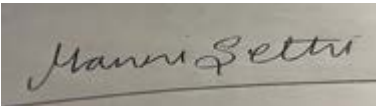


**Prior Authorization Review Panel  
MCO Policy Submission**

A separate copy of this form must accompany each policy submitted for review.  
Policies submitted without this form will not be considered for review.

<b>Plan: Keystone First</b>	<b>Submission Date:</b> 4/1/2024
<b>Policy Number:</b> ccp.1156	<b>Effective Date:</b> 4/2015 <b>Revision Date:</b> March 1, 2024
<b>Policy Name: Fluorescence in situ hybridization for cervical cancer screening</b>	
<b>Type of Submission – Check all that apply:</b>  New Policy <input checked="" type="checkbox"/> Revised Policy* Annual Review – No Revisions Statewide PDL	
<b>*All revisions to the policy <u>must</u> be highlighted using track changes throughout the document.</b>  <b>Please provide any clarifying information for the policy below:</b>  Please see track changes below.	
<b>Name of Authorized Individual (Please type or print):</b>  Manni Sethi, MD, MBA, CHCQM	<b>Signature of Authorized Individual:</b>  



# Fluorescence in situ hybridization for cervical cancer screening

Clinical Policy ID: CCP.1156

Recent review date: 3/2024

Next review date: 7/2025

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

*Keystone First has developed clinical policies to assist with making coverage determinations. Keystone First'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 by Keystone First 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. Keystone First'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. Keystone First's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First will update its clinical policies as necessary. Keystone First'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 2023, an estimated 13,960 new cases of invasive cervical cancer and 4,310 deaths from the disease will occur in the United States (American Cancer Society, 2023a). While all women are at risk for cervical cancer, virtually all diagnosed cases are in women older than age 30. Most cases are related to human papilloma virus 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, 2020). Stage-based treatment includes either surgery, radiation therapy, or chemotherapy (American Cancer Society, 2023b).

Screening offers the best chance for detecting cervical cancer in the early stages when treatment can be most successful. The most commonly used screening methods used to detect cervical precancer and early-stage cervical cancer are human papillomavirus tests, which analyze deoxyribonucleic acid in cervical cells; and Papanicolaou tests, which are cytology assessments of cervical cells (American Cancer Society, 2023c).

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 (Uhlig, 2013).

Persistent infection with high-risk human papillomavirus initiates integration of the virus' deoxyribonucleic acid into the chromosomal deoxyribonucleic acid of cervical cells. Fluorescent in situ hybridization can be used to determine the physical status of human papillomavirus (Andonovska, 2014).

## Findings

The U.S. Preventive Services Task Force guideline for cervical cancer screening mentioned that fluorescence in situ hybridization was used to test for human papillomavirus strains associated with cervical cancer, along with other approaches (U.S. Preventive Services Task Force, 2018). Organizations with screening guidelines that do not mention the test include:

- The American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology (American Cancer Society, 2020; Saslow, 2012).
- The American College of Obstetricians and Gynecologists (2023).
- The World Health Organization (2021).
- The Canadian Task Force on Preventive Health Care (Dickinson, 2013).

The Agency for Healthcare Research and Quality 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 (Agency for Healthcare Research and Quality, 2013).

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. 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 (Earley, 2014).

A study of 200 women included 104 with abnormal cytology from Papanicolaou 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 fluorescent/chromogenic in situ hybridization with immunohistochemistry to detect human epidermal growth factor receptor 2 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.

In 2023, we updated the references and added no new relevant literature to the policy. No policy changes are warranted.

In 2024, we added a meta-analysis of 26 studies that observed 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 conclude in situ hybridization is insufficiently studied (Itkin, 2021).

We also added a study of 164,137 unvaccinated females from the Wenzhou province in China not vaccinated for human papillomavirus. Fluorescence in situ hybridization revealed 17.35% tested positive for the virus (19.10% of the outpatient and 12.82% of the healthy groups (Chen, 2023).

No policy changes are warranted.

## References

On December 26, 2023, 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),” “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.

American Cancer Society. Key statistics for cervical cancer. <https://www.cancer.org/cancer/types/cervical-cancer/about/key-statistics.html>. Last updated January 12, 2023. (a)

American Cancer Society. Treating cervical cancer. <https://www.cancer.org/cancer/types/cervical-cancer/treating.html>. Last updated 2023. (b)

American Cancer Society. Screening tests for cervical cancer. <https://www.cancer.org/cancer/types/cervical-cancer/detection-diagnosis-staging/screening-tests.html>. Last updated January 3, 2023. (c)

American Cancer Society. Signs and symptoms of cervical cancer. <https://www.cancer.org/cancer/types/cervical-cancer/detection-diagnosis-staging/signs-symptoms.html>. Last updated January 3, 2020.

American College of Obstetricians and Gynecologists. Updated cervical cancer screening guidelines. Practice Advisory. <https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2021/04/updated-cervical-cancer-screening-guidelines>. Published April 2021. Reaffirmed 2023.

Andonovska J. Fluorescent in situ hybridization in the detection of human papillomavirus in cervical lesions. *Int J Infect Dis*. 2014;21(1):454. Doi: 10.1016/ijid.2014.03.1357.

Chen Q, Qu W, Zhao Y, et al. The prevalence of HPV among 164,137 women in China exhibited some unique epidemiological characteristics. *Infect Agent Cancer*. 2023;18(1):72. Doi: 10.1186/s13027-023-00553-4.

Dickinson J, Tsakonas E, Conner Gorger S, et al. Canadian Task Force on Preventive Health Care. Recommendations on screening for cervical cancer. *CMAJ*. 2013;185(1):35-45. Doi: 10.1503/cmaj.121505.

Earley A, Lamont JL, Dahabreh IJ, Cowan J, Feldman S, Uhlig K. Fluorescence in situ hybridization testing for the diagnosis of high-grade cervical abnormalities: A systematic review. *J Low Genit Tract Dis*. 2014;18(3):218-227. Doi: 10.1097/LGT.0000000000000007.

Luhn P, Houldsworth J, Cahill L, et al. Chromosomal gains measured in cytology samples from women with abnormal cervical cancer screening results. *Gynecol Oncol*. 2013;130(3):595-600. Doi: 10.1016/j.ygyno.2013.06.005.

Obermann EC, Savic Prince S, Barascud A, et al. Prediction of outcome in patients with low-grade squamous intraepithelial lesions by fluorescence in situ hybridization analysis of human papillomavirus, TERC, and MYC. *Cancer Cytopathol*. 2013;121(8):423-431. Doi: 10.1002/cncy.21280.

Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *CA Cancer J Clin*. 2012;62(3):147-172. Doi: 10.3322/caac.21139.

Uhlig K, Earley A, Lamont J, et al. Fluorescence in situ hybridization (FISH) or other in situ hybridization (ISH) testing of uterine cervical cells to predict precancer and cancer. Agency for Healthcare Research and Quality. Technology Assessments. <https://www.ncbi.nlm.nih.gov/books/NBK284799/>. Published 2013.

U. S. Preventive Services Task Force. Recommendation statement - cervical cancer: Screening for cervical cancer. *JAMA*. 2018;674-686. Doi: 10.1001/jama.2018.10897.

Upendram P, Sahni S, Mohiuddin K, et al. Amplification of specific chromosomal regions assessed by fluorescent in situ hybridization on Pap smears to be added as screening tool for identifying women at risk of progressing to cervical cancer. *Tumour Biol*. 2017;39(10):1010428317698363. Doi: 10.1177/1010428317698363.

World Health Organization. WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention. <https://www.who.int/publications/i/item/9789240030824>. Published July 6, 2021.

Yan M, Schwaederle M, Arguello D, Millis SZ, Gatalica Z, Kurzrock R. HER2 expression status in diverse cancers: Review from 37,992 patients. *Cancer Metastasis Rev.* 2015;34(1):157-164. Doi: 10.1007/s10555-015-9552-6.

Yan M, Schwaederle M, Arguello D, Millis SZ, Gatalica Z, Kurzrock R. HER2 expression status in diverse cancers: Review from 37,992 patients. *Cancer Metastasis Rev.* 2015;34(1):157-164. Doi: 10.1007/s10555-015-9552-6.

## 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.

3/2022: Policy references updated.

3/2023: Policy references updated.

3/2024: Policy references updated.