary and is covered for women with an equivocal or ASCUS Pap smear result in order to better determine the need for referrals to colposcopy; to serve as an adjunct to the Pap smear in the identification of women who may be at increased risk for squamous intraepithelial lesions (SIL); to distinguish between infections with HPV types which are principally associated with low-grade squamous intraepithelial lesions (LSIL), and HPV types typically associated with SIL of all grades, especially high-grade SIL (HSIL) and invasive cancer of the cervix; to aid in the diagnosis of sexually transmitted disease.
Background:

Ninety-five percent (95%) of cervical neoplasia is considered to be due to infection with human papillomavirus (HPV). HPV is a sexually transmitted disease which occurs after a woman becomes sexually active. Not all HPV viral types are oncogenic, not all infect the cervix, and only a small number of women who develop HPV infection, even with the oncogenic forms of HPV, will develop in-situ or invasive cervical cancer. It has been well established that the majority of squamous cell cancers of the cervix progress through a series of well-defined preinvasive lesions and that during this usually lengthy process, the disease can be easily detected by Pap smear screening. During this preinvasive stage, cervical squamous intraepithelial lesions (SIL) can be controlled with nearly uniform success.

The Bethesda System (TBS) was introduced (1988) as a standardized grading system for Pap smears. Frankly negative or positive smears are reported as such. In between these two extremes are various levels of equivocal abnormality. These may be due to inflammatory disease or may be precursors of a malignant process.

Atypical squamous cells of unknown significance (ASCUS); atypical glandular cells of unknown significance (AGUS); low-grade squamous intraepithelial lesions (LSIL) and high-grade squamous intraepithelial lesions (HSIL) are designations given to these undetermined cell types.

Screening for cervical carcinoma or precursors to cervical carcinoma with Pap smears has potential weaknesses:

- the interpretation of the smear may be difficult or erroneous; and
- sampling errors occur.

Except for a subset of Pap smear results, no consistent methodological approach to the woman who has a Pap smear with one of these undetermined cell types has been developed. Women with HSIL or AGUS reports are recommended to have colposcopy directed biopsy and endocervical curettage, as the risk of an cervical cancer precursor is significant (15% of women with AGUS have HSIL or adenocarcinoma in situ), and those with HSIL or in-situ carcinoma on biopsy are recommended to have resectional or ablation procedures.

ASCUS or LSIL, however, are a more problematic issue, for almost all of these findings are the result of benign disease (5-10% of women with ASCUS have HSIL disease; the majority of LSIL regress without treatment, but 15% of women with LSIL on Pap smear will have HSIL on colposcopy and biopsy). A diagnosis of ASCUS identifies a woman who is at greater than background risk for prevalent and incipient cervical intraepithelial neoplasia 2 (CIN2), CIN3, and cancer. Studies have shown that 20% - 60% of ASCUS changes are associated with CIN at colposcopic evaluation, but the vast majority of
these (greater than 70%) are CIN1, a sign of usually benign HPV infection. The question of whom to refer for colposcopy and possible biopsy is such concern that the National Cancer Institute funded a trial to evaluate the best triage option for women with equivocal and low-grade Pap smears in a randomized trial that began in 1995, ending in 2001.

Three follow-up options have been proposed for women with ASCUS or LSIL: immediate colposcopy, accelerated repeat Pap testing, and testing for the presence of HPV. Immediate colposcopy would theoretically detect all HSILs. However, the positive predictive value would be extremely low due to the low (5-10%) prevalence of high-grade disease among women with ASCUS, whereas the anxiety and costs generated are high. Repeat cytology may not be cost-effective due to a high rate of repeat abnormal cytology findings requiring colposcopic evaluation. Additionally, accuracy of the Pap test is low (sensitivity = 51%-66%) and reproducibility is poor.

More than 70 types of HPV have been identified. However, only 23 of these infect the uterine cervix; of these, only one-half are associated with SIL or invasive cervical cancer. These are further classified into low-risk types, HPV 6 and 11, and high-risk types, most commonly 16, 18, 31, and 45, which account for more than 80 percent of all invasive cervical cancers. An unknown percentage of women infected with HPV will develop either low-grade SIL (LSIL) or high-grade SIL (HSIL). One-third of all grades of SIL will regress, whereas 41 percent persist and 25 percent progress. Of lesions that progress, 10 percent progress to carcinoma in-situ and 1 percent to invasive cancer. Three-quarters of all grades of SIL will not progress.

Because the large majority of women with ASCUS, AGUS, or LSIL will not have HSIL or in-situ carcinoma, it has recently been recommended by some that testing for HPV infection could be an alternative to triaging women to biopsy or observation.

One HPV DNA test by Digene Corporation is FDA approved for marketing under a PMA developed in 1995. The Hybrid Capture HPV DNA Assay is approved to aid in the triage of patients with equivocal or ASCUS Pap smear results in order to better determine the need for referrals to colposcopy; to serve as an adjunct to the Pap smear in the identification of women who may be at increased risk for squamous intraepithelial lesions (SIL); to distinguish between infections with HPV types which are principally associated with low-grade squamous intraepithelial lesions (LSIL), and HPV types typically associated with SIL of all grades, especially high-grade SIL (HSIL) and invasive cancer of the cervix; to aid in the diagnosis of sexually transmitted disease. On 31 March 2003, the FDA expanded approval of the Digene HC2 High-Risk HPV DNA Test to include use for screening in conjunction with the Pap smear of women over the age of 30.

Two qualitative, in-vitro tests designed for HPV genotyping have been approved by the FDA. Cervista™ HPV 16/18, which is marketed by Hologic Inc., was approved by the FDA in March 2009. Cervista™ HPV 16/18 specifically detects HPV 16 and 18. Most
recently, in March 2011, the FDA approved the cobas® HPV Test (Roche Diagnostics) which allows for HPV 16 and 18 genotyping concurrently with high-risk testing. In August 2009, the American College of Obstetricians and Gynecologists published a practice bulletin on cervical cytology screening. (16) A systematic review of the MEDLINE database for the period of June 1985 to July 2009 was described and graded recommendations provided. However, details of the strength of evidence and quality of included studies were not provided. Level A recommendations (good and consistent evidence) were:

- Cervical cancer screening should begin at 21 years, and avoided prior.
- Cervical cancer screening is recommended every two years for women between the ages of 21 and 29 years. Screening interval may be increased to every three years in women 30 years and older who have had three consecutive negative pap smears and no history of Cervical Intraepithelial Neoplasia (CIN) grade 2 or 3, immunosuppression or HIV, and who have not been exposed to diethylstilbestrol in utero.
- Both liquid-based and conventional methods of cervical cytology are acceptable.
- Cervical screening should be discontinued in women after total hysterectomy for benign indications (non-cancerous).
- Co-testing cytology with HPV DNA testing is an acceptable strategy in women over 30 years. Patients testing negative for both should not be rescreened for 3 years.

References:


**Application to Products**

This policy applies to ARBenefits. Consult ARBenefits Summary Plan Description ( SPD) for additional information.

Last modified by: Date: