Biomarker Testing for Barrett's Esophagus and Other Esophageal Disorders

Medical Policy #: 02.04.81
Original Effective Date: October 2021
Reviewed: October 2022
Revised: October 2021

NOTICE: This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations, or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This medical policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

This Medical Policy document describes the status of medical technology at the time the document was developed. Since that time, new technology may have emerged, or new medical literature may have been published. This Medical Policy will be reviewed regularly and updated as scientific and medical literature becomes available; therefore, policies are subject to change without notice.

DESCRIPTION

Tests that integrate microscopic analysis with molecular tissue or biomarker analysis are being used to aid in the treatment of Barrett's esophagus and other esophageal disorders. The tests are intended to be used adjunctively when a definitive pathologic diagnosis cannot be made, because of the inadequate specimen or equivocal histologic or cytologic findings, to inform appropriate surveillance or surgical strategies.

Barrett's Esophagus Assay (TissueCypher)

TissueCyphers Barrett's Esophagus Assay is a novel tissue biomarker test and has been validated to predict progression to high-grade dysplasia (HGD) and esophageal adenocarcinoma (EAC) in patients with Barrett's esophagus (BE).

EsoGuard
According to the PAVmed website, Esoguard is a biomarker test used to detect non-dysplactic Barrett's Esophagus (BE) include short segment and long segment, dysplastic BE including both low- and high-grade forms, adenocarcinoma of the esophagus including intramucosal, or adenocarcinoma of the gastroesophageal junction. It uses next-generation sequencing (NGS) of bisulfate converted DNA to detect the presence of Vimentin (mVIM) and CyclinA1 (mCCNA1) methylation signatures at 31 sites within those genes, to purportedly identify individuals with Barrett's esophagus.

Esophageal String Test (EST)
EnteroTrack noted the Esophageal String Test (EST) combines a string-containing capsule device, the EnteroTracker®, and Lab-Developed Tests (LDTs) for frequent, quantitative monitoring of individuals with eosinophilic esophagitis with disease biomarkers validated under CAP/CLIA standards.

A capsule containing a yard-long string is swallowed after one end of the string is taped to the individual's cheek. The string passes through the gastrointestinal tract (stretching through the esophagus, stomach, and the upper region of the small intestine) and becomes coated with digestive secretions. It is then removed and analyzed for eosinophil-derived protein biomarkers that may indicate inflammation (e.g., active eosinophilic esophagitis). The EST-captured liquid biopsy sample represents longitudinal and cross sections of the upper GI tract that can contain proteins, epithelial and inflammatory cells, bacteria, and DNA as well as intraluminal pH. A verified (2) statistical algorithm uses LDT-measured biomarker levels from the EST mucosal sample to generate an EoEScore™, a percentage probability of eosinophilic esophageal inflammation for the patient. The EoEScore™ is then reported to the ordering physician with clinical guidance for its interpretation and use.

Populations
The relevant population of interest is patients with Barrett's esophagus or other esophageal disorders (e.g., eosinophilic esophagitis). It is unclear what other clinical characteristics would identify candidates for Esoguard™, Esophageal String Test™, Barrett's Esophagus Assay/Tissue Cypher® or what previous testing is appropriate.

Interventions
The tests being considered are the Esoguard™, Esophageal String Test™, or Barrett's Esophagus Assay/Tissue Cypher® in addition to standard prognostic practices.

Comparators
The following tests and practices are currently being used to predict developing Barrett's esophagus: standard prognostic techniques generally include grading of dysplasia from endoscopy with biopsy.

Outcomes
Outcomes of interest are survival and conversion to esophageal cancer. It is not clear how the test would fit into the diagnostic pathway and effect treatment or surveillance recommendations, therefore, complete specification of other important outcomes is not possible. Because it is not yet clear how this test would be used in practice, follow-up time for outcomes is unclear.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Barrett's Esophagus Assay (TissueCypher)
(2021) Diehl et al. reported, the aim of this study was to evaluate the impact of TissueCypher on clinical decision-making in the management of BE. TissueCypher was ordered for 60 patients with non-dysplastic (ND, n=18) BE, indefinite for dysplasia (IND, n=25), and low-grade dysplasia (LGD, n=17). TissueCypher reports a risk class (low, intermediate or high) for progression to HGD or EAC within 5 years. The impact of the test results on BE management decisions was assessed.

Fifty-two of 60 patients were male, mean age 65.2±11.8, and 43 of 60 had long segment BE. TissueCypher results impacted 55.0% of management decisions. In 21.7% of patients, the test upstaged the management approach, resulting in endoscopic eradication therapy (EET) or shorter surveillance interval. The test down staged the management approach in 33.4% of patients, leading to surveillance rather than EET. In the subset of patients whose management plan was changed, upstaging was associated with a high-risk TissueCypher result, and downstaging was associated with a low-risk result ($P < 0.0001$).

TissueCypher was used as an adjunct to support a surveillance-only approach in 33.4% of patients. Upstaging occurred in 21.7% of patients, leading to therapeutic intervention or increased surveillance. These results indicate that the TissueCypher test may enable physicians to target EET for TissueCypher high-risk BE patients, while reducing unnecessary procedures in TissueCypher low-risk patients.

The study limitations are that this was a single-center experience with only two physicians providing management plans before and after receipt of test results. Data on adherence to management plan recommendations or outcomes were not collected. Our center is an expert BE referral center, and the test was ordered selectively rather than consecutively, which resulted in a higher proportion of patients with IND and LGD than would be seen in a typical community practice setting. ix of the 60 patients had

previously undergone EET and had biopsies showing residual BE when TissueCypher was ordered. While a small study on TissueCypher has been conducted in this setting, the majority of clinical studies on the test have been completed in patients who have not been previously treated. Because this was a prospective study assessing physician decision-making, there is a risk of the Hawthorne effect where participants may alter their behavior because they are being observed.

In summary, objective risk stratification provided by the TissueCypher test had a significant impact on physician decision-making in management of patients with BE. Physicians upstaged management of their patients when the test reported high-risk scores and down staged management recommendations in response to low-risk scores, indicating that the TissueCypher test has clinical utility with the potential to both improve patient outcomes and reduce overuse of procedures in management of BE. TIssueCypher Barrett's Esophagus Assay is a novel tissue biomarker test and has been validated to predict progression to high-grade dysplasia (HGD) and esophageal adenocarcinoma (EAC) in patients with Barrett's esophagus (BE). Additional studies are needed to determine the impact of test results in the community setting where the majority of patients have ND BE.

(2021) Klos et al. completed a literature review which concluded, TissueCypher is an emerging test to improve the risk stratification of patients with Barrett's esophagus. With further research, given high NPV, TissueCypher could potentially offer cost-effective management for low-risk patients, while giving us a better understanding of which patients are at high risk for progression.

(2020) Frei et al. noted an automated risk prediction assay has previously been shown to objectively identify patients with nondysplastic Barrett's esophagus (NDBE) who are at increased risk of malignant progression. To evaluate the predictive performance of the assay in 76 patients with NDBE of which 38 progressed to high-grade dysplasia/esophageal adenocarcinoma (progressors) and 38 did not (nonprogressors) and to determine whether assessment of additional (spatial) levels per endoscopy and/or multiple (temporal) time points improves assay performance. In a blinded, nested case-control cohort, progressors and nonprogressors were matched (age, sex, and Barrett's esophagus length). All random biopsy levels from the baseline endoscopy (spatial samples) and all available previous endoscopies back to 10 years before progression (temporal samples) were assayed. Because the 1:1 ratio of progressors to nonprogressors does not reflect the real-world Barrett's population, negative and positive predictive values were adjusted for prevalence.

Seventy-six patients (58 men), mean age of 63 ± 9 years, were studied. A high-risk score was associated with a prevalence-adjusted annual progression rate of 6.9%. The assay identified 31% of progressors when assessing a single biopsy level from the baseline endoscopy. Sensitivity increased to 50% and 69% in spatial and temporal analyses, respectively, while specificity remained at 95%.

The assay identified a significant subset of NDBE patients who progress at a rate comparable with published estimates for expert-confirmed low-grade dysplasia. Assessing additional spatial and temporal biopsies increased the predictive accuracy, allowing for identification of most future progressors. Additional studies will evaluate the predictive performance of the assay in low-prevalence settings.

EsoGuard
Based on review of the peer reviewed medical literature there is currently a lack of evidence regarding the effectiveness of this assay/test.

Esophageal String Test (EST)
(2019) Ackerman et al. Molecular and Biomarker Testing note in a prospective, multisite study, children, and adults (ages 7–55 years) undergoing a clinically indicated esophagogastroduodenoscopy performed an Esophageal String Test (EST) with an esophageal dwell time of 1 hour. Subjects were divided into 3 groups: active EoE, inactive EoE, and normal esophageal mucosa. Eosinophil-associated protein levels were compared between EST effluents and esophageal biopsy extracts. Statistical modeling was performed to select biomarkers that best correlated with and predicted eosinophilic inflammation.

One hundred thirty-four subjects (74 children, 60 adults) with active EoE (n = 62), inactive EoE (n = 37), and patient controls with a normal esophagus (n = 35) completed the study. EST-captured eosinophil-associated biomarkers correlated significantly with peak eosinophils/high-power field, endoscopic visual scoring, and the same proteins extracted from mucosal biopsies. Statistical modeling, using combined eotaxin-3 and major basic protein-1 concentrations, led to the development of EoE scores that distinguished subjects with active EoE from inactive EoE or normal esophagi. Eighty-seven percent of children, 95% of parents, and 92% of adults preferred the EST over endoscopy if it provided similar information.

Results support not only the EST's ability to capture mucosal inflammation but also in its ability to reflect gross evidence of surface inflammation. Comparison of EST-captured biomarkers to a pediatric- and adult-validated endoscopic EoE reference score (EREFS) (18) identified significant correlations of proximal, distal, and total EREFS with the levels of EST-captured EAPs, including Eot2 and Eot3, which showed the greatest correlations to total EREFS scores. These findings further validate the EST as a correlate for endoscopic assessment of disease activity in pediatric and adult patients with EoE. Other novel methods to assess the esophageal mucosa in patients with EoE include transnasal endoscopy, the Cytosponge, and tethered confocal microscopy. Transnasal endoscopy requires an endoscopic device, specialized training, provides a small sample size, and requires consultation with a pathologist. The Cytosponge may be more challenging to swallow and retrieve in children. Tethered microscopy requires specialized equipment. In contrast to mucosal biopsy, the EST is able to capture biomarkers along the entire length of the esophagus, thus maximizing epithelial and luminal interrogation.

Limitations of the study include the use of patient controls with an endoscopically and histologically normal esophagus, and that comparisons between subjects with active/inactive EoE were cross-sectional rather than longitudinal in the same subject. Since the study was not designed to track patients with respect to treatments, this was not fully addressed and will be the focus of future studies. Limitations of the 1-hour EST include that it cannot be used in patients who are unable to swallow pills or in those with esophageal narrowing or allergy to the gelatin capsule. A potential confounding variable is that atopic patients may swallow EAPs derived from nasal, pulmonary, or ocular secretions; these secretions may adhere to the EST and increase the EST EAP concentrations. We have not noted any correlation between self-reported comorbid allergic disease and increased levels of the EAPs in EST samples.

Results from the current study support use of the 1-hour EST as a surrogate for quantifying mucosal eosinophilic inflammation in patients with a known or suspected diagnosis of EoE. Dual quantitation of the EST-captured EAPs, Eot3 and MBP-1, can be converted by nomogram or its underlying algorithm into an "EoEScore" with multiple relevant uses including monitoring disease activity and screening for undiagnosed EoE. Use of this minimally invasive tool can improve the quality of patient's lives, reduce costs in clinical practice, and accelerate progress of therapeutic trials.

Summary of Evidence
Based on review of the peer reviewed medical literature currently there is insufficient evidence that biomarker testing for Barrett's esophagus and other esophageal disorders is an effective method to aid in the diagnosis or management of individuals when other testing methods, such as endoscopic ultrasound and microscopic analysis and staining, fail or are inconclusive. While the evidence reviewed appears to be promising additional studies are needed as there is lack of evidence demonstrating that the use of biomarker and molecular testing in the diagnosis and management of Barrett's esophagus and other esophageal disorders results in improved clinical outcomes. The current NCCN guidelines includes the following: "biomarkers such as aneuploidy and loss of herterozygosity of p53 have been associated with increased risk of progression of Barrett esophagus to HGD and/or adenocarcinoma. However, these biomarkers require further prospective evaluation as predictors of risk for the development of HGD and adenocarcinoma of the esophagus in patients with Barrett esophagus." The evidence is insufficient to determine the effects of this technology on net health outcomes.

Practice Guidelines and Position Statements

American College of Gastroenterology (ACG)
(2022) The ACG released guidelines on the diagnosis and management of Barrett esophagus. The guidelines stated:

- We could not make recommendations regarding chemoprevention or use of biomarkers in routine practice due to insufficient data.
- We suggest that a swallowable, nonendoscopic capsule sponge device combined with a biomarker is an acceptable alternative to endoscopy for screening for BE in

those with chronic reflux symptoms and other risk factors (strength of recommendation: conditional; quality of evidence: very low).

- Given the low sensitivity and specificity of the above biomarkers, the panel could not make a recommendation for routine use of p53 IHC or TissueCypher for risk stratification in patients with BE undergoing surveillance. Nevertheless, the panel does not recommend against the use of these biomarkers given that their predictive performance has been shown to be better in some cases than the histologic diagnosis, raising the possibility that these biomarkers may provide some benefit in a subset of patients with BE, particularly in those without dysplasia. The challenge for future research is to better define this subset and to demonstrate that the use of biomarkers in Barrett's populations improves on risk stratification available by clinical prediction models. The use of biomarkers ultimately should impact harder end points such as cancer incidence or death. We include recommendation 13 to document that this recommendation went through the formal GRADE review process with consideration by the authoring panel and to provide the data underpinning this decision.
  (*Accessed September 2022*)

American Gastroenterological Association (AGA)

(2011) In the Medical Position Statement on the Management of Barrett's Esophagus it was suggested against the use of molecular biomarkers to confirm the histologic diagnosis of dysplasia or as a method of risk stratification for patients with Barrett's esophagus at this time. Although biomarkers show promise, they cannot be used to confirm the diagnosis of Barrett's dysplasia and have not been shown to predict which patients with Barrett's are at risk for progression. To date, neither individual biomarkers nor panels of markers can be recommended. (Weak recommendation, low quality evidence). (*Accessed September 2022*)

American Gastrointestinal Society (AGS)

(2011) The ACG suggests against the use of molecular biomarkers to confirm the histologic diagnosis of dysplasia or as a method of risk stratification for patients with Barrett's esophagus at this time (weak recommendation, low-quality evidence). (*Accessed October 2022*).

National Comprehensive Cancer Network (NCCN)

(Version 4. 2022) The NCCN clinical practice guidelines for Esophageal and Esophagogastric Junction Cancers noted the following,

- Additionally, biomarkers such as aneuploidy and loss of herterozygosity of p53 have been associated with increased risk of progression of Barrett esophagus to HGD and/or adenocarcinoma. However, these biomarkers require further prospective evaluation as predictors of risk for the development of HGD and adenocarcinoma of the esophagus in patients with Barrett esophagus."
- in the diagnosis, classification, and molecular characterization of esophageal and EGJ cancers. Classification based on histologic subtype and molecular features helps to improve early diagnosis and has implications for therapy. An

accumulation of genetic aberrations occurs during esophageal carcinogenesis, including overexpression of growth factors and/or receptors, alterations in DNA damage response, and loss of genomic stability. Characterization of these pathways has enabled the application of molecular pathology to aid in the diagnosis, classification, and treatment of esophageal and EGJ cancers. (*Accessed September 2022*)

Regulatory Status

Device	Manufacturer	Description
Esoguard™	PAVmed	Esoguard is a *biomarker* test using next-generation sequencing (NGS) of bisulfate converted DNA to detect the presence of Vimentin (mVIM) and CyclinA1 (mCCNA1) methylation signatures at 31 sites within those genes, to purportedly identify individuals with Barrett's esophagus.
Esophageal String Test™	EnteroTrack™	Esophageal String Test ™ is a *biomarker* designed to allow frequent, quantitative monitoring of individuals with eosinophilic esophagitis.
Tissue Cypher®	Cernostics	Tissue Cypher® is intended for individuals with diagnoses at the early end of the Barrett's spectrum (nondysplastic [ND], indefinite for dysplasia [IND] or low-grade dysplasia [LGD]) and combines analysis of multiple protein-based biomarkers with tissue structure information from endoscopic biopsies to predict the risk of progression to high-grade dysplasia (HGD) and esophageal adenocarcinoma (EAC) in individuals with Barrett's esophagus.

PRIOR APPROVAL

Not Applicable.

POLICY

See Related Medical Policy:

- 02.01.23 Treatment for Gastroesophageal Reflux Disease (GERD)
- 02.04.52 Topographic Genotyping
- 02.01.63 Endoscopic Radiofrequency Ablation or Cryoablation for Barrett Esophagus
- 02.01.66 Confocal Laser Endomicroscopy

Biomarker testing for the diagnosis and management of Barrett's esophagus and other esophageal disorders is considered **investigational** including but not limited to the following, because the evidence is insufficient to determine the effects of the technology on health outcomes:

- EsoGuard (0114U)
- Esophageal String Test (0095U)
- TissueCypher Barrett's Esophagus Assay (0108U)

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 0095U Inflammation (eosinophilic esophagitis), ELISA analysis of eotaxin-3 (CCL26 [C-C motif chemokine ligand 26]) and major basic protein (PRG2 [proteoglycan 2, pro eosinophil major basic protein]), specimen obtained by swallowed nylon string, algorithm reported as predictive probability index for active eosinophilic esophagitis
- 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
- 0114U Gastroenterology (Barrett's esophagus), VIM and CCNA1 methylation analysis, esophageal cells, algorithm reported as likelihood for Barrett's esophagus

SELECTED REFERENCES

- Bennett C, Moayyedi P, Corley DA, et al. BOB CAT: A Large-Scale Review and Delphi Consensus for Management of Barrett's Esophagus With No Dysplasia, Indefinite for, or Low-Grade Dysplasia. Am J Gastroenterol. May 2015; 110(5): 662-82; quiz 683. PMID 25869390
- Shaheen NJ, Falk GW, Iyer PG, et al. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. Am J Gastroenterol. Jan 2016; 111(1): 30-50; quiz 51. PMID 26526079
- Interpace Diagnostics. Advancing patient care through molecular diagnostic testing. 2021; https://www.interpace.com/diagnostic-products. Accessed October 4, 2021.
- PAVmed. EsoGuard esophageal DNA test. http://www.pavmed.com/esoguard/. Accessed October 4, 2021.
- EnteroTrack. The Esophageal String Test™. https://enterotrack.com/enterotracker-overview . Accessed October 4, 2021.

- Diehl, David L et al. “TissueCypher Barrett's esophagus assay impacts clinical decisions in the management of patients with Barrett's esophagus.” Endoscopy international open vol. 9,3 (2021): E348-E355. doi:10.1055/a-1326-1533
- Frei, N.F., Konte, K. Bossart, E.A., et al Independent Validation of a Tissue Systems Pathology Assay to Predict Future Progression in Nondysplastic Barrett's Esophagus: A Spatial-Temporal Analysis, Clinical and Translational Gastroenterology: October 2020 - Volume 11 - Issue 10 - p e00244 doi: 10.14309/ctg.0000000000000244
- Spechler SJ, Sharma P, Souza RF, et al. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. Gastroenterology. Mar 2011; 140(3): 1084-91. PMID 21376940
- Shaheen, N.J., Falk, G., Iyer, P. etal.,Clinical Guideline: Diagnosis and Management of Barrett’s Esophagus, American Journal of Gastroenterology: January 2016 - Volume 111 - Issue 1 - p 30-50 doi: 10.1038/ajg.2015.322
- National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: esophageal and esophagogastric junction cancers. Version 4.2022. https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf
- American Gastroenterological Association Medical Position Statement on the Management of Barrett’s Esophagus. 2011.
- https://www.gastrojournal.org/action/showPdf?pii=S0016-5085%2811%2900084-9
- Hayes, Inc. Precision Medicine Research Brief. *TissueCypher Barrett’s Esophagus Assay (Cernostics)*. Hayes, Inc.; January 27, 2021.
- Shaheen, N. J., Falk, G. W., Iyer, P. G., et al. (2022). Diagnosis and Management of Barrett's Esophagus: An Updated ACG Guideline. The American journal of gastroenterology, 117(4), 559–587. https://doi.org/10.14309/ajg.0000000000001680
- Shaheen, N.J. Falk, G.W. Iyer, P..G. et al. Diagnosis and Management of Barrett's Esophagus: An Updated ACG Guideline. The American Journal of Gastroenterology: April 2022 - Volume 117 - Issue 4 - p 559-587 doi: 10.14309/ajg.0000000000001680
- Mittal, S. K., Abdo, J., Adrien, M. et al. (2021). Current state of prognostication, therapy and prospective innovations for Barrett's-related esophageal adenocarcinoma: a literature review. Journal of gastrointestinal oncology, 12(4), 1197–1214. https://doi.org/10.21037/jgo-21-117
- Klos, H.; Mahmood, S.Tahir, M. Using TissueCypher to Detect the Progression of Neoplasia in Barrett’s Esophagus - A Literature Review. The American Journal of Gastroenterology: October 2021 - Volume 116 - Issue - p S180-S181 doi: 10.14309/01.ajg.0000774104.84334.c4

POLICY HISTORY

Date	Reason	Action
October 2022	Annual Review	Policy Renewed
October 2021	Annual Review	Policy Revision, New Policy Created

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

*CPT® is a registered trademark of the American Medical Association.