Prior Authorization Review Panel
MCO Policy Submission

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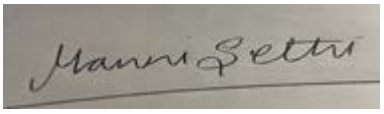
Plan: Keystone First Community HealthChoices	**Submission Date**: 5/1/2024
Policy Number: ccp.1454	**Effective Date:** 5/2020 **Revision Date:** April 1, 2024
Policy Name: Molecular analysis for targeted therapy for esophageal cancer	
Type of Submission – Check all that apply: **New Policy** **x Revised 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:** 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 therapy for esophageal cancer

Clinical Policy ID: CCP.1454

Recent review date: 4/2024

Next review date: 8/2025

Policy contains: Esophageal cancer; esophagogastric junction cancer; adenocarcinoma; gene expression profiling; molecular testing; tumor biomarker

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 esophageal cancer is clinically proven and, therefore, may be medically necessary for indications according to the National Comprehensive Cancer Network clinical practice guidelines and U.S. Food and Drug Administration-approved package labeling for indication and usage (2018, 2019, 2020).

Molecular analysis is clinically proven and, therefore, may be medically necessary when all of the following criteria are met (Bartley, 2016; National Comprehensive Cancer Network, 2023):

- Member is diagnosed with either unresectable locally advanced, locally recurrent, or suspected metastatic esophageal cancer.
- Member has a Karnofsky performance score ≥ 60% or an Eastern Cooperative Oncology Group performance score ≤ 2.
- Any of the following testing indications:
  - Human epidermal growth factor receptor 2 (HER2) testing using a U.S. Food and Drug Administration-approved companion diagnostic test (see Appendix) specific for gastric or esophagogastric junction adenocarcinoma to identify candidates for trastuzumab therapy.
  - Microsatellite instability (MSI) using polymerase chain reaction or mismatch repair testing using immunohistochemistry performed in Clinical Laboratory Improvement Amendments-approved laboratories to assess candidacy for pembrolizumab therapy.

- Programmed death ligand 1 (PD-L1) testing using a U.S. Food and Drug Administration-approved companion diagnostic test (see Appendix) to assess candidacy for pembrolizumab therapy.
- Tumor mutational burden testing using an approved test (see Appendix) to assess candidacy for pembrolizumab therapy (U.S. Food and Drug Administration, 2020b).
- Neurotrophic receptor tyrosine kinase gene fusion testing to assess candidacy for the kinase inhibitors entrectinib or larotrectinib (Appendix; U.S. Food and Drug Administration, 2018b, 2019; 2023a).

For members who are unable to undergo a traditional tissue biopsy, circulating tumor deoxyribonucleic acid (a.k.a. "liquid biopsy") using a validated next-generation sequencing-based comprehensive genomic profiling assay performed in a Clinical Laboratory Improvement Amendments-approved laboratory may be considered (Appendix; National Comprehensive Cancer Network, 2023; U.S. Food and Drug Administration, 2023a).

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

Limitations

All other uses of molecular analysis for assessing candidacy for targeted treatment in esophageal cancer are investigational and, therefore, not medically necessary.

Alternative covered services

Guideline-directed testing and treatment.

Background

Advances in cancer biology and technology have enabled more treatment options through the selective targeting of three molecular biomarkers for members with various tumor types. The three biomarkers associated with esophageal cancer are HER2 positivity, microsatellite instability status and PD-L1 expression (Nakamura, 2021).

Esophageal cancers comprise approximately 1% of all cancers diagnosed in the United States (National Cancer Institute, 2021a). They are more common among men than women and equally common among whites and African Americans. Esophageal cancers are aggressive in nature and begin in the inner mucosal layer, and almost half of patients present with metastatic disease at initial diagnosis.

The most common histologic types of esophageal cancer — adenocarcinoma and squamous cell carcinoma — arise from the two types of cells lining the esophagus (National Cancer Institute, 2021a). These two forms of differ in their pathology, location, genetic stimulus and implications for treatment and prognosis (National Comprehensive Cancer Network, 2023). Both environmental and genetic factors are risk factors for developing esophageal cancers.

Squamous cell carcinoma most often develops in the esophageal upper middle portion near the tracheal bifurcation, has a poorer prognosis, and is the most frequent cell type found in African Americans (National Cancer Institute, 2021a). Tobacco and alcohol use are major risk factors. Certain hereditary predisposition syndromes (e.g., tylosis, Bloom syndrome, and Fanconi anemia) are associated with elevated risk for esophageal squamous cell cancers.

Adenocarcinoma originates in the esophageal glandular cells typically found in the distal portion of the esophagus and is more common among caucasians. The two major underlying causes of esophageal adenocarcinoma are gastroesophageal reflux disease and Barrett's esophagus.

In many instances, esophageal cancer is a treatable disease, but rarely curable (National Comprehensive Cancer Network, 2023). The overall five-year survival rate in treated patients ranges from 5% to 30% and may be higher among the rare patient who presents with very early stage disease. The presence or absence of nodal

metastases is one of the most important prognostic factors for survival. However, these cancers are histopathologically heterogeneous, which challenges the ability to accurately predict outcomes and choose optimal treatment.

Local and systemic treatment options are available, but their selection relies primarily on histologic and anatomic diagnosis. They may be offered alone or in combination with other modalities such as endoscopic treatment, surgical intervention, chemotherapy, and radiation therapy. Palliative chemotherapy and targeted therapies for esophageal cancer can also confer an overall survival benefit compared to best supportive care (Janmaat, 2017). Compared to other tumor types, development of targeted therapy for esophageal cancer lags behind, which underscores the need for more effective therapeutic options.

Tumor gene expression profiling

Multiple genetic variants may be implicated during esophageal carcinogenesis. Refining the molecular characterization of esophageal tumors may aid in understanding tumor biology, predicting survival, and gauging metastatic potential (Pennathur, 2019). Molecular diagnostics detect genetic material (deoxyribonucleic acid and ribonucleic acid), proteins, or related molecules that provide information about health or disease.

Gene expression is the process by which a gene is activated to messenger ribonucleic acid and the proteins made from the ribonucleic acid, and it is a major determinant of the biology of both normal and malignant cells (National Cancer Institute, 2021b). Gene expression profiling employs next-generation sequencing to identify all of the genes encoded in the genome of a cell or tissue responsible for making messenger ribonucleic acid. Some tests may add fluorescent *in situ* hybridization and immunohistochemistry to their multiplatform analysis of tumors. Such information may enable individualized targeted therapy, avoid unnecessary treatment, and improve quality of life. An example of a cancer profiling test is the Caris Molecular Intelligence Tumor Profiling (Caris Life Sciences, Irving, Texas).

Findings

Genetic variants involved in esophageal cancer most commonly involve an overexpression of growth factors and genetic receptors, alterations in deoxyribonucleic acid damage response, and loss of genomic stability. According to guidelines molecular testing, considered standard of care is currently limited to known molecular variants for which targeted therapies have demonstrated improved patient outcomes in those with locally advanced, unresectable, and metastatic esophageal and esophagogastric junction disease. Treatment is based on HER2 status, microsatellite instability status, PD-L1 expression, and, in limited cases, neurotrophic receptor tyrosine kinase gene fusion status (Bartley, 2016; National Comprehensive Cancer Network, 2023). Candidates for testing should have adequate functional status defined as a Karnofsky performance score ≥ 60% or an Eastern Cooperative Oncology Group performance score ≤ 2 (National Comprehensive Cancer Network, 2023).

Immunohistochemistry, *in situ* hybridization techniques, and targeted polymerase chain reaction are considered the assays of choice (National Comprehensive Cancer Network, 2023). Laboratory analysis testing of the HER2 status is imperative for the esophageal adenocarcinoma patient to monitor the best targeted benefit of treatment (Subasinghe, 2018). There is insufficient evidence to support next-generation sequencing at the time of initial diagnosis for clinical decision making but may be used selectively for treatment identification in patients with advanced cancer in later stages of therapy. The role of circulating tumor deoxyribonucleic acid (i.e., liquid biopsy) for genomic profiling is unclear.

The National Comprehensive Cancer Network (2023) recommends the following:

- HER2 testing using immunohistochemistry for all patients with esophageal carcinomas at the time of diagnosis if metastatic disease is documented or suspected (see Appendix). The National Comprehensive Cancer Network recommends a modified HER2 four-tiered scoring system refined by

Hoffman. *In situ* hybridization techniques are recommended for equivocal results for immunohistochemistry (2+ score).
- Microsatellite instability using polymerase chain reaction or mismatch repair testing using immunohistochemistry performed in Clinical Laboratory Improvement Amendments-approved laboratories to identify candidates for PD-1 inhibitors.
- PD-L1 testing using a U.S. Food and Drug Administration-approved companion diagnostic test to aid in identifying patients for PD-1 inhibitors (see Appendix).
- Selective use of next-generation sequencing in potential candidates for entrectinib or larotrectinib when limited tissue is available and sequential testing of HER2 expression, microsatellite instability, and neurotrophic receptor tyrosine kinase gene fusions would exhaust the sample.
- Referral to cancer genetics specialist for genetic risk assessment for patients with a known hereditary cancer predisposition syndrome associated with esophageal cancers; they offer no specific recommendations for genetic testing for risk assessment.

The following targeted agents have been approved by the U.S. Food and Drug Administration for treatment of advanced esophageal and esophagogastric junction cancers:

- Trastuzumab is indicated in combination with cisplatin and capecitabine or 5-fluorouracil for the treatment of adult patients with HER2-overexpressing metastatic gastric or esophagogastric junction adenocarcinoma who have not received prior treatment for metastatic disease (U.S. Food and Drug Administration, 2018a).
- Pembrolizumab is indicated for the treatment of (U.S. Food and Drug Administration, 2020b):
    - Recurrent locally advanced or metastatic esophageal squamous cell carcinoma with disease progression after one or more prior lines of systemic therapy in adult patients whose tumors express PD-L1 (Combined Positive Score ≥10).
    - Recurrent locally advanced or metastatic gastric or esophagogastric junction adenocarcinoma with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and, if appropriate, HER2/neu-targeted therapy in adult patients whose tumors express PD-L1 (Combined Positive Score ≥1).
    - In adult and pediatric patients with unresectable or metastatic, microsatellite instability-high or mismatch repair deficient solid tumors that have progressed following prior treatment and with no satisfactory alternative treatment options.
- Ramucirumab is indicated as a single agent or in combination with paclitaxel for treatment of advanced or metastatic gastric or esophagogastric junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy for patients with human vascular endothelial growth factor receptor 2 antagonist (U.S. Food and Drug Administration, 2019a).
- Entrectinib and larotrectinib are indicated for treatment of neurotrophic receptor tyrosine kinase gene fusion-positive solid tumors without a known acquired resistance mutation that are metastatic or where surgical resection is likely to result in severe morbidity and that have no satisfactory alternative treatments or that have progressed following treatment (U.S. Food and Drug Administration, 2018b, 2019).
- Selpercatinib and dabrafenib/trametinib have recently been approved as targeted treatments for advanced disease (National Comprehensive Cancer Network, 2023).

Molecular profiling of esophageal cancers and gastric cancers has revealed similarities and differences that are important in understanding tumor biology (Pennathur, 2019). The National Cancer Institute's Cancer Genome Atlas Program is a joint effort by National Cancer Institute and the National Human Genome Research Institute to molecularly characterize more than 20,000 primary cancer and matched normal samples spanning 33 cancer

types, including esophageal cancers. Their analysis of 164 esophageal carcinomas identified several important molecular features (Cancer Genome Atlas Research Network Analysis Working Group, 2017):

- Esophageal squamous cell carcinomas share more genetic features with head and neck squamous cell carcinomas than with esophageal adenocarcinomas and may benefit from therapeutic approaches that are similar to head and neck squamous cell carcinomas.
- Esophageal adenocarcinomas strongly resembled the chromosomal instability subtype of gastric adenocarcinoma, but some molecular features, including deoxyribonucleic acid hypermethylation, occurred disproportionally in esophageal adenocarcinomas.
- Esophageal adenocarcinomas and squamous cell carcinomas share many of the same alterations in somatic pathways, but different genes within those pathways were affected, likely reflecting distinct pathophysiology and suggesting different therapeutic approaches.
- Squamous cell carcinomas showed frequent genomic amplifications of the *CCND1* and *SOX2* and/or *TP63* genes.
- Adenocarcinomas demonstrated more common amplification of the *ERBB2, VEGFA,* and *GATA4* and *GATA6* genes.
- An etiological role of human papillomavirus, which has been demonstrated in other squamous cell cancers, has not been confirmed in the three molecular subclasses of esophageal squamous cell carcinomas.

In addition, several systematic reviews and meta-analyses have attempted to identify other individual biomarkers (Creemers, 2018; Findlay, 2015; Li, 2017; Wang, 2017), pre-treatment gene expression profiles from ribonucleic acid sequencing (Gao, 2018; Visser, 2017), and circulating tumor deoxyribonucleic acid (a.k.a. liquid biopsy) (Creemers, 2017; Guraya, 2018) for prognosis and prediction of treatment response in esophageal cancer, with variable results. The variation in biomarkers that reached statistical significance across studies reflects the underlying heterogeneity of the study populations, tumor biology, laboratory detection methods, and reporting of findings that complicate any evidence synthesis. The lack of clarity also reflects limitation in the understanding of the roles many variants play in cancer genesis (e.g., microribonucleic acids). Potentially reliable variants still require validation in prospective trials within the context of high-throughput sequencing and gene expression to determine their clinical significance. Until such validation occurs, these additional biomarkers and comprehensive tumor genomic profiles offer the greatest value in clinical trial enrollment.

In 2021, we updated the references, including those for U.S. Food and Drug Administration-approved devices and product labels for ramicirumab (2020a) and pembrolizumab (2020b), and made the following policy changes based on updates to the National Comprehensive Cancer Network guidelines (2020) and product labeling:

- Tumor mutational burden reflects the total number of mutations found in the deoxyribonucleic acid of cancer cells. Solid tumors that have a high number of mutations (e.g., ≥ mutations/megabase) appear to be more likely to respond to certain types of immunotherapy. The U.S. Food and Drug Administration (2020d) expanded the indication for pembrolizumab to include any solid tumor that expresses high tumor mutational burden, as determined by an approved test (Appendix), for patients whose cancer has progressed following prior treatment and who have no satisfactory alternative treatment options. We added this indication to the policy.
- We added neurotrophic receptor tyrosine kinase gene fusion testing for patients 12 years and older with solid tumors and advanced disease to assess candidacy for the kinase inhibitors entrectinib or larotrectinib. An approved companion diagnostic test for the detection of neurotrophic receptor tyrosine kinase gene fusion in solid tumors is now available larotrectinib, but not for entrectinib (Appendix).
- We changed the coverage for liquid biopsy from investigational to medically necessary for members who are unable to undergo a traditional tissue biopsy, using a validated next-generation sequencing-

based genomic profiling assay performed in a Clinical Laboratory Improvement Amendments-approved laboratory. One nucleic acid based tumor profiling test has been approved for liquid biopsy for esophageal cancer (Appendix).

In 2023, we updated the references, including those for the U.S. Food and Drug Administration-approved devices (2023a, 2023b). We also added several systematic reviews/meta-analyses:

- In 10 studies (n = 5,595), adverse events from PD-1 based blockade therapies for esohageal cancer ranged from 79.5% to 98.0%, (24.0% to 64.0% for grade three events or higher) (Luo, 2023).
- In four studies of esophageal squamous cell carcinoma (n = 429), a high expression of sitruin-1 was linked with a higher T-stage, more advanced tumor/nodes/metastases stage, and poorer overall survival, making it a promising prognostic biomarker (Otsuka, 2022).

In 2024, we added a new guideline from the American Society of Clinical Oncology on immunotherapy and targeted therapy for advanced gastroesophageal cancers; recommendations were similar to those of the National Comprehensive Cancer Network (Shah, 2023).

We added a meta-analysis of five randomized controlled trials (n = 3,363 participants with advanced esophageal cancer) tha found immunochemotherapy based on PD-1/PD-L1 immunochemistry had significantly greater survival compared to standard chemotherapy, but not when the PD-L1 combined positive score was < 1. Toxicity of immunochemotherapy was higher, with no significant difference in treatment-related mortality (Jin, 2023).

References

On January 22, 2024, 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 “Esophageal Neoplasms" (MeSH), “Esophageal Squamous Cell Carcinoma/drug therapy” (MeSH), “Biomarkers” (MeSH), and “MicroRNAs” (MeSH). 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

4/2020: initial review date and clinical policy effective date: 5/2020

4/2021: Policy references updated. Coverage expanded.

4/2022: Policy references updated.

4/2023: Policy references updated.

4/2024: Policy references updated.

Appendix

U.S. Food and Drug Administration list of cleared or approved companion *in vitro* diagnostic devices and nucleic acid based tests

A companion *in vitro* diagnostic device provides information that is essential for the safe and effective use of a corresponding therapeutic product. The use of an *in vitro* companion diagnostic device with a specific therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, as well as in the labeling of any generic equivalents and biosimilar equivalents of the therapeutic product.

Nucleic acid based tests analyze variations in the sequence, structure, or expression of deoxyribonucleic acid and ribonucleic acid in order to diagnose disease, medical conditions, or infection with an identifiable pathogen, or to determine genetic carrier status.

Diagnostic name	PMA/510(k)/HDE	Diagnostic manufacturer	Trade name (generic) – NDA/BLA
PD-L1 IHC 22C3 pharmDx	P150013 P150013/S006 P150013/S009 P150013/S011 P150013/S014 P150013/S016 P150013/S027	Dako North America, Inc.	Esophagogastric junction adenocarcinoma and esophageal squamous cell carcinoma: • KEYTRUDA (pembrolizumab) – BLA 125514

Diagnostic name	PMA/510(k)/HDE	Diagnostic manufacturer	Trade name (generic) – NDA/BLA
HercepTest	P980018/S018	Dako Denmark A/S	Gastric and esophagogastric cancer: • Herceptin (trastuzumab) – BLA 103792
HER2 FISH pharmDx Kit	P040005 P040005/S005 P040005/S006 P040005/S009	Dako Denmark A/S	Gastric and esophagogastric cancer: • Herceptin (trastuzumab) – BLA 103792
FoundationOne Liquid CDx	P190032	Foundation Medicine, Inc.	Tumor profiling, liquid biopsy
FoundationOne CDx	P170019/S016 P170019/S017	Foundation Medicine, Inc.	Tumor mutation burden for solid tumors (≥ 10 mutations per megabase): • Keytruda (pembrolizumab) – BLA 125514 Neurotrophic receptor tyrosine kinase 1/2/3 gene fusions for solid tumors: • Vitrakvi (larotrectinib) – NDA 210861, 211710

Sources: U.S. Food and Drug Administration (2023a, 2023b).