02.04.81 Biomarker Testing for Barrett's Esophagus and Other Esophageal Disorders

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Related Policies:

- 02.01.66 Confocal Laser Endomicroscopy
- 02.01.63 Endoscopic Radiofrequency Ablation or Cryoablation for Barrett Esophagus
- 02.04.81 Miscellaneous Investigational Treatments for Reflux Disease

Summary

Description

Multi-analyte assays with algorithmic analyses (MAAAs) analyze multiple markers (biomarkers) that may be associated with a particular disease state and are designed to evaluate disease activity or an individual's risk for disease. This evidence review will focus on MAAAs associated with Barrett's esophagus and other esophageal disorders (eosinophilic esophagitis).

Summary of Evidence

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 with eosinophilic esophagitis who receive multi-analyte assays with algorithmic analyses (MAAAs) Esophageal String Test (EST), the evidence includes two prospective case studies. While these studies may be promising, no randomized controlled trials (RCTs) were found, and it remains unclear whether this test could be used to guide management in individual patients. RCTs are needed to validate the clinical utility of the Esophageal String Test (EST) in its use to improve patient outcomes in guiding management. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information

Not applicable.

OBJECTIVE

The object of this evidence review is to determine whether multi-analyte assays with algorithmic analyses (MAAAs) analyzing multiple markers (biomarkers) improves the net health outcome in the management of individuals with Barrett's esophagus (BE) and other esophageal disorders (eosinophilic esophagitis).

PRIOR APPROVAL

Not applicable.

POLICY

Multi-analyte assays with biomarker analysis including but not limited to the following:

- Esophageal String Test

- TissueCypher Barrett's Esophagus Assay

is considered **investigational** for the management of Barrett's Esophagus and other esophageal disorders (i.e., eosinophilic esophagitis) because the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

POLICY GUIDELINES

Note:
Iowa House File 2668 (Iowa Code section 514C.36) requires that certain health plans issued or renewed on or after January 1, 2025 "provide coverage for biomarker testing for the purposes of diagnosing, treating, appropriately managing, or monitoring a disease or condition in a covered person when the biomarker testing has demonstrated clinical utility." Iowa House File 2668 defines clinical utility as "sufficient medical and scientific evidence indicating that the use of a biomarker test will provide meaningful information that affects treatment decisions and guides improvement of net health outcomes, including an improved quality of life or longer survival." Wellmark has reviewed this Medical Policy in light of Iowa House File 2668.

Coding

See the Codes table for details.

BACKGROUND

Barrett's Esophagus

Barrett's esophagus (BE) is a complication of chronic esophagitis and is characterized by metaplasia in the epithelial lining of the esophagus that replaces the stratified squamous epithelium that normally lines the distal esophagus. The resulting cellular change is pre-malignant phase that may lead to esophageal cancer. Endoscopic biopsies to screen for high-grade dysplasia (HGD) or esophageal carcinoma (EAC) are recommended.

There have been a number of promising molecule markers for cancer risk that have been proposed as alternatives to biopsies to identify dysplasia in BE including TissueCypher. TissueCypher Barrett's Esophagus Essay (Castle Biosciences Inc), also known as TSP-9 assesses 15 characteristics from 9 protein-based biomarkers in an esophagus tissue sample during an upper gastrointestinal endoscopy (EGD) in individuals with BE in order to identify candidates for eradication therapy (high-risk individuals) or reduced surveillance (low-risk individuals). This test calculates a risk score ranging from 1 to 10, and is reported as low, intermediate or high-risk of progression to HDG/EAC. The 9 protein biomarkers assessed in this testing include the following: p16, Alpha-methylacyl-CoA racemase (AMACR), p53, Human epidermal growth factor receptor 2 (HER2), Cytokeratin-20 (K20), CD68, Cyclo-oxygenase-2 (COX-2), Hypoxia-inducible factor 1-alpha subunit (HIF-1α) and CD45RO.

Eosinophilic Esophagitis

Eosinophilic esophagitis is a chronic immune system disease in which white blood cells called eosinophils build up in the esophagus which is a reaction to foods, allergens or acid reflux that can inflame or injure the esophageal tissue. Damaged esophageal tissue can lead to difficulty swallowing or cause food to get stuck when swallowing.

Esophageal string test is a test that is performed in the office which involves swallowing a capsule attached to a string. The capsule dissolves in the stomach and releases a sponge that the provider will pull out of the mouth using the string, and as the sponge is pulled out it will sample the esophageal

tissues to analyze the eosinophil-derived protein biomarkers that indicate inflammation e.g., active eosinophilic esophagitis without endoscopy.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (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.

RATIONALE

This evidence review was created in October 2021 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through December 2025.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Clinical Context and Test Purpose

In individuals with BE or eosinophilic esophagitis, the purpose of utilizing multi-analyte assays with algorithmic analyses (MAAAs) analyzing multiple markers (biomarkers) is to evaluate disease activity or an individual's risk for disease to inform treatment management.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest are individuals with BE or signs or symptoms of eosinophilic esophagitis.

Interventions

The tests being considered are the following:

- TissueCypher Barrett's Esophagus Essay
- Esophageal String Test

Comparators

The following practice is currently being used to make decisions regarding BE: Upper endoscopy with biopsy.

The following practice is currently being used to make decisions regarding eosinophilic esophagitis: Upper endoscopy with biopsy, and laboratory testing looking for higher than usual eosinophil counts or total immunoglobulin E levels that may suggest an allergy.

Outcomes
The general outcomes of interest are test validity, correct treatment, avoiding unnecessary subsequent testing, harms of invasive testing, and quality of life (QOL).

Study Selection Criteria
For the evaluation of the clinical validity of the tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described
- Included a validation cohort separate from the development cohort.

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).

Review of Evidence

TissueCypher Barrett's Esophagus Essay

Clinical Validity
Davison et al. (2020) conducted an independent, blinded validation study of the TissueCypher assay to predict the progression to high-grade dysplasia (HGD) or esophageal adenocarcinoma (EAC) in patients with BE. The study included 58 patients who progressed to HGD/EAC and 210 matched non-progressors. Participants had biopsies at baseline assessed by subspecialists in a blinded manner. The authors estimated the sensitivity and specificity of the test at 5 years for a 3-tier classification (defined as low, intermediate, or high risk) were 29% and 86%, respectively; using a 2-tier classification system (low risk and combined intermediate/high risk) increased the sensitivity and specificity to 40% and 86%. Expert diagnosis of LGD yielded a sensitivity and specificity of 19% and 88%, respectively, and a sensitivity and specificity of the original diagnosis (i.e. diagnosis recorded in the health records, not diagnosed by study subspecialists) of LGD were 26% and 66%, respectively. The prevalence-adjusted PPV was 23%, with a prevalence-adjusted NPV of 96.4% for TissueCypher. The assay stratified BE patients based on progression risk, with the high-risk group at 4.7-fold increased risk (95% CI, 2.5 to 8.8; p<.0001) compared to the low-risk group, and had a superior prediction of risk than stratification by p53 status alone (Hazard ratio [HR], 1.6; 95 %CI, 0.8 to 3.5). The high-risk class provided predictive power independent of pathologic diagnosis and other clinical variables. Participants with non-dysplastic Barrett's esophagus (NDBE) who scored high-risk progressed at a higher rate (26%) than patients with subspecialist-confirmed low-grade dysplasia (21.8%) at 5 years. Multivariate analyses found that when evaluating the TissueCypher test's performance with several clinical variables (age, sex, original diagnosis, segment length, subspecialist diagnosis, p53 status, and the presence of hiatal hernia), that classification as high-risk by the assay remained a significant predictor of progression.

Frei et al. (2020) conducted a blinded, case-control validation study of the TissueCypher assay to predict future progression in NDBE. The study included 76 individuals with NDBE, of which 38 progressed to HGD/EAC and 38 who did not progress from the Amsterdam ReBus cohort; endoscopy selection was 2 to 5 years prior to HGD/EAC progression for individuals who progressed and 5 years prior to the end of surveillance for non-progressors. The assay identified 31% of progressors when assessing a single biopsy level (most distal biopsy closest to the gastroesophageal junction) from the baseline endoscopy

and had a sensitivity and specificity of 30.4% and 95%, respectively. The PPV at 5 years was 24.6% with an NPV of 96.6%. In a spatial analysis using multiple biopsy levels, the sensitivity, specificity, 5-year PPV, and NPV increased to 49.8%, 95%, 34.8%, and 97.7%, respectively. A spatial-temporal analysis using data from multiple biopsy levels at multiple time points resulted in an increased sensitivity of 68.5%. The study found that individuals who scored high risk were 3.23 (95% CI, 1.6 to 6.5; P=.0032) times more likely to progress to HGD/EAC than individuals with low-risk categorization.

Khoshiwal et al. (2023) compared the risk stratification performance of the TissueCypher assay versus benchmarks of generalist and expert pathology in patients with BE with LGD. The study included 154 patients, of which 24 progressed to HGD/EAC within 5 years. Slides were made available for review on a web-based platform by 14 expert pathologists from multiple countries, including the United States. TissueCypher demonstrated higher sensitivity (70.8%, 95% CI, 54% to 88%) than the mean pathology review (63.2%, range 33% to 88%) in detecting patients who progressed. However, the specificity wasn't significantly different between groups (78.5% for TissueCypher vs. 73.5% for expert pathologist review). Prevalence-adjusted PPV wasn't significantly different between groups (TissueCypher, 23.7% vs pathologist review, 22.6%), but NPV was higher for the TissueCypher test (93.6% vs. 91.4%; p=.00002).

Davison et al. (2023) evaluated the performance of TissueCypher versus current clinicopathologic variables in a pooled analysis of 699 patients (n=40 HGD/EAC; n=150 progressors; n=509 no progression) with BE from 5 published studies, including the studies by Khoshiwal et al. (2023), Frie et al. (2020), and Davidson et al (2020). The pathology diagnosis was NDBE in 56.1% of individuals, 9% had indeterminate dysplasia (IND), and 34.9% had LGD; in expert pathology review, provided by GI subspecialist pathologists in the studies, 81.1% of patients had NDBE, 7.2% had IND, and 11.7% had LGD. TissueCypher scored 16% of patients as high risk, 13.7% as intermediate risk, and 70.2% as low risk of developing HGD/EAC within 5 years. The authors determined the pooled sensitivity of TissueCypher in detecting progressors was 62.3% compared to 28.3% for expert pathologist review (p<.05); however, specificity was higher for expert review compared to TissueCypher (93.1% vs. 79.8%). The NPV (97.3% vs. 96.1%) and PPV (25.1% vs. 18.4%) appeared similar between the TissueCypher and expert pathologist review. However, the number needed to predict, the number of individuals who need to be examined in order to correctly predict the diagnosis of one person, was significantly lower in the TissueCypher group (n=32) compared to expert pathologist diagnosis (n=70; p<.05) of LGD. A multivariable analysis (including hatial hernia presence, segment length, age, sex, NDBE, IND, or LGD status, and TissueCypher result found that TissueCypher categorization of intermediate-risk (HR vs. low-risk, 2.21; 95% CI, 1.30 to 3.71) and high-risk (HR vs. low-risk, 5.26; 95% CI, 3.52 to 8.13) were significant predictors of progression to HGD or EAC.

Clinical Utility

No direct evidence of clinical utility was identified, as published studies comparing health outcomes in individuals managed with standard of care compared to adjunct screening with TissueCypher are not available.

Diehl et al. (2021) prospectively evaluated the impact of TissueCypher on clinical decision-making in the management of BE. The study included 60 individuals with BE categorized as NDBE (n=18), IND (n=25), or LGD (n=17). All patients were evaluated by 2 physicians with their clinical management approach recorded both before and after receiving the results of the TissueCypher assay. The TissueCypher results impacted 55.0% (33/60) of management decisions. In 21.7% (13/60) of patients, the test upstaged the management approach, resulting in endoscopic eradication therapy (EET) or shorter surveillance intervals. The test downstaged the management approach in 33.4% (20/60) 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<.0001).

Duits et al. (2023) evaluated the TissueCypher assay compared to generalist (n=16) or expert pathologist (n=14) review for risk stratification for progression to EAC/HGD in BE patients with LGD. Pathologist participants were recruited from multiple countries, including the United States. The study included 154 patients with LGD, 24 of which progressed to HGD or EAC within 5 years of follow-up. Management decisions were simulated 500 times with varying pathology reviewers. TissueCypher with standard pathology review significantly increased the percentage of individuals receiving appropriate management from a median value of 80.8% (Interquartile range [IQR], 64 to 92) with standard pathologic review alone to 100% (IQR, 81 to 100; p=.0007). The percentage of patients with 100% of simulations receiving appropriate management significantly increased from 9.1% for pathology alone to 58.4% when TissueCypher results were used as an adjunct to pathology and further to 77.3% when only TissueCypher results were used. TissueCypher increased the percentage of progressors receiving EET from a median of 24.4% (IQR, 2 to 79) to 46.8% (IQR, 23 to 88).

Peabody et al. (2023) conducted a three-arm randomized controlled trial to determine the impact of the TissueCypher assay on adherence to evidence-based guidelines for simulated patients with Barrett's esophagus. The study included 259 practicing gastroenterologists and gastrointestinal surgeons. Each physician was assigned to one of 3 groups: Intervention 1, which received TissueCypher results; Intervention 2, which had the option to order TissueCypher; and the control arm, which did not have the TissueCypher information or the option to order the test. Each physician completed 2 rounds of data collection, where they cared for 3 simulated patients (NDBE, IND, and LGD which had 3 variants [a high-risk clinical profile with a high-risk TissueCypher result, a low-risk clinical profile but a high-risk TissueCypher result, and a high-risk clinical profile with a low-risk TissueCypher result]); at the end of the first data collection period, physicians who were assigned to either intervention 1 or 2 switched to the other arm for the second data collection period. Intervention 1, which received TissueCypher results, was significantly more likely to correctly assess the risk of progression to HGD/EAC and offer treatment in accordance with guidelines compared to the control group (6.9%, 95% CI 1.4% to 12.3%); this resulted in a diagnosis and treatment score (DxTx), assessing how accurately adherence was to guideline-based practices, increase of 4.2% across groups which the authors state represents a statistical and clinically significant finding. For cases requiring annual endoscopic surveillance, there was a significant improvement in adherence for intervention 1, with a difference-in-difference of 18.5% (p=.019). No differences between groups were identified for the assessment of simulated cases requiring guideline-recommended EET. Intervention 2, which had the option to order TissueCypher, ordered the test in 21.9% of cases. Those who ordered the test performed similarly to intervention 1 and adhered more closely to clinical guideline recommendations, but those who did not order the test performed similarly to the control group.

Esophageal String Test

In 2022, McGowan et al summarized the existing literature for several promising invasive tests to measure the disease activity of eosinophilic esophagitis (EoE). Retrospective and prospective observational studies, peer-reviewed reviews, and systematic reviews were selected. The Esophageal Sting Test has been assessed in two studies to date Ackerman et al (2019) below and Furuta et al in 2013. In the Furuta et al 2013 study in 41 patients, ages 7-20 years, undergoing an endoscopy with biopsy, the EST was swallowed the night prior to the EGD and remained in place until the time of the endoscopy (~16 hours). Of the 41 patients enrolled, 14 were found to have active EoE, 8 had inactive EoE, 4 had GERD, and 15 were healthy controls. The authors found that the levels of eosinophil-associated proteins in the EST samples correlated significantly with the peak and mean number of tissue eos/hpf, as well as the levels of eosinophil-associated proteins. This study provided the proof of concept that an esophageal string could be utilized to measure the degree of eosinophilic inflammation in EoE. In summary EST may be a promising non-invasive technique for assessing esophageal eosinophilia,

however, EST does have some notable limitations: first, 14% of consented patients in the most recent study (Akerman et al 2019 below) were unable to complete the procedure due to gagging, which suggests that the EST may not be a viable option in all patients; and second, the EST has not yet been validated for longitudinal use, so it remains unclear whether this test could be used to guide management in individual patients. The authors concluded “Further research into whether these tools could be used in these clinical situations is clearly needed and will help guide how they can be implemented in clinical practice, especially for the Allergist-Immunologist.”

In 2019 Ackerman et al in a prospective, multisite study, children and adults (ages 7-55 years) undergoing a clinically indicated esophagogastroduodenoscopy performed an Esophageal String Test (EST) to determine whether a 1-hour EST accurately distinguishes active from inactive eosinophilic esophagitis (EoE). 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. 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. An EoE Endoscopic Reference Score (EREFS) was recorded for each subject. Scores noted and graded the presence of the following esophageal features: edema, rings, exudates, furrows, and stricture. All EAPs from mucosal biopsy sample extracts correlated significantly with mucosal eosinophil counts, ranging from r = 5 0.61 for Eot3 to 0.40 for Eot2 (all P < 0.0001). Similarly, there was a significant correlation of all EAPs from 1-hour EST string samples with mucosal eosinophil counts, ranging from r = 5 0.70 and 0.68 for CLC/Gal-10 and Eot3, respectively, to r = 5 0.53 for Eot2) (all P < 0.0001). No serious adverse events were recorded. Of the 134 subjects 44% completed a follow-up survey. Limitations of this study included 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; and study was not designed to track patients with respect to treatments and should be the focus of future studies. Limitations of the 1-hour EST include that it cannot be utilized in patients who cannot swallow pills or in those individuals with esophageal narrowing or allergy to 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. The authors concluded results from the current study support the use of the 1-hour EST as a surrogate for quantifying mucosal eosinophilic inflammation in patients with a known or suspected diagnosis of EoE.

Section Summary

Direct evidence of clinical utility for the adjunctive use of TissueCypher was not identified. Indirect evidence of clinical utility includes retrospective and prospective validation studies, as well as physician impact studies evaluating the test's influence on clinical decision-making in simulated cases. Clinical utility studies have focused on the impact of TissueCypher results on patient management decisions. One author found that TissueCypher results influenced 55% of management decisions, leading to both upstaging (21.7%) and downstaging (33.4%) of treatment approaches. Another study reported that incorporating TissueCypher results significantly increased the percentage of patients receiving guide-line 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. Clinical validity studies have evaluated the TissueCypher assay's ability to predict progression to high-grade dysplasia or esophageal adenocarcinoma in patients with Barrett's esophagus. Sensitivities ranged from 29% to 71%, with specificities between 78.5% and 95%. PPVs ranges from 23% to 25% with NPVs ranging from 94% to 97% across the included TissueCypher validation studies. The assay showed improved risk stratification compared to expert pathologist review in some studies. Hazard ratios for high-risk versus low-risk groups ranged from 3.23 to 5.26, indicating increased progression risk for patients classified as high-risk by

TissueCypher. The use of adjunct TissueCypher is intended to classify individuals with Barret Esophagus 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.
For individuals with eosinophilic esophagitis who receive multi-analyte assays with algorithmic analyses (MAAAs) Esophageal String Test (EST), the evidence includes two prospective case studies. While these studies may be promising, no randomized controlled trials (RCTs) were found, and it remains unclear whether this test could be used to guide management in individual patients. RCTs are needed to validate the clinical utility of the Esophageal String Test (EST) in its use to improve patient outcomes in guiding management. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Gastroenterology (ACG)

In 2022, the American College of Gastroenterology (ACG) updated the guideline on diagnosis and management of Barrett’s esophagus that included the following recommendations:

- “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).
- “We could not make a recommendation on the use of predictive tools (p53 staining and TissueCypher) in addition to standard histopathology in patients undergoing endoscopic surveillance of BE.”
    - “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."

- "Although TissueCypher uses automated image analysis to eliminate subjectivity in interpretation, various external factors such as cell stress, DNA damage, and ongoing GERD might alter some, if not all, of the 15 features detected on the panel producing erroneous estimates; the same holds true for these factors in altering expression levels of p53."

American Society for Gastrointestinal Endoscopy (ASGE)

In 2019, the American Society for Gastrointestinal Endoscopy (AGS) guideline on screening and surveillance of Barrett's esophagus included the following information under Future Directions:

- "Future studies that refine and validate existing prediction tools for screening are required, and these tools may require the addition of noninvasive genetic or blood biomarkers. Before we embrace the new generation of less-invasive screening techniques and replace our current approach of using standard endoscopy for screening, these new techniques need to demonstrate high diagnostic performance characteristics, easy implementation at primary care level and high uptake in the at-risk population."

National Comprehensive Cancer Network (NCCN)

The National Comprehensive Cancer Network (NCCN) current clinical practice guidelines (4.2025) for Esophageal and Esophagogastric Junction Cancers noted the following,

- "Additionally, biomarkers such as aneuploidy and loss of heterozygosity 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."

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review can be located at clinicaltrials.gov.

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CODES

To report provider services, use appropriate CPT codes, HCPCS codes, Revenue codes, and/or ICD diagnosis codes.

Codes	Number	Description
CPT		
	0095U	Eosinophilic esophagitis, 2 protein biomarkers (Eotaxin-3 [CCL26 {C-C motif chemokine ligand 26}] and Major Basic Protein [PRG2 {proteoglycan 2, pro eosinophil major basic protein}], enzyme-linked immunosorbent assays (ELISA), specimen obtained by esophageal string test device, algorithm reported as probability of active or inactive 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 (TissueCypher Barrett’s Esophagus Assay)
HCPCS		
	None	
Type of Service	Laboratory	
Place of Service	Physician Office/Outpatient	

POLICY HISTORY

Date	Reason	Action
December 2025	Interim Review	Policy Renewed
October 2025	Annual Review	Policy Renewed
October 2024	Annual Review	Policy Renewed
October 2023	Annual Review	Policy Revised

Date	Reason	Action
October 2022	Annual Review	Policy Renewed
October 2021		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

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