DRAFT Medical Coverage Policy | Adjunctive Techniques for Screening, Surveillance, and Risk Classification of Barrett Esophagus and Esophageal Dysplasia

EFFECTIVE DATE: 07|01|2025
POLICY LAST REVIEWED: 03|19|2025

OVERVIEW

Several adjunctive technologies and tests are available for screening, surveillance, and risk stratification of Barrett esophagus (BE). TissueCypher is a tissue systems pathology test that analyzes biopsy samples to predict the risk of progression to high-grade dysplasia or esophageal adenocarcinoma in patients with BE. BarreGen is a molecular test designed to assess mutational load in BE patients. EsoCheck is a non-endoscopic cell collection device used in conjunction with EsoGuard, a DNA methylation test, to detect BE and esophageal dysplasia. These technologies and tests are intended to complement standard procedures in the screening, surveillance, and risk stratification of individuals with BE or at risk of developing BE.

The following test(s) are addressed in this policy:

- TissueCypher® Barrett's Esophagus Assay (Cernostics/Castle BioSciences) – CPT code 0108U
- EsoCheck®/EsoGuard™ (Lucid Diagnostics) – CPT code 0114U
- BarreGEN (Interpace Diagnostics) – CPT code 81479

MEDICAL CRITERIA

Not applicable

PRIOR AUTHORIZATION

Medicare Advantage Plans and Commercial Products

Unless otherwise noted, for any test filed with an Unlisted CPT code, the medical necessity criteria in the Proprietary Laboratory Analyses (PLA) and Multianalyte Assays with Algorithmic Analyses (MAAA) policy would be used. Please see the Related Policies section.

POLICY STATEMENT

Medicare Advantage Plans and Commercial Products

The following tests are considered not covered for Medicare Advantage Plans and not medically necessary for Commercial Products as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome:

- EsoCheck and Esoguard for the screening and surveillance of Barrett esophagus and esophageal dysplasia.
- TissueCypher for assessing the risk of progression to high-grade dysplasia or esophageal adenocarcinoma in individuals with Barrett esophagus.
- BarreGen for assessing the risk of progression to high-grade dysplasia or esophageal adenocarcinoma in individuals with Barrett esophagus.

Medicare Advantage Plans and Commercial Products

There is no specific CPT coding for some of the services referenced in this policy. Therefore, an Unlisted CPT code should be used (see Coding Section for details). All Unlisted genetic testing CPT codes require prior authorization to determine what service is being rendered and if the service is covered or not medically necessary. See the Related Policies section.

Prior authorization is required for Medicare Advantage Plans and recommended for Commercial Products and is obtained via the online tool for participating providers. See the Related Policies section.

Note: Laboratories are not allowed to obtain clinical authorization or participate in the authorization process on behalf of the ordering physician. Only the ordering physician shall be involved in the authorization, appeal or other administrative processes related to prior authorization/medical necessity.

In no circumstance shall a laboratory or a physician/provider use a representative of a laboratory or anyone with a relationship to a laboratory and/or a third party to obtain authorization on behalf of the ordering physician, to facilitate any portion of the authorization process or any subsequent appeal of a claim where the authorization process was not followed and/or a denial for clinical appropriateness was issued, including any element of the preparation of necessary documentation of clinical appropriateness. If a laboratory or a third party is found to be supporting any portion of the authorization process, BCBSRI will deem the action a violation of this policy and severe action will be taken up to and including termination from the BCBSRI provider network. If a laboratory provides a laboratory service that has not been authorized, the service will be denied as the financial liability of the participating laboratory and may not be billed to the member.

Commercial Products
Some genetic testing services are not covered and a contract exclusion for any self-funded group that has excluded the expanded coverage of biomarker testing related to the state mandate, R.I.G.L**. §27-19-81** described in the Biomarker Testing Mandate policy. For these groups, a list of which genetic testing services are covered with prior authorization, are not medically necessary or are not covered because they are a contract exclusion can be found in the Coding section of the Genetic Testing Services and Proprietary Laboratory Analyses policies. Please refer to the appropriate Benefit Booklet to determine whether the member's plan has customized benefit coverage. Please refer to the list of Related Policies for more information.

COVERAGE
Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage, or Subscriber Agreement for applicable not medically necessary/not covered benefits/coverage.

BACKGROUND
Barrett Esophagus
Barrett esophagus (BE) is a condition in which the squamous epithelium that normally lines the esophagus is replaced by specialized columnar-type epithelium known as intestinal metaplasia in response to irritation and injury caused by gastroesophageal reflux disease (GERD). Barrett esophagus occurs in the distal esophagus. It may involve any length of the esophagus, be focal or circumferential, and is visualized on endoscopy with a different color than background squamous mucosa. Confirmation of BE requires a biopsy of the columnar epithelium and microscopic identification of intestinal metaplasia. The prevalence of BE in the United States is estimated at 5.6%. Risk factors associated with the development of BE include GERD, male gender, central obesity, and age over 50 years. The diagnosis of GERD is associated with a 10% to 15% risk of BE. However, a population-based analysis from Sweden observed that 40% of the study cohort with esophageal cancer reported no prior history of GERD symptoms.

Cancer Risk and Management
Intestinal metaplasia is a precursor to esophageal adenocarcinoma, and patients with BE are at a 40-fold increased risk for developing this disease compared to the general population. However, there are few data to guide recommendations about management and surveillance, and many issues are controversial. Guidelines from the American College of Gastroenterology (ACG) and a consensus statement from an international group of experts (Benign Barrett's and CAncer Taskforce) on the management of BE are published. The ACG recommendations for surveillance are stratified by the presence and grade of dysplasia.

When no dysplasia is detected, ACG has reported the estimated risk of progression to cancer ranges from 0.2% to 0.5% per year and endoscopic surveillance every 3 to 5 years is recommended. For low-grade dysplasia, the estimated risk of progression is 0.7% per year, and endoscopic therapy is preferred; however, endoscopic surveillance every 12 months is considered an acceptable alternative. It is recommended that both

options are discussed with the patient. Precise estimates of cancer risk are not available for individuals with low-grade dysplasia due to large disparities among studies on its natural history. Interobserver variability in the diagnosis of low-grade dysplasia with standard biopsy may be responsible, with expert pathologists commonly downgrading initial diagnoses made by community pathologists.

The Benign Barrett's and CAncer Taskforce consensus group did not endorse routine surveillance for people without dysplasia and was unable to agree on surveillance intervals for low-grade dysplasia.

For high-grade dysplasia, the estimated risk of progression is about 7% per year, and ACG has recommended endoscopic eradication therapy, with the type of procedure dependent on patient age and life expectancy, comorbidities, the extent of dysplasia, local expertise in surgery and endoscopy, and patient preference. Approximately 40% of patients with high-grade dysplasia on biopsy are found to have associated carcinoma in the resection specimen.

For patients who are indefinite for dysplasia, a repeat endoscopy should be performed at 3 to 6 months following optimization of acid suppressive medications. A surveillance interval of 12 months is recommended if an indefinite for dysplasia reading is confirmed on repeat endoscopy in these individuals. Many patients who are indefinite for dysplasia show regression to nondysplastic BE with subsequent endoscopic evaluation. It is unclear whether some cases of regression are observed due to sampling error.

Regulatory Status
On May 31, 2019, the FDA approved Lucid Diagnostics Inc.'s EsoCheck Cell Collection Device for use in collecting and retrieving surface cells of the esophagus in adults and adolescents aged 22 years and older. An update to the PMA was posted on February 7, 2023 which provided a revised indication for the use in the collection and retrieval of surface cells of the esophagus in the general population of adults and adolescents, 12 years of age and older.

BarreGEN assesses the degree of cumulative genetic derangement of the following 10 genetic loci of tumor suppressor genes (in parentheses), specifically assessing the presence of loss of heterozygosity mutations and new alleles consistent with microsatellite instability: 1p (CMM1, L-myc), 3p (VHL, HoGG1), 5q (MCC, APC), 9p (CDKN2A), 10q (PTEN, MXI1), 17p (TP53), 17q (RNF43, NME1), 18q (SMAD4, DCC), 21q (TFF1, PSEN2) and 22q (NF2).

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). EsoGuard (Lucid Diagnostics) and TissueCypher (Castle BioSciences) are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

For individuals at increased risk of BE who undergo screening with adjunctive EsoGuard and EsoCheck, the evidence includes observational studies of diagnostic accuracy and clinical utility. Relevant outcomes are test validity, overall survival, disease-specific survival, change in disease status, and quality of life. Studies have reported sensitivities of 85% to 92.9% and specificities of 72.2% to 85% for detecting BE and BE-related neoplasia. Clinical utility studies have shown high concordance (97.9% to 98.8%) between EsoGuard results and endoscopy referral decisions, but lack comprehensive follow-up data on confirmatory endoscopy outcomes. In cases where BE or esophageal adenocarcinoma were identified by EsoGuard, management changes included referral for invasive confirmatory procedures, but health outcomes from these changes were not reported. Risks associated with overdiagnosis and overtreatment require elucidation. No direct evidence of clinical utility was identified. Because EsoGuard and EsoCheck are intended to guide patient management decisions regarding referral for confirmatory endoscopy and potentially replace or supplement current

screening standards, direct evidence of improvement in health outcomes is required. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with non-dysplastic, indefinite dysplasia, or low-grade dysplasia BE who undergo standard screening with adjunctive TissueCypher, the evidence includes multiple clinical validity studies and physician impact studies. Relevant outcomes are test validity, overall survival, disease-specific survival, change in disease status, and quality of life. Clinical validity studies have reported sensitivities ranging from 29% to 71% and specificities between 79% to 95% for predicting progression to high-grade dysplasia or esophageal adenocarcinoma. Hazard ratios for high-risk versus low-risk groups ranged from 3.23 to 5.26, indicating increased progression risk for individuals classified as high-risk by TissueCypher. The assay showed improved risk stratification compared to expert pathologist reviews in several studies. Clinical utility studies have focused on the impact of TissueCypher results on patient management decisions. One author found that TissueCypher results influenced more than half of management decisions, leading to both upstaging and downstaging of treatment approaches. Another study reported that incorporating TissueCypher results significantly increased the percentage of patients receiving guideline-appropriate management compared to pathology review alone. A randomized trial using simulated patients found that physicians with access to TissueCypher results were more likely to correctly assess progression risk and offer guideline-concordant treatment. However, these studies primarily relied on simulated cases or management decision changes, and long-term patient outcomes resulting from TissueCypher-guided management have not been directly assessed. The use of adjunct TissueCypher is intended to classify individuals with BE based on their risk of progression to high-grade dysplasia or esophageal adenocarcinoma, this can change patient management decisions regarding the initiation of treatment such as esophageal eradication therapy or enhanced surveillance. Therefore, direct evidence of improvement in health outcomes is required. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have Barrett esophagus who receive standard prognostic techniques plus topographic genotyping (BarreGEN molecular testing), no studies were identified. the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

CODING

Medicare Advantage Plans and Commercial Products

The following CPT code(s) are not covered for Medicare Advantage Plans and not medically necessary for Commercial Products:

This code can be used for TissueCypher® Barrett's Esophagus Assay test:

0108U Gastroenterology (Barrett's esophagus), whole slide-digital imaging, including morphometric analysis, computer-assisted quantitative immunolabeling of 9 protein biomarkers (p16, AMACR, p53, CD68, COX-2, CD45RO, HIF1a, HER-2, K20) and morphology, formalin-fixed paraffin-embedded tissue, algorithm reported as risk of progression to high-grade dysplasia or cancer

This code can be used for EsoCheck/EsoGuard test:

0114U Gastroenterology (Barrett's esophagus), VIM and CCNA1 methylation analysis, esophageal cells, algorithm reported as likelihood for Barrett's esophagus

The following Unlisted CPT code requires prior authorization. This code can be used for BarreGEN, as there is no specific code assigned to the test.

81479 Unlisted molecular pathology procedure

RELATED POLICIES

Biomarker Testing Mandate
Proprietary Laboratory Analyses (PLA) and Multianalyte Assays with Algorithmic Analyses (MAAA)

PUBLISHED

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