Fluorescence in situ hybridization for cervical cancer screening

Clinical Policy ID: CCP.1156

Recent review date: 3/2025

Next review date: 7/2026

Policy contains: Cervical cancer screening; fluorescence in situ hybridization; human papillomavirus; Papanicolaou (Pap) smear.

First Choice Next has developed clinical policies to assist with making coverage determinations. First Choice Next'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, on a case by case basis, by First Choice Next 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. First Choice Next'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. First Choice Next's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, First Choice Next will update its clinical policies as necessary. First Choice Next's clinical policies are not guarantees of payment.

Coverage policy

Fluorescence in situ hybridization for cervical cancer screening is investigational/not clinically proven and, therefore, not medically necessary.

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

- Human papillomavirus tests,
- Papanicolaou smear.
- Cervical tissue biopsy.

Background

Cervical cancer, or cancer of the cervix uteri, is a relatively rare cancer. In 2024, an estimated 13,820 new cases of invasive cervical cancer and 4,360 deaths from the disease will have occurred in the United States (American Cancer Society, 2024a). While all women are at risk for cervical cancer, virtually all diagnosed cases are in women between the ages of 35 and 44, with the average age of 50 years. Most cases are related to human

papillomavirus infection. 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, whereas vaginal bleeding may accompany advanced cases (American Cancer Society, 2024b). Stage-based treatment includes either surgery, radiation therapy, or chemotherapy (American Cancer Society, 2024c).

Screening offers the best chance for detecting earlier stage invasive cervical cancer when treatment can be most successful and for detecting precancers that are likely to progress to invasive cancer (cervical intraepithelial neoplasia grade 2, cervical intraepithelial neoplasia grade 3, and adenocarcinoma in situ). The most commonly used screening methods are human papillomavirus tests, which analyze deoxyribonucleic acid in cervical cells, and Papanicolaou tests, which are cytology assessments of cervical cells (American Cancer Society, 2023).

Molecular testing for human papillomavirus has shifted the screening strategy from cytological testing alone to a combination of cytology and molecular testing. U.S. Food and Drug Administration-approved testing platforms incorporate messenger ribonucleic acid or deoxyribonucleic acid (DNA) polymerase chain reaction-based testing or DNA non-polymerase chain reaction-based testing. Human papillomavirus tests are more automated and reproducible than cytology, but no platform will detect every high-grade squamous intraepithelial lesion/cervical intraepithelial neoplasia grade 2 (Salazar, 2019).

Fluorescence in situ hybridization 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 visualized under ultraviolet light. In cervical cancer screening, fluorescence in situ hybridization would serve as an additional screening test to improve detection of precancerous lesions or earlier stage cervical cancer (Uhlig, 2013).

Findings

Guidelines

Advances in screening test technology have influenced recommendations for cervical cancer screening, particularly the inclusion of human papillomavirus testing in screening protocols. According to the U.S. Preventive Services Task Force, molecular testing for human papillomavirus must be approved as a standalone test by the U.S. Food and Drug Administration for cervical cancer screening (U.S. Preventive Services Task Force, 2018). The American Cancer Society (Fontham, 2020), the American Society for Colposcopy and Cervical Pathology (Marcus, 2021), and the American College of Obstetricians and Gynecologists (2024) have endorsed these testing recommendations.

As of this writing, no laboratory test using fluorescence in situ hybridization (e.g., OncoFish® by Ikonisys, Inc., New Haven, Connecticut) has been approved for cervical cancer screening (U.S. Food and Drug Administration, 2024).

Evidence review

The Agency for Healthcare Research and Quality (2013) reviewed the literature, including 227 full texts of the efficacy of fluorescence in situ hybridization as a screening method for cervical cancer. The panel found evidence of this test to be limited, citing need for more research on standardizing techniques, comparing different hybridization tests, and analyzing the test as an add-on human papillomavirus and cytology tests.

The review included analysis of 10 studies that failed to document consistently better sensitivity or specificity with fluorescence in situ hybridization testing for identification of pre-malignant lesions. Sensitivity and specificity were 76% and 79% for low-grade intraepithelial lesions, and 78% and 79% for high-grade cervical intraepithelial neoplasia, with no association between test results and clinical outcomes (Uhlig, 2013).

A meta-analysis of nine studies (n = 1,082) explored the ability of fluorescence in situ hybridization to detect high-grade cervical abnormalities, including cancer and precancerous lesions. The ability to detect abnormalities as low-grade squamous intraepithelial lesions in the telomerase ribonucleic acid component gene was low (sensitivity 76%). The specificity of lesions detected as high-grade cervical intraepithelial neoplasia also had a low rate of 78%. Other analyses only included a small number of studies, and authors were unable to make firm conclusions about the test's use in a well-defined screening context, which would stratify participants by human papillomavirus status (Earley, 2014).

A study of 200 women included 104 with abnormal cytology from Papanicolau smear and 96 with normal cytology. The positive predictive value of fluorescence in situ hybridization was 47%, compared to a much higher 73% of hybridization and human papillomavirus presence. Authors observed a 94% sensitivity for combined high-risk human papillomavirus and fluorescence in situ hybridization screening (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 pre-cancer (Luhn, 2013).

One study of 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).

A review of 21,642 persons with various cancers compared the ability of either fluorescence/chromogenic in situ hybridization with immunohistochemistry to detect human epidermal growth factor receptor 2 (HER2) amplification or overexpression (an effective therapeutic target in breast and gastric cancer). Of the 303 cases of cervical cancer, hybridization matched immunohistochemistry in 294, 97.03% (Yan, 2015).

In 2022, we updated the references and added no new relevant literature to the policy. No policy changes are warranted.

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In 2024, we added a meta-analysis of 26 studies in which immunohistochemistry tests resulted in a greater proportion of cervical cancer cases with overexpression of the HER2 gene than (mostly fluorescence) in situ hybridization (17.0% versus 5.9%). Authors concluded in situ hybridization was insufficiently studied (Itkin, 2021). No policy changes are warranted.

In 2025, we updated the references and guidelines and identified no new relevant research to add to the policy. No policy changes are warranted.

References

On January 16, 2025, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were "uterine cervical diseases (MeSH)," "early detection of cancer (MeSH)," "in situ hybridization, fluorescence (MeSH)," "fluorescence in situ hybridization," and "cervical cancer screening." We included the best available evidence according to established evidence

hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

Agency for Healthcare Research and Quality. Fluorescence in situ hybridization (FISH) or other in situ hybridization (ISH) testing of uterine cervical cells to predict precancer and cancer. https://www.cms.gov/medicare/coverage/determinationprocess/downloads/id89ta.pdf. Published February 16, 2013.

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Policy updates

1/2015: initial review date and clinical policy effective date: 4/2015

4/2016: Policy references updated.

4/2017: Policy references updated.

4/2018: Policy references updated.

4/2019: Policy references updated. Policy number changed to CCP.1156.

3/2020: Policy references updated.

3/2021: Policy references updated.

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3/2023: Policy references updated.

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