Corporate Medical Policy

Esophageal Pathology Testing AHS – M2171 “Notification”

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Policy Effective July 21, 2020

Description of Procedure or Service

The esophagus is a long tube that serves to connect the mouth to the stomach. Although the esophagus is primarily a connecting organ, it experiences significant chemical and mechanical trauma. The esophagus has mechanisms and structures to withstand this damage, but molecular injury is common (Zhang et al., 2018). Both serological and genetic markers have been suggested to identify, diagnose, or assess risk in the esophagus.

Eosinophilic esophagitis (EoE) is one such condition, as its nonspecific symptoms (pain, issues swallowing, vomiting, and so on) may be accompanied by inflammatory markers in the esophagus (Bonis, 2019). Similarly, esophageal cancer is characterized by several nonspecific symptoms, while a predecessor condition, Barrett’s Esophagus (BE), may have no clinical symptoms at all (Saltzman, 2018; Spechler, 2019).

Related Policies
Molecular Panel Testing of Cancers for Diagnosis, Prognosis, and Identification of Targeted Therapy AHS – M2109

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for esophageal pathology testing when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Esophageal Pathology Testing is covered

1. Reimbursement is allowed for analysis of PD-L1 expression by immunohistochemistry in esophageal, gastric, or esophagogastric junction cancer tumors before first-line therapy
Esophageal Pathology Testing AHS – M2171 “Notification”

PD-1 inhibitors, such as pembrolizumab, in patients with locally advanced, recurrent, or metastatic disease (See Notes 1 & 2).

2. Microsatellite instability analysis or MMR analysis is considered medically necessary for individuals with locally advanced, recurrent, or metastatic esophageal, gastric, or esophagogastric junction cancer for whom PD-1 inhibitors, such as pembrolizumab, are being considered for therapy (See Notes 1 & 2).

3. Genetic testing of HER2 is considered medically necessary for individuals with esophageal, gastric, or esophagogastric junction cancer for whom trastuzumab is being considered for therapy (See Notes 1 & 2).

4. Testing for NTRK gene fusion is considered medically necessary for individuals with esophageal, gastric, or esophagogastric junction cancer before first-line or subsequent therapy with larotrectinib or entrectinib (See Notes 1 & 2).

**When Esophageal Pathology Testing is not covered**

1. The use of genetic testing, including the use of molecular panel tests and gene expression profiling, to assess the risk of eosinophilic esophagitis (EoE) is considered not medically necessary.

2. The use of genetic testing, including the use of molecular panel tests and gene expression profiling, to diagnose or monitor eosinophilic esophagitis (EoE) is considered not medically necessary.

3. Testing for risk of Barrett’s esophagus and/or esophageal, including esophagogastric junction cancer using a molecular classifier, such as the BarreGEN test, is considered not medically necessary.

4. Epigenetic analysis, including but not limited to methylation analysis, of the likelihood for Barrett’s esophagus (such as EsoGuard), esophageal, or esophagogastric junction cancer is considered investigational.

5. Reimbursement is not allowed for wide-area transepithelial sampling (WATS) for the determination of risk, the detection, or the prognosis of Barrett’s esophagus, esophageal cancers, and/or esophagogastric junction cancers.

6. The use of the Esophageal String Test (EST) to diagnose, assess, or monitor eosinophilic esophagitis (EoE) is considered investigational.

7. Liquid biopsy—the use of a non-invasive blood, saliva, or other body fluid to test for circulating tumor cells (CTCs), cell-free tumor DNA (cfDNA) fragments, and/or ribonucleoprotein complexes—for genomic profiling of esophageal and esophagogastric junction cancers is considered not medically necessary.

Note 1: For guidance on molecular panel testing of cancers, including esophageal and esophagogastric junction cancers, for targeted therapy, please see AHS-M2109 Molecular Panel Testing of Cancers for Diagnosis, Prognosis, and Identification of Targeted Therapy.

Note 2: For 5 or more gene tests being run on a tumor specimen (i.e. non-liquid biopsy) on the same platform, such as multi-gene panel next generation sequencing, please refer to AHS-R2162 Reimbursement Policy.
Esophageal Pathology Testing AHS – M2171 “Notification”

Policy Guidelines

Background
The esophagus is a long tube that connects the mouth to the stomach. Its primary function is to transport food from the mouth to the stomach. However, this organ is often exposed to difficult conditions, from the abrasive food to the acidic conditions of the stomach. Although mechanisms are in place to protect against injury (namely the tough squamous cells), it is common to see injury or disease in the esophagus (Zhang et al., 2018).

Many serological and genetic markers have been proposed as tools to assist in evaluation of esophageal pathology. Eosinophilic esophagitis (EoE), Barrett’s esophagus (BE), and esophageal cancer are typically diagnosed with histological analysis from endoscopic biopsy (Bonis, 2019; Saltzman, 2018; Spechler, 2019), but biopsies frequently require careful consideration and resources to perform properly (NCCN, 2019). For these reasons, serum and genetic markers have been suggested as noninvasive markers for esophageal pathologies.

Eosinophilic Esophagitis (EoE)
Eosinophilic esophagitis (EoE) marked by the presence of eosinophils in the esophagus. Eosinophils are typically associated with mitigating inflammation but are not normally found in the esophagus. EoE is represented by a broad set of clinical symptoms, such as difficulty swallowing, chest or abdominal pain, and feeding dysfunction. Diagnosis is established through endoscopy with biopsies to confirm eosinophilia. The current diagnostic criteria sets the cutoff for eosinophilia at ≥15 eosinophils per high power field, (60 eosinophils per mm²) although this figure has been heavily discussed (Bonis, 2019; Dellon et al., 2018).

Laboratory tests have been suggested as a noninvasive adjunct for EoE. Serum IgE will be elevated in up to 60% of EoE patients, as allergy has a strong association with EoE. Many other markers, such as eotaxin-3, major basic protein-1, tryptase, chemokines, and serum eosinophil count, have all been suggested to assist in evaluation of EoE (Bonis, 2019; Dellon et al., 2018). Immune system factors may also contribute to pathology. Since eosinophils are not normally found in the esophagus, their presence in the esophagus may suggest an underlying issue with the immune system. Various interleukins, mast cells, and T cells have all been proposed as contributing to pathogenesis, but the exact pathway and mechanisms are not completely understood (Rothenberg, 2018). Genetic features have also been used for EoE evaluation. Twin studies and family histories have indicated a role for genetics in EoE. Several genes have also been identified as potential risk factors, such as \textit{CAPN14} (an interleukin-13 regulator), \textit{TSLP} (a basophil regulator), and \textit{CCL26} (promotes eosinophil movement into esophagus) (Sherrill & Rothenberg, 2014).

Wen et al developed a diagnostic gene expression panel (“EDP”) for EoE. The authors identified candidate genes using two cohorts of EoE and control patients, then validated these genes with a separate cohort of 194 patients (91 active EoE, 57 control, 34 ambiguous, 12 reflux). The panel was found to identify EoE patients at 96% sensitivity and 98% specificity. The authors also noted that the panel could separate patients in remission from unaffected patients (Wen et al., 2013).

Shoda et al used an “EoE Diagnostic Panel” (EDP) to further classify EoE cases by histologic, endoscopic, and molecular features. The EDP consisted of 95 esophageal transcripts purported to identify EoE among both unaffected patients and patients with other conditions. 185 biopsies were studied. The authors identified three clear subtypes of EoE; subtype 1 with a normal-appearing esophagus and mild molecular changes, subtype 2 with an inflammatory and steroid-responsive phenotype, and subtype 3 with a “narrow-caliber” esophagus and severe molecular alterations. These findings were replicated in a 100-biopsy sample (Shoda et al., 2018).

Tests are commercially available for EoE. Noninvasive tests (as an alternative to endoscopy) have been recently popular. The Esophageal String Test (EST) is one such alternative. The patient
swallows a gelatin-coated capsule with a string wrapped inside. Once the capsule is in the patient’s stomach, the gelatin dissolves, allowing the capsule to pass through. The string itself is used to collect samples from the patient’s esophagus and is easily removed from the patient. From there, the sample is analyzed for several biomarkers (major basic protein-1, eotaxins 2 and 3, and so on) to provide a probability% (a trademarked “EoEscore”) of esophageal inflammation (Ackerman et al., 2019; Entertrack, 2019).

**Barrett’s Esophagus (BE)**

Barrett’s Esophagus (BE) is a condition in which the normal squamous tissue lining the esophagus is replaced by metaplastic columnar epithelium. This new epithelium contains gastric features and is typically caused by chronic gastroesophageal reflux disease (GERD). This condition predisposes to esophageal cancer. When noxious substances (gastric acid, bile, et al) are exposed to the squamous esophageal tissue, the damage is usually repaired through regeneration of these squamous cells. In BE cases, this damage is repaired not through creation of new squamous cells, but through metaplastic columnar cells. The exact reason for this is unknown. Although these metaplastic cells are more resistant to reflux-based damage than the normal squamous cells, these cells frequently show the oxidative DNA damage that is typical of cancer. Mutations in the p53 tumor suppressor gene appear to be the catalyst for cancers, as acquisition of this mutation in conjunction with the replication of the genome is conducive to carcinogenesis (Spechler, 2019).

Vollmer performed a review assessing incidence of adenocarcinoma detected during surveillance of BE. The author identified 55 studies encompassing 61371 total patients. Of the 61371 total patients, 1106 developed adenocarcinoma. Overall, the author found that the model created from the studies “predicted the per-person probability of developing cancer in 5 years of complete follow-up is approximately 0.0012”. Variables affecting this probability included mean time of follow-up, definition of Barrett’s metaplasia, and fraction of patients followed up for at least 5 years (Vollmer, 2019).

Proprietary tests are commercially available for assessment of BE, usually to evaluate risk (BE progression to cancer, risk of BE itself, and such). For example, BarreGen, offered by Interpace Diagnostics, uses tumor mutational load (a measure intended to capture total genomic instability of a sample) to calculate risk of progression. Although many ways can estimate mutational load, BarreGen tests 10 key genomic loci which are as follows: “1p (CMM1, L-myc), 3p (VHL, HoGG1), 5q (MCC, APC), 9p (CDKN2A), 10q (PTEN, MXII), 17p (TP53), 17q (RNF43, NME1), 18q (SMAD4, DCC), 21q (TFF1, PSEN2) and 22q (NF2)”. These loci encompass integral tumor suppressors and are proposed to provide an accurate picture of genomic instability (Interpace, 2019; Trindade et al., 2019). Another test, TissueCypher, also proposes to predict likelihood of progression from BE to esophageal cancer. The test measures 9 protein biomarkers that represent morphological and cellular changes (p53, p16, AMACR, CD68, COX2, HER2, K20, HIF1-alpha, CD45RO). These biomarkers are quantified and converted to a risk score (1-10) and probability of progression (Cernotics, 2019). Finally, a proprietary imaging system, WATS3D, is commercially available. This imaging system samples from a wider area, as opposed to only taking focal samples in a traditional biopsy. This technology also provides a 3-dimensional image of the sampled area. This technology purports to provide more precise sampling than the traditional 4-quadrant biopsies, claiming an increased detection rate of BE and other dysplasias (Diagnostics, 2019).

**Esophageal Cancer**

Esophageal cancers are largely divided into two groups; squamous cell carcinomas (SCCs) and adenocarcinomas (EAC). SCCs usually begin in the middle of the esophagus whereas adenocarcinomas often originate near the gastroesophageal junction. Both share a number of risk factors, such as smoking. Due to the numerous environmental risk factors for both types of cancer, it is difficult to ascertain the true impact of genetic factors (Gibson, 2018). These cancers are
Esophageal Pathology Testing AHS – M2171 “Notification”

primarily diagnosed through histologic examination, usually obtained through endoscopy (Saltzman, 2018).

Advancements have been in the molecular characterization of both types of cancer. \textit{TP53} mutations are the most common mutation seen in both types of cancer. Other frequently mutated genes in adenocarcinoma include \textit{ELMO1} and \textit{DOCK2} (enhance cell motility), \textit{ARID1A}, \textit{SMARCA4} and \textit{ARID2} (chromatin remodelers), and \textit{SPG20} (traffics growth factor receptors). Barrett’s esophagus, as the precursor to adenocarcinomas, includes certain similarities in genetic mutations but at a less severe rate. Further, the rate of overlap tended to increase with higher degree of dysplasia (Testa, Castelli, & Pelosi, 2017).

SCC mutations tend to be in genes associated with specific cellular pathways. Genes in ubiquitous pathways, such as \textit{EGFR}, \textit{NOTCH3}, and \textit{Rb}, are frequently mutated in SCC. The molecular profile of esophageal SCC tends to align more with other squamous cell cancers (such as head and neck cancers) rather than EAC (Testa et al., 2017). Numerous gene expression studies have been performed to further classify molecular subtypes of esophageal cancer (Gonzaga et al., 2017; McLaren et al., 2017; Visser, Franken, Brosens, Ruurda, & van Hillegersberg, 2017). Gene expression profiles may have utility in assessing response to treatment, prognosis, or risk assessment.

Li et al investigated potential biomarkers for lymph node metastasis for esophageal squamous cell carcinoma. 6 studies encompassing 70 patients were included. The authors identified 9 biomarkers and 4 cellular mechanisms that influence lymph node metastasis. From there, they identified three biomarkers with broader influence on prognosis of disease, \textit{PTEN}, \textit{STMN1}, and \textit{TNFAIP8}. The authors suggested that those three biomarkers should be researched further (Li, Qi, Hu, & Wang, 2019).

Plum et al evaluated \textit{HER2} overexpression’s impact on prognosis of esophageal adenocarcinoma (EAC). 428 EAC patients that underwent a “transthoracic thoraco-abdominal esophagectomy” were included. The authors identified 44 patients with \textit{HER2} positivity (IHC score 3+ or 2+ with gene amplification). This cohort was found to have a better overall survival (OS, 70.1 months vs 24.6 months), along with better histology, absence of lymphatic metastases, and lower tumor stages. The authors also noted a similarity in results to a large 2012 study (Plum et al., 2019).

Frankell et al examined the molecular landscape of esophageal adenocarcinoma (EAC). The authors assessed 551 genomically characterized EACs. A total of 77 driver genes and “21 non-coding driver elements” were identified. The authors also found an average of 4.4 driver events per tumor. A three-way association was found, between hyper-mutation, \textit{Wnt} signaling, and loss of immune signaling genes. Finally, the authors also identified “sensitizing events” (events causing a tumor to be more susceptible to a therapy) to CD4/6 inhibitors in over half of the EAC cases studied (Frankell et al., 2019).

\textit{Validity and Utility}

Ackerman et al evaluated the ability of the 1-hour Esophageal String Test (EST) to distinguish between active eosinophilic esophagitis (EoE), inactive eosinophilic esophagitis, and normal esophagi. 134 patients (62 active EoE, 37 inactive EoE, 35 normal) were included. The authors found that eotaxin 3 measured from both EST samples and the control biopsy extracts to be the best marker for distinguishing active EoE from inactive EoE (by both sensitivity and specificity). Addition of major basic protein 1 (MBP-1) improved sensitivity by 0.039 (0.652 to 0.693) and specificity by 0.014 (0.261 to 0.275) across all patients (Ackerman et al., 2019).

Hao et al performed a cost-effectiveness analysis of an “adenocarcinoma risk prediction multi-biomarker assay” (TissueCypher’s Barrett’s Esophagus Assay). A hypothetical cohort of 10000 patients with BE diagnoses (including non-dysplastic intestinal metaplasia [NBDE], indefinite for dysplasia [IND], and low-grade dysplasia [LGD]) was created. A Markov decision model was used
to compare BE management costs between assay use and the standard of care (SOC). A surveillance interval of 5 years was used. Low-risk patients were found to have a 16.6% reduction in endoscopies. High-risk patients were found to have a 58.4% increase in endoscopic treatments (compared to the SOC arm), leading to a death total of 111 for the assay arm compared to 204 in the SOC arm (a 45.6% reduction). Overall, the authors calculated the incremental cost-effectiveness ratio (ICER) to be $52,483/quality-adjusted life-year (QALY), and they found that “the probability of the Assay being cost-effective compared to the SOC was 57.3% at the $100,000/QALY acceptability threshold” (Hao, Critchley-Thorne, Diehl, & Snyder, 2019).

Eluri et al aimed to validate a genomic panel intended to represent tumor mutational load (TML). Previously, the authors evaluated a panel of 10 genomic loci from which a TML score was calculated. This mean TML was found to be significantly higher in 23 Barrett’s Esophagus (BE) patients that had progressed to high-grade dysplasia (HGD) or esophageal adenocarcinoma (EAC) as compared to 46 that had not progressed. The area under the curve in this prior study was found to be 0.95 at a mutational load (ML) cutoff of 1 (on a scale of 1-10). In the present study, 159 subjects were included. Cases had “baseline nondysplastic BE (NDBE) and developed HGD/EAC ≥ 2 years later”. 58 subjects were progressors and 101 were nonprogressors. The authors identified no difference in mean ML in pre-progression tissue in both cohorts (“ML = 0.73 ± 0.69 vs. ML = 0.74 ± 0.61”). The area under the curve at the cutoff of ML 1 was only 0.50, and the authors concluded that the “utility of the ML to stratify BE patients for risk of progression was not confirmed in this study” (Eluri et al., 2018).

Trindade et al evaluated tumor mutational load’s (ML) ability to “risk-stratify those that may progress from non-dysplastic Barrett’s oesophagus (BE) to dysplastic disease”. 28 patients were included, and ML levels were compared between those that progressed to dysplasia and those who had not. 8 total patients progressed to dysplasia (6 low-grade, 2 high-grade), and 7 of these patients had “some level” of genomic stability detected (ML ≥.5 on a scale of 1 to 10). 10 of the 20 patients that did not progress to dysplasia had “no” ML level. The authors also noted that at an ML of ≥1.5, the risk of progression to high-grade dysplasia was 33%, with a sensitivity of 100% and specificity of 85%. The authors concluded “that ML may be able to risk-stratify progression to high-grade dysplasia in BE-IND. Larger studies are needed to confirm these findings” (Trindade et al., 2019).

Moinova et al evaluated the ability of two DNA methylation signatures to detect BE. Methylation signatures of the \textit{VIM} and \textit{CCNA1} loci were evaluated in 173 patients with or without BE. \textit{CCNA1} methylation was found to have an area under the curve of 0.95 for distinguishing BE-related dysplasia compared to normal esophagi. When the data for \textit{VIM} methylation was added, the resulting sensitivity was 95%, and the resulting specificity was 91%. These findings were replicated in a validation cohort of 86 patients, with the combination of methylation markers detecting BE metaplasia at 90.3% sensitivity and 91.7% specificity (Moinova et al., 2018).

Critchley-Thorne et al validated a pathology panel to predict progression of BE to esophageal cancer. The authors identified 15 potential biomarkers, which were evaluated in both training and validation sets. This “classifier” separated patients into three different risk classes; low, intermediate, and high in the training set of 183. The authors calculated the hazard ratio of intermediate to low risk at 4.19 and high to low at 14.73. In the validation set (n = 183), the concordance index (an estimation of area under the curve) of the 15-factor classifier was 0.772, the best of the amounts tested (3, 6, 9, 12, 15, 17). The authors also noted that this classifier provided independent prognostic information that were outperformed predictions based on other clinicopathological factors, such as segment length, age, and p53 overexpression (Critchley-Thorne et al., 2016).

**Applicable Federal Regulations**

A search for “esophagus” on the FDA website on December 16, 2019 yielded 0 relevant results. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid...
Esophageal Pathology Testing AHS – M2171 “Notification”

(CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA ‘88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Guidelines and Recommendations

**United European Gastroenterology (UEG), The European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), the European Academy of Allergy and Clinical Immunology (EAACI), and the European Society of Eosinophilic Oesophagitis (EUREOS) (2017)**

These joint guidelines were published by a task force of 21 physicians and researchers for eosinophilic esophagitis (EoE). In it, they note that noninvasive biomarkers (inflammatory factors, total IgE, chemokines, tryptase, et al) are “not accurate” to diagnose or monitor EoE. They remark that absolute serum eosinophil count fared best in correlating with severity of disease but had a diagnostic accuracy of 0.754. The guidelines state that histology is necessary for monitoring. The String Test was also mentioned as having good preliminary results but required further corroboration (Lucendo et al., 2017).


These newly published international diagnostic criteria primarily include endoscopic findings. Although the guidelines emphasize ruling out other diagnoses (in which biomarkers may be useful), it does not mention any serum or genetic factors for EoE itself (Dellon et al., 2018).

**National Comprehensive Cancer Network (NCCN, 2019)**

The NCCN notes four syndromes that predispose to an increased risk for esophageal and esophagogastric junction (EGJ) cancers; tylosis with esophageal cancer (including Howel-Evans syndrome), familial Barrett’s esophagus, Bloom Syndrome (BLM), and Fanconi Anemia (FANC A-E). The RHBDF2 gene has been associated with tylosis (with non-epidermolytic palmoplantar keratosis) for genetic risk assessment, but no gene has been validated for familial Barrett’s esophagus. The NCCN concludes that “there are insufficient data to support the use of next-generation sequencing (NGS) at the time of initial diagnosis for clinical decision-making”, except for identifying treatments or clinical trial enrollment. Liquid biopsy also has an “unclear” role for genomic profiling of these cancers. Discussion of gene expression patterns or tumor mutational burden was not identified (NCCN, 2019).

The NCCN notes that MMR/MSI and PD-L1 testing “should be considered” on “locally advanced, recurrent, or metastatic” esophageal and EGJ cancers in patients who are candidates for treatment with PD-1 inhibitors. The NCCN also identifies three targeted therapeutic agents currently approved by the FDA; trastuzumab, ramucirumab, and pembrolizumab. Trastuzumab is based on HER2 status and pembrolizumab is based on MMR/MSI status. Select TRK inhibitors have also been FDA-approved for NTRK gene fusion-positive tumors. Finally, the NCCN remarks that a validated next generation sequencing (NGS) assay performed in a CLIA-approved laboratory may be used for the identification of HER2 amplification, MSI, and NTRK gene fusions (NCCN, 2019).
Genetic biomarkers such as aneuploidy and loss of p53 heterozygosity have been proposed as useful for identifying increased risk of progression in BE patients, but the NCCN remarks that these biomarkers require “further prospective evaluation” (NCCN, 2019).

Wide-area transepithelial sampling (WATS) has also been used to detect esophageal carcinomas in BE patients. However, the NCCN remarks that the “utility and accuracy of WATS for detecting high-grade dysplasia/adenocarcinoma in patients with BE needs to be evaluated in larger phase III randomized trials” (NCCN, 2019).

American College of Gastroenterology (ACG, 2016)

The ACG published guidelines on the diagnosis and management of Barrett’s Esophagus. In it, they state that no single biomarker (including genetic abnormalities) is “adequate” as a risk stratification tool. Further, they remark that an entire panel of biomarkers may be required, but no panels were ready for clinical practice (Shaheen, Falk, Iyer, & Gerson, 2016).

European Society for Medical Oncology (ESMO, 2016)

ESMO does not mention any molecular testing for diagnosis or risk assessment of esophageal cancer. Testing for HER2 is mentioned for targeted therapy with trastuzumab. The guidelines recommend following the 2016 ACG guidelines regarding Barrett’s Esophagus screening (Lordick et al., 2016).

American Society for Gastrointestinal Endoscopy (ASGE, 2019)

The ASGE recommends the WATS3D as an adjunct to “Seattle protocol biopsy sampling” (conditional recommendation, low quality of evidence). However, in the “Future Directions” section, the ASGE notes that the noninvasive genetic or blood biomarkers need to demonstrate “high diagnostic performance characteristics, easy implementation at a primary care level, high uptake in the at-risk population, and low cost”. The ASGE also notes that overall, “there is insufficient evidence on the effectiveness of screening for BE” (Qumseya et al., 2019).

Pan-Asian adapted ESMO Clinical Practice Guidelines: a JSMO-ESMO initiative endorsed by CSCO, KSMO, MOS, SSO and TOS

The only biomarker mentioned in these guidelines is HER2; intended “to select patients with metastatic oesophageal adenocarcinoma for treatment with…trastuzumab”. The guidelines go on to state that evidence for the role of other biomarkers or agents is “limited” (Muro et al., 2019).

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: 81301, 81479, 88104, 88271, 88272, 88273, 88274, 88275, 88341, 88342, 88344, 88360, 88361, 88367, 88368, 88369, 88373, 88374, 88377, 0095U, 0108U, 0114U*
Esophageal Pathology Testing AHS – M2171 “Notification”

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

**Scientific Background and Reference Sources**


Esophageal Pathology Testing AHS – M2171 “Notification”


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Esophageal Pathology Testing AHS – M2171 “Notification”


**Policy Implementation/Update Information**

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<thead>
<tr>
<th>Date</th>
<th>Details</th>
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<tbody>
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<td>5/12/20</td>
<td>New policy developed. BCBSNC will provide coverage for esophageal pathology testing when it is determined to be medically necessary because the medical criteria and guidelines are met. Medical Director review 4/2020. <strong>Policy noticed 5/12/2020 for effective date 7/21/2020.</strong> (jd)</td>
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