Clinical Policy Title: Fluorescence in situ hybridization for cervical cancer screening

Clinical Policy Number: CCP.1156

Effective Date: April 1, 2015
Initial Review Date: January 21, 2015
Most Recent Review Date: March 5, 2019
Next Review Date: March 2020

Related policies:
None.

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

Coverage policy

AmeriHealth Caritas considers the use of fluorescence in situ hybridization for cervical cancer screening to be investigational and, therefore, not medically necessary.

Limitations:

All other uses of fluorescence in situ hybridization for cervical cancer screening are considered investigational and, therefore, not medically necessary.

Alternative covered services:

- Pap smear.
- Cervical tissue biopsy.
**Background**

Cervical cancer, or cancer of the cervix uteri, is a relatively rare cancer. In 2018, an estimated 13,240 cases of the disease were expected in the United States, with 4,170 deaths expected. After three decades of steady decline in incidence, the U.S. rate has not changed from 2005 to 2015. The five-year survival rate for diagnosed cases has remained relatively unchanged since the 1970s, at 68 to 72 percent (Noone, 2018).

While all women are at risk for cervical cancer, virtually all diagnosed cases are in women over age 30. Most cases are related to infection by human papilloma virus, a common sexually transmitted disease. Other risk factors are presence of human immunodeficiency virus, multiple sex partners, long-term use of birth control pills, having given birth to more than three children, and smoking.

Early-stage cervical cancer typically has no obvious symptoms. Thus, it is critical for women, especially those with a known risk factor, to consult their health care providers for screening. Advanced cases may be accompanied by vaginal bleeding. The major screening tests are Pap smears and the human papillomavirus test.

When diagnosed, cervical cancer cases are classified by stage, representing the size and extent of the cancer. Treatment includes either surgery, radiation therapy, or chemotherapy (U.S. Centers for Disease Control and Prevention, 2017).

Fluorescence in situ hybridization can detect recurrent diagnostic changes in hematological malignancies. For cervical cancer screening, it is a technique used to detect presence or absence of a specific genetic sequence in cells using a probe with a complementary polynucleotide sequence. The probe is tagged with a fluorescent compound and then visualized under ultraviolet light (Uhlig, 2013).

Persistent infection with high-risk human papillomavirus initiates integration of the virus’ DNA into the chromosomal DNA, which often occurs in cervical cancer. Fluorescence in situ hybridization can be used to determine the physical status of human papillomavirus (Andonovska, 2014).

Fluorescence in situ hybridization is also used for disorders other than cervical cancer; systematic reviews of multiple studies of chronic leukocytic leukemia, soft tissue cancers, and bile duct cancers appear in the professional literature.

**Searches**

AmeriHealth Caritas searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality.
- The Centers for Medicare & Medicaid Services.
• Cochrane reviews.

We conducted searches on February 6, 2019. Search terms were “fluorescence in situ hybridization” and “cervical cancer screening.”

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**

The U.S. Preventive Services Task Force guideline for cervical cancer screening mentioned that fluorescence in situ hybridization was use to test for human papillomavirus strains associated with cervical cancer, along with other approaches (U.S. Preventive Services Task Force, 2018). No such mention is made for the latest screening guideline of the American Cancer Society, American Society for Colposcopy and Cervical Pathology, American Society for Clinical Pathology in 2012; the American College of Obstetricians and Gynecologists in 2016; or the Canadian Task Force on Preventive Health Care in 2013 (Committee on Practice Bulletins — Gynecology, 2016; Dickinson, 2013; Saslow, 2012).

A review by the Agency for Healthcare Research and Quality of 10 studies failed to document consistently better sensitivity or specificity with fluorescence in situ hybridization testing for identification of CIN2+ or CIN3+ than would be expected by chance, with no association between test results and clinical outcomes (Uhlig, 2013).

A meta-analysis of nine studies (n = 1082) explored the ability of fluorescence in situ hybridization to detect high-grade cervical abnormalities, including cancer and precancerous lesions. Ability to detect abnormalities as low-grade squamous intraepithelial lesions in the telomerase RNA component gene was low (sensitivity 76 percent). The specificity of lesions detected as high-grade cervical intraepithelial neoplasia also had a low specificity rate of 78 percent. Other analyses only included a small number of studies, and authors were unable to make firm conclusions (Earley, 2014).

A study of 200 women included 104 with abnormal cytology from Pap smears and 96 with normal cytology. The positive predictive value of fluorescence in situ hybridization was 47 percent, compared to a much higher 73 percent of hybridization and human papillomavirus presence, along with a 94 percent sensitivity (Upendram, 2017).
A study of 168 women with an abnormal cervical cancer screening result used fluorescence in situ hybridization to analyze the number of chromosomal gains at 3q26, 5p15 and 20q13. The median number of cells with at least three signals increased with the severity of cervical lesions, and thus suggested that fluorescence in situ hybridization at these three loci simultaneously could represent a biomarker for detecting severity of lesions in cervical precancer (Luhn, 2013).

In one study, 320 patients with abnormal cytology lesions and 50 normal samples were assessed using fluorescence in situ hybridization. A significant (P < .0001) correlation was observed between hybridization and polymerase chain reaction. A significant correlation (P < .0001) was also found between presence of human papillomavirus detected by hybridization and disease progression, in patients with low-grade squamous intraepithelial lesions (Obermann, 2013).

Policy updates:

A total of six guidelines/other and four peer-reviewed references were added to, and four guidelines/other and five peer-reviewed references removed from, this policy in February 2019.

The policy number was changed from CP#01.01.02 to CCP.1156 in February 2019.

References

Professional associations/other:


**Peer-reviewed references:**


**Centers for Medicare & Medicaid National Coverage Determinations:**

No National Coverage Determinations identified as of the writing of this policy.
Local coverage determinations:

No Local Coverage Determinations identified as of the writing of this policy.

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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