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.

Plan: Keystone First Community Health Choices	**Submission Date**: 1/1/2024
Policy Number: ccp.1474	**Effective Date:** 1/2021 **Revision Date:** December 1, 2023
Policy Name: Molecular analysis for targeted treatment in cervical cancer	

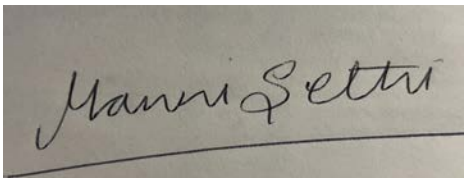
Type of Submission – Check all that apply:

New Policy
x Revised Policy*
Annual Review – No Revisions
Statewide PDL

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any clarifying information for the policy below:

New Policy See tracked changes below.

Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	**Signature of Authorized Individual:** 

Keystone First
Community HealthChoices

Molecular analysis for targeted treatment in cervical cancer

Clinical Policy ID: CCP.1474

Recent review date: 12/2023

Next review date: 4/2025

Policy contains: Cervical cancer; entrectinib; gynecological cancer; larotrectinib; NTRK; PD-L1; pembrolizumab.

Keystone First Community HealthChoices has developed clinical policies to assist with making coverage determinations. Keystone First Community HealthChoices' 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 Community HealthChoices 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 Community HealthChoices' 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 Community HealthChoices' clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First Community HealthChoices will update its clinical policies as necessary. Keystone First Community HealthChoices' clinical policies are not guarantees of payment.

Coverage policy

Molecular analysis for targeted therapy for cervical cancer is clinically proven and, therefore, may be medically necessary for indications specified in National Comprehensive Cancer Network (2023) clinical practice guidelines and U.S. Food and Drug Administration-approved package labeling for indication and usage, when using validated tests performed in Clinical Laboratory Improvement Amendment-certified laboratories:

- To assess candidacy for pembrolizumab, with or without bevacizumab (U.S. Food and Drug Administration, 2020b, 2021c, 2021d).
    - Programmed death-ligand 1 protein expression (encoded by gene CD274) using the PD-L1 IHC 22C3 pharmDx test (Dako North America Inc., Carpinteria, California).
    - Detection of mismatch repair (encoded by genes MLH1, MSH2, MSH6, and PMS2).
    - Microsatellite instability testing.
    - Tumor mutational burden using the FoundationOne® CDx assay (Foundation Medicine Inc., Cambridge, Massachusetts).
- To assess candidacy for tisotumab vedotin using validated neurotrophic tyrosine receptor kinase 1/2/3 gene fusion (U.S. Food and Drug Administration, 2023).
- To assess candidacy for entrectinib using validated neurotrophic tyrosine receptor kinase 1/2/3 gene fusion testing (U.S. Food and Drug Administration, 2019).
- To assess candidacy for larotrectinib, neurotrophic tyrosine receptor kinase 1/2/3 gene fusion testing using the FoundationOne CDx assay (U.S. Food and Drug Administration, 2020b, 2021b).

- To assess candidacy for selpercatinib using RET (re-arranged during transfection) gene fusion testing (National Comprehensive Cancer Network, 2023).

For any determinations of medical necessity for medications, refer to the applicable state-approved pharmacy policy.

Limitations

Molecular testing for any molecular variant other than the ones listed in the Coverage section (above) are investigational/not clinically proven and, therefore, not medically necessary for targeted therapy provision in cervical cancer.

Next-generation sequencing methods for tumor profiling other than the tests listed in the Coverage section (above) are investigational/not clinically proven and, therefore, not medically necessary, as their clinical utility has not been established for predicting response to the targeted therapies approved for use in members with recurrent, progressive, or metastatic cervical cancer.

Alternative covered services

Validated testing per standard of care for cervical cancer management.

Background

Cervical cancer is one of the most common cancers in women (American Cancer Society, 2023). Cervical cancer occurs most commonly between the ages of 35 and 44, but more than 20% of cases occur in women over age 65, particularly in the absence of regular screening before age 65. The primary risk factor for cervical cancer is human papillomavirus infection. Routine screening, vaccination, and treatment of precancerous lesions can prevent most cases of cervical cancer, but cervical cancer rates remain high among underscreened populations.

Approximately 90% of cervical cancers are squamous cell (epidermoid) carcinoma, and approximately 10% are adenocarcinoma, which is associated with a poorer prognosis (American Cancer Society, 2023). Other cell types occur rarely.

The revised Fédération Internationale de Gynécologie et d'Obstétrique staging system is most often used to define cervical cancer, differentiate survival outcomes, and guide treatment allocation (Bhatla, 2019). The system incorporates pre- or intraoperative clinical assessment, imaging (without preference for modality), and/or pathological measurement to estimate tumor type, size, location, and extent of spread.

Treatment choice depends on staging and several patient factors, including age, cell type, desire to preserve fertility, pregnancy status, medical condition, and biomarker status. Treatment options for localized primary disease include surgery, radiation therapy, and chemotherapy that may be offered alone or in combination for curative intent or palliative purposes (National Cancer Institute, 2023a). For patients with recurrent, persistent, or metastatic disease, targeted therapies (e.g., angiogenesis inhibitors, immune checkpoint inhibitors, and kinase inhibitors) are available.

Molecular testing is indicated to detect biomarkers that predict a favorable response to targeted therapies. For certain cancers, validated companion diagnostic tests are available that provide information essential for the safe and effective provision of a corresponding therapeutic product (U.S. Food and Drug Administration, 2020a).

Findings

A limited number of targeted treatments are available for patients with cervical cancer. These treatments are indicated for cervical cancer or solid tumors with specific molecular signatures that are predictive of treatment response and improved patient survival. Targeted treatments are currently limited to recurrent, progressive, or

metastatic disease settings, as stipulated in product labeling and National Comprehensive Cancer Network guidance (2023).

Angiogenesis inhibitors bevacizumab and approved biosimilars are indicated as first-line treatment options when used in combination with paclitaxel and cisplatin or paclitaxel and topotecan (U.S. Food and Drug Administration, 2021d). Initial regulatory approval of bevacizumab was based on the phase III randomized trial, GOG 240 (Clinicaltrials.gov identifier NCT00803062), which demonstrated a statistically significant and clinically meaningful improvement in overall survival when bevacizumab was added to chemotherapy (median survival 16.8 vs 12.9 months, hazard ratio 0.74, 95% confidence interval .58 to .94, *P* = .01). The role of testing for vascular endothelial growth factor by a validated enzyme immunoassay has not been established for predicting treatment response in cervical cancer (Du, 2014).

Neurotrophic tyrosine receptor kinase gene fusion testing is indicated to assess candidacy for the kinase inhibitors, larotrectinib and entrectinib (National Comprehensive Cancer Network, 2023). Both larotrectinib and entrectinib were approved for neurotrophic tyrosine receptor kinase gene fusion-positive solid tumors that have no known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity or have progressed following treatment and have no satisfactory alternative treatments (U.S. Food and Drug Administration, 2019, 2021c). Methods for detecting neurotrophic tyrosine receptor kinase gene fusion are immunohistochemistry, fluorescence in situ hybridization, reverse transcriptase polymerase chain reaction, and sequencing (Solomon, 2019). At that time, a U.S. Food and Drug Administration-approved companion test for detection of neurotrophic tyrosine receptor kinase gene fusion in solid tumors was not available.

Pembrolizumab is preferred as a second-line treatment option for treating cervical cancer with programmed death-ligand 1 protein expression (National Comprehensive Cancer Network, 2023). Pembrolizumab was first approved for patients with high amounts of programmed death-ligand 1 protein (defined as a combined positive score ≥ 1) detected using a U.S. Food and Drug Administration-approved companion diagnostic test (U.S. Food and Drug Administration, 2021a, 2021b). The PD-L1 IHC 22C3 pharmDx test was approved to assess candidacy for pembrolizumab based on the results of the KEYNOTE-158 study (Clinicaltrials.gov identifier NCT02628067) that investigated the validity of PD-L1 IHC 22C3 pharmDx in 98 participants with recurrent or metastatic cervical cancer. Seventy-seven participants (79%) had tumors that expressed high amounts of the programmed death-ligand 1 protein and received at least one line of chemotherapy in the metastatic setting. Treatment with pembrolizumab achieved an objective response rate of 14.3% (95% confidence interval 7.4 to 24.1). No treatment response was observed in patients whose tumors did not have high programmed death-ligand 1 expression.

Pembrolizumab is also approved for solid tumors with mismatch repair deficiency or microsatellite instability-high defects (U.S. Food and Drug Administration, 2021b). Mismatch repair status detects protein expression encoded by genes MLH1, MSH2, MSH6, and PMS2 using immunohistochemistry. Microsatellite instability testing uses polymerase chain reaction and fragment analysis of normal tissue or blood paired with tumor tissue to detect changes in short repeated deoxyribonucleic acid sequences (microsatellites). Microsatellite testing that shows mutations in 30% or more microsatellites is called microsatellite instability-high. A U.S. Food and Drug Administration-approved companion test for detection of mismatch repair deficiency or microsatellite instability is not available.

In 2020, under accelerated approval, the U.S. Food and Drug Administration (2021b) expanded the indications for pembrolizumab to include patients with unresectable or metastatic tumors with high tumor mutational burden (defined as ≥ 10 mutations/megabase) that have progressed following prior treatment and have no other satisfactory treatment options. The approval was based on the results of the KEYNOTE-158 study in which 30% of patients with tumor mutational burden-high tumors achieved a treatment response in contrast to only 6% of patients who did not have tumor mutational burden-high tumors. In half of the participants who responded to the

treatment, their tumors did not begin to grow again for at least two years. The U.S. Food and Drug Administration (2020b, 2021b) approved the FoundationOne CDx assay as a companion diagnostic for tumor mutational burden assessment in solid tumors.

In 2021, we updated the references and added a testing requirement to assess candidacy for larotrectinib using an approved companion diagnostic, in this case the FoundationOne CDx test, based on updated drug product labeling (U.S. Food and Drug Administration, 2020b, 2021c). F

In 2022, we added the U.S. Food and Drug Administration's September 2021 approval of tisotumab vedotin-tftv for adults with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy (National Cancer Institute, 2023b; U.S. Food and Drug Administration, 2023).

As of late 2022, the experience of treating advanced cervical cancer with entrectinib, Larotrectinib, and tisotumab vedotin are limited to clinical trials and case study reports. Pembrolizumab is the subject of two recent systematic reviews, which contained few studies with a control group (Qi, 2022; Schmidt, 2022).

In 2023, we updated the references, including adding RET gene fusion testing for selpercatinib candidacy to the coverage section.

References

On September 13, 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 neoplasms/therapy" (MeSH), "uterine cervical neoplasms/drug therapy" (MeSH), and "Biomarkers, Tumor/metabolism" (MAJR). 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.

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Policy updates

12/2020: initial review date and clinical policy effective date: 1/2021

12/2021: Policy references updated. Coverage modified.

12/2022: Policy references updated.

12/2023: Policy references updated.