Molecular analysis for targeted therapy for esophageal cancer

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

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Coverage policy

Molecular analysis is clinically proven and, therefore, medically necessary when all of the following criteria are met (Bartley, 2016; National Comprehensive Cancer Network, 2019):

- Member is diagnosed with either unresectable locally advanced, locally recurrent, or suspected metastatic esophageal cancer.
- Karnofsky performance score ≥ 60% or an Eastern Cooperative Oncology Group performance score 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 using immunohistochemistry or mismatch repair testing using polymerase chain reaction performed in Clinical Laboratory Improvement Amendments-approved laboratories to identify candidates for programmed death protein 1 receptor (PD-1) inhibitors.
Programmed death ligand 1 (PD-L1) testing using a U.S. Food and Drug Administration-approved companion diagnostic test (see Appendix) to aid in identifying candidates for pembrolizumab therapy.

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

Limitations

All other uses of molecular analysis in esophageal cancer are investigational.

The use of circulating tumor deoxyribonucleic acid (a.k.a. “liquid biopsy”) is investigational, as evidence of clinical efficacy has not been established (National Comprehensive Cancer Network, 2019).

There is insufficient evidence to support next-generation sequencing at the time of initial diagnosis to support clinical decision making except for members who are 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 (National Comprehensive Cancer Network, 2019).

Alternative covered services

Guideline-directed testing and treatment.

Background

Esophageal cancers comprise approximately 1% of all cancers diagnosed in the United States (National Cancer Institute, 2020). They are more common among men than women and equally common among whites and African Americans. Esophageal cancers are aggressive diseases that 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 — represent the two types of cells lining the esophagus (National Cancer Institute, 2020). These two forms of esophageal cancer differ in their pathology, tumor location, and genetic stimulus and have implications for treatment and prognosis (National Comprehensive Cancer Network, 2019). Both environmental and genetic factors are implicated in the risk of developing esophageal cancers.

Squamous cell carcinoma most often develops in the upper portion of the esophagus near the tracheal bifurcation and middle portion, has a poorer prognosis, and is the most frequent esophageal cancer cell type found in African Americans (National Cancer Institute, 2020; National Comprehensive Cancer Network, 2019). Tobacco use and alcohol consumption are its 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 glandular cells of the esophagus typically found in the distal esophagus and is more common among whites. The two major underlying causes of esophageal adenocarcinoma are esophagogastric reflux disease and Barrett’s esophagus, and these are conditions to which obesity contributes.

In most cases, esophageal cancer is a treatable disease, but it is rarely curable (National Comprehensive Cancer Network, 2019). The overall five-year survival rate in patients amenable to definitive treatment 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 outcome and choose optimal treatment.
Local and systemic treatment options are available, and their selection relies primarily on histologic and anatomic diagnosis. The treatment options may be offered alone or in combination and include endoscopic treatment, surgery, 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, 2020). 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**

According to current guidelines, the genetic variants involved in esophageal cancer most commonly involve overexpression of growth factors and genetic receptors, alterations in deoxyribonucleic acid damage response, and loss of genomic stability (National Comprehensive Cancer Network, 2019). Molecular testing considered standard of care is currently limited to known molecular variants for which targeted therapies have demonstrated improved patient outcomes in patients with locally advanced, unresectable, and metastatic esophageal and esophagogastric junction. Choice of 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, 2019). Candidates for testing should have adequate functional status defined as a Karnofsky performance score $\geq 60\%$ or an Eastern Cooperative Oncology Group performance score $\leq 2$.

Immunohistochemistry, *in situ* hybridization techniques, and targeted polymerase chain reaction are considered the gold standard assays of choice (National Comprehensive Cancer Network, 2019). 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 (2019) 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 immunohistochemistry or mismatch repair testing using polymerase chain reaction 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 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):
  o 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).
  o 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).
  o 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, 2019b).

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.

References

On January 22, 2020, 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.


### Policy updates

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

### Appendix

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

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.

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

Source: U.S. Food and Drug Administration (2020a).