7.01.167	Adjunctive Techniques for Screening, Surveillance, and Risk Classification of Barrett Esophagus and Esophageal Dysplasia		
Original Policy Date:	January 1, 2025	**Effective Date:**	January 1, 2025
Section:	7.0 Surgery	**Page:**	Page 1 of 27

Policy Statement

I. Wide-area transepithelial sampling with three-dimensional computer-assisted analysis (WATS3D) is considered **investigational** for all indications, including but not limited to the screening and surveillance of Barrett esophagus and esophageal dysplasia.

II. EsoCheck and Esoguard are considered **investigational** for the screening and surveillance of Barrett esophagus and esophageal dysplasia.

III. TissueCypher is considered **investigational** for assessing the risk of progression to high-grade dysplasia or esophageal adenocarcinoma in individuals with Barrett esophagus.

IV. BarreGen is considered **investigational** for assessing the risk of progression to high-grade dysplasia or esophageal adenocarcinoma in individuals with Barrett esophagus.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Coding
See the Codes table for details.

Description

Several adjunctive technologies and tests are available for screening, surveillance, and risk stratification of Barrett esophagus (BE). The wide-area transepithelial sampling with three-dimensional analysis (WATS3D) is performed during the endoscopic examination of the esophagus, using a computer-assisted brush biopsy procedure as an adjunct to standard four-quadrant forceps biopsy. 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.

Related Policies

- Endoscopic Radiofrequency Ablation or Cryoablation for Barrett Esophagus
- Oncologic Applications of Photodynamic Therapy, Including Barrett Esophagus

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract

language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

On May 31, 2019, the FDA approved Lucid Diagnostics Inc.'s EsoCheck Cell Collection Device (K222366) for use in collecting and retrieving surface cells of the esophagus in adults and adolescents aged 22 years and older (product code: EOX). An update to the PMA (K230339) 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)[,9,]

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), TissueCypher (Castle BioSciences), and WATS3D (CDx Diagnostics), formerly known as EndoCDx, 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.

Rationale

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.[1,] The prevalence of BE in the United States is estimated at 5.6%.[2,] 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.[3,] However, a population-based analysis from Sweden observed that 40% of the study cohort with esophageal cancer reported no prior history of GERD symptoms.[4,]

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.[1,] 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)[3,] and a consensus statement from an international group of experts (Benign Barrett's and CAncer

Taskforce) on the management of BE are published.[5,]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.[3,] 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.[6,]

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.[5,] 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.[3,] Approximately 40% of patients with high-grade dysplasia on biopsy are found to have associated carcinoma in the resection specimen.[7,]

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.[3,] 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.[8,]

Literature Review

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.

Direct evidence that a medical test is clinically useful is preferred and supports greater certainty of effect. Combined use of wide-area transepithelial sampling with three-dimensional computer-assisted analysis (WATS3D) with standard biopsy techniques for screening and surveillance of Barrett esophagus (BE) is intended to replace the current standard of care for guiding patient management decisions regarding initiation of treatment or surveillance; therefore, direct evidence of improvement in health outcomes is required.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Screening and Surveillance of Barrett Esophagus and Esophageal Dysplasia with WATS3D

Clinical Context and Test Purpose

The American Gastroenterological Association has defined BE as replacement of normal epithelium at the distal esophagus by intestinal metaplasia, which predisposes to malignancy.[1,] Although grading of dysplasia in mucosal biopsies is the current standard for assessing the risk of malignant

transformation, esophageal inflammation may mimic or mask dysplasia, and interobserver variability may yield inconsistent risk classifications.[10,] Therefore, additional diagnostic and prognostic information that is less prone to sampling error may be potentially useful.

The purpose of adjunctive WATS3D in the surveillance and screening of BE and esophageal dysplasia is to confirm a diagnosis and inform a decision to proceed to appropriate treatment or management that improves the net health outcome.

The following PICOs are proposed to select literature to inform this review.

Populations

The relevant surveillance population includes individuals with a history of BE, with or without prior dysplasia, who undergo endoscopic surveillance for esophageal dysplasia and cancer.

The relevant screening population includes individuals at increased risk of BE. The American College of Gastroenterology recommends consideration of screening in men with chronic (>5 years) and/or frequent (weekly or more) symptoms of gastroesophageal reflux disease (GERD) and 2 or more risk factors for BE or esophageal adenocarcinoma (EAC), including:[3,]

- Age > 50 years
- Caucasian race
- Central obesity: waist circumference >102 cm or waist-to-hip ratio >0.9
- Current or past history of smoking
- Confirmed first-degree relative with a history of BE or EAC

Given the significantly lower risk of EAC in women with chronic GERD symptoms, screening in women is not recommended but may be *considered* in individual cases with 2 or more risk factors, including:[3,]

- Age > 50 years
- Caucasian race
- Chronic and/or frequent GERD
- Central obesity: waist circumference >88 cm or waist-to-hip ratio >0.8
- Current or past history of smoking
- Confirmed first-degree relative with a history of BE or EAC

Interventions

The test being considered is adjunctive (concurrent) screening or surveillance with WATS3D (CDx Diagnostics). The manufacturer's website describes WATS3D as an "[artificial intelligence]-powered diagnostic platform to help prevent esophageal cancer."[11,]

WATS3D represents a novel endoscopic device and imaging process intended to facilitate the detection of BE and esophageal dysplasia in an effort to prevent progression to EAC. The device uses an abrasive sampling brush to create a wide area tissue sample that captures the full thickness of the epithelium, penetrating into the submucosa. A proprietary 3D computer image system processes tissue brushings with artificial intelligence-based neural network analytics to detect and highlight potential abnormalities to WATS3D-certified pathologists.

WATS3D is intended to be used in addition to standard four-quadrant forceps biopsy during white-light endoscopy. Adjunctive use of WATS3D is purported to overcome limitations of the Seattle protocol, including sampling error and high interobserver variability in the diagnosis of dysplasia. However, it is unclear how adjunctive use of WATS3D fits into the clinical management pathway, particularly in the case of discordant test results where forceps biopsy is negative or reports a lower grade of dysplasia.

Comparators

The comparator of interest is standard esophageal screening or surveillance only, defined as random four-quadrant forceps biopsy during white-light endoscopy with grading of dysplasia. Biopsy samples are typically obtained at 1-cm intervals in patients with prior dysplasia and 2-cm intervals in patients without dysplasia. This biopsy sampling procedure is also known as the Seattle protocol. Due to high interobserver variability in the interpretation of dysplasia of any grade, guidelines recommend review by 2 pathologists, at least 1 of whom has specialized training in gastrointestinal pathology.

Evidence-based guidelines note that there is no direct evidence on the effectiveness of surveillance or screening for BE with traditional forceps biopsy. Despite limited evidence, surveillance has become standard practice for individuals with BE based on the unproven assumption that this practice will allow for earlier detection of treatable disease, resulting in a reduction of mortality related to EAC and prolonged survival. Screening for BE is recommended by medical societies based on the assumption that detection of BE will lead to enrollment in surveillance programs.[1,] The overall certainty in the evidence for the association between endoscopic surveillance and EAC-related mortality is considered low to very low by the American Society for Gastrointestinal Endoscopy.[12,]

Outcomes

The outcomes of interest for diagnostic accuracy include test validity. Beneficial outcomes of a true test result are the initiation of appropriate treatment or surveillance or avoidance of unnecessary procedures or surveillance. Harmful outcomes from a false-positive test result include unnecessary treatments and/or surveillance and negative psychosocial sequelae. Harmful outcomes from a false-negative test result include failure to receive timely and appropriate treatment or surveillance.
The primary outcomes of interest for clinical utility are overall survival, disease-specific survival, change in disease status (i.e., progression to cancer), and quality of life.

The timing of follow-up for screening and surveillance is weeks for diagnosis to years for survival outcomes. In patients with non-dysplastic BE, the risk of progression to cancer ranges from 0.2% to 0.5% per year and endoscopic surveillance every 3 to 5 years is generally recommended.[3,]

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes (length of life, quality of life, and ability to function) for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs). Combined use of WATS3D with standard biopsy techniques for screening and surveillance of BE is intended to replace the current standard of care for guiding patient management decisions regarding initiation of treatment or surveillance; therefore, direct evidence of improvement in health outcomes is required.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- The study was conducted on the marketed version of the technology;
- To assess direct evidence of clinical utility, controlled studies that have compared health outcomes for patients managed with and without the test were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

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, more effective therapy, or avoid unnecessary therapy or testing.

Studies evaluating the clinical validity of WATS3D are outside of the scope of this evidence review and are summarized for informational purposes only.

A multicenter RCT published by DeMeester et al (2022) was excluded from this evidence review as it was not designed to evaluate the adjunctive (concurrent) use of WATS3D compared to forceps biopsy alone.[13,]

Review of Evidence

Clinical Validity

Studies evaluating the clinical validity of WATS3D have focused on the assessment of diagnostic yield and their finding are summarized for informational purposes only.

Systematic Reviews

Codipilly et al (2022) conducted a systematic review and meta-analysis of studies reporting on the incremental yield of WATS3D-detected dysplasia (indefinite for dysplasia, low-grade dysplasia [LGD], high-grade dysplasia [HGD], or esophageal adenocarcinoma [EAC]) over standard forceps biopsy (FB).[14,] Seven studies representing 18,842 patients were identified for analysis. The incremental yield of WATS3D over FB for any dysplasia or EAC was 7.2% (95% CI, 3.9% to 11.5%; I^2=92.1%). The incremental yield for HGD/EAC was 2.1% (95% CI, 0.4% to 5.3%; I^2=92.7%). The corresponding incremental yields in a surveillance subpopulation were similar at 6.9% and 2.4%, respectively. Among 4 studies, WATS3D was negative in 62.5% of cases where FB identified dysplasia. Among 5 studies where indefinite for dysplasia cases were excluded from a WATS3D-positive diagnosis of dysplastic Barrett esophagus (BE), the incremental yield of WATS3D was 7.3% (95% CI, 3.3% to 12.8%; I^2=86.3%) – mainly driven by diagnoses of LGD. Importantly, no studies were identified that reported progression rates to HGD/EAC or mortality with a WATS3D-only diagnosis of dysplasia.

Many of the included screening studies have incomplete descriptions of selection criteria, and it is unclear whether their populations adhere to guideline recommendations for screening. Two studies noted that detected cases of BE in short-segment patients may actually reflect intestinal metaplasia of the cardia, which is thought to carry a significantly lower risk of cancer development compared to traditional BE.[15,16,] These studies were also enriched with women in whom screening is generally not recommended by professional guidelines. In several studies, outcomes were not stratified by grade of dysplasia.

Two of the included surveillance studies were enriched with patients with a prior history of dysplasia.[17,18,] It is also unclear to what extent these surveillance results are generalizable to community-based centers, where adherence to endoscopic biopsy guidelines is poor.[18,]

One study by Trindade et al (2023) not included in the Codipilly et al (2023) meta-analysis reported an incremental diagnostic yield of 2.4% with adjunctive WATS3D for detection of dysplasia in patients with known or suspected BE.[9,] This increased yield was noted in patients with both short- and long-segment BE. Another pooled analysis of 2 prospective, industry-sponsored observational registries by Corbett et al (2022) evaluating patients following endoscopic eradication therapy reported an absolute yield for intestinal metaplasia and dysplasia detection of 16% and 4.4%, respectively.[19,] The number of patients needed to test for detection of dysplasia was 22.9.

Randomized Controlled Trials

van Munster et al (2023) published the results of a multicenter RCT evaluating the role of WATS3D in patients with known BE and a recent history of dysplasia with no visible lesions or following prior endoscopic resection.[20,] Patients were randomized to receive either WATS3D followed by standard

forceps biopsy (FB) or vice versa. Out of 147 patients included for analysis, 21 had HGD/EAC detected by both WATS3D and FB, 18 had HGD/EAC detected by WATS3D alone, and 12 had HGD/EAC detected by FB alone. Thus, the detection rate was not found to differ between use of WATS and FB as a single modality (p=.36). Adjunctive use of WATS resulted in a 10% absolute increase (95% CI, 6% to 16%) in the diagnostic yield of HGD/EAC compared to FB alone. The absolute detection rate did not significantly differ based on order of randomization. The majority of individuals excluded from analysis resulted from inadequate WATS3D specimens (n=23/25). Long-term disease progression or mortality outcomes were not reported.

Clinical Utility

No direct evidence of clinical utility was identified, as published studies comparing health outcomes in screening or surveillance populations managed with and without the adjunctive use of WATS3D are not available.

Shaheen et al (2024) conducted a prospective registry study to assess the yield of intestinal metaplasia (IM) and dysplasia detection using WATS3D as an adjunct to FB in patients with gastroesophageal reflux disease (GERD) undergoing screening for BE.[21,] The study included 23,933 patients (mean age 57.4 years; 42% male; 86.7% white) from 78 community practices who received both WATS3D and FB in the same endoscopic session and had no prior history of BE, IM or dysplasia in the esophageal mucosa. Analyses stratified patients into several sub-groups based on the appearance of their columnar-lined epithelium (CLE): regular CLE, irregular (1 cm of CLE extending into the tubular esophagus), potential short-segment BE (≥1 cm but <3cm of CLE extending into the tubular esophagus), or potential long-segment BE (≥3 cm of CLE extending into the tubular esophagus). The WATS3D diagnostic yield for IM was significantly higher than FB in the entire study cohort (25.6% vs 16.3%; p=.0001) and in each of the 4 endoscopic subgroups separately (p<.001). The adjunctive yield of WATS3D for IM detection was 76.5% in patients meeting endoscopic criteria for BE with an absolute yield of 18.1%. Among 6,829 patients with ≥1 cm of columnar-lined epithelium (CLE), 2,878 (42.1%) had IM identified by either FB or WATS3D, but WATS3D detected IM in an additional 1,317 patients (19.3%) not detected by FB alone. In the total cohort, the number needed to test (NNT) with WATS3D was 6 to identify an additional case of histology-proven IM. Of the 3,993 patients who had IM detection by WATS3D but were negative on FB, 90.7% had changes in medical management (starting or modifying surveillance 79%, proton pump inhibitor [PPI] started or increased 56.7%, or interventional treatment [e.g. antireflux surgery, ablation, or endoscopic mucosal resection] 1.2%). For dysplasia detection, WATS3D had an adjunctive yield of 80.5% overall and an absolute yield of 0.5%. Of 240 patients with any grade of dysplasia, 107 (44.6%) were detected solely by WATS3D with an NNT of 224. Of the 107 patients who had dysplasia detection by WATS3D but were negative on FB, 97.1% had changes in medical management (starting or modifying surveillance 89.7%, PPI started or increased 67.1%, or interventional treatment 4.7%).

Shaheen et al (2022) conducted a retrospective analysis of the manufacturer database from 2013 to 2019 to gauge progression of NDBE, crypt dysplasia (CD), and LGD as categorized by the initial WATS3D finding.[22,]A total of 4545 WATS3D patients with 2 WATS3D samplings ≥12 months apart in routine care were identified, including 4374 with NDBE, 128 with CD, and 43 with LGD. Progression was defined as a subsequent finding of HGD or esophageal adenocarcinoma on FB sampling. Mean follow-up time was 1.97 years (range, 1.0 to 6.42). In patients with baseline NDBE, progression was 0.08% per patient-year (95% CI, 0.02% to 0.14%). Progression of baseline CD was significantly higher, at 1.42% per patient-year (95% CI, 0% to 3.01%). For baseline LGD, progression was 5.79% per patient-year (95% CI, 1.02% to 10.55%). For the 16 patients with progression (0.33%), baseline WATS3D diagnoses were positive for NDBE in 7, CD in 3, and LGD in 5. Baseline FB diagnoses for the progressors included 9 cases of NDBE, 3 with indefinite for dysplasia, and 4 with LGD. The overall concordance of initial WATS3D readings with initial FB readings was only reported for 2499 patients (55%) in the analysis cohort, which included 27 discordant cases of NDBE, 50 discordant cases of CD, and 13 discordant cases of LGD as identified by WATS3D. The study was limited by short duration of

follow-up and low number of progressors. Comparative rates of progression based on available initial FB readings were not reported.

Singer and Smith (2021) developed a decision analytic model to compare the effectiveness of FB screening with and without WATS3D in chronic GERD patients.[23,] The reference cohort consisted of 60-year-old white males with GERD not previously screened for BE. The model assumed that negative FB and discordant positive WATS3D would be entered into a surveillance protocol, and that cases with true-negative FB but false-positive WATS3D would enter a surveillance protocol and later be removed after 2 rounds of negative FB "confirmed" the false-positive status of the original positive WATS3D screening. A standard surveillance interval of 3 years was assumed. The study concluded that 320 to 337 individuals would need to be screened for BE with WATS3D to avert 1 case of cancer and that 328 to 367 individuals would need to be screened to avert 1 cancer death. The authors noted that their results would be revisited after longitudinal studies ascertain stable estimates of the uncertainty of the added yield and false-positive rate for WATS3D.

Kaul and coworkers (2020) identified 432 consecutive screening or surveillance patients from WATS3D clinical registries with a WATS3D positive diagnosis of either BE or dysplasia and a concurrent session negative FB result for those specific diagnoses.[24,] Corresponding patient physicians were contacted and asked to complete a survey to elucidate what patient management actions resulted from these test results. Physicians were not previously provided with any recommendations regarding how to manage these discordant cases, and such recommendations are not currently available in society guidelines. Of 317 patients diagnosed with BE, 96.2% were enrolled in a surveillance program, 3.7% underwent either ablation or antireflux surgery, 53.6% were started on a proton-pump inhibitor (PPI), and 6.6% had their PPI dose increased. Follow-up data was available for 149/317 BE patients (47%) who subsequently underwent follow-up endoscopy with forceps biopsy and WATS3D. Six of these patients received a subsequent diagnosis of LGD which was missed by forceps biopsy in all cases. WATS3D impacted the management of 94.9% and 94.1% of all LGD and HGD patients, respectively. Follow-up data was available for 28/98 LGD patients (29%) and 4/17 HGD patients (24%). Among the LGD patients, 3 developed HGD as diagnosed by WATS3D alone. Among the HGD patients, 1 was diagnosed with EAC as identified by both WATS3D and forceps biopsy. In discordant cases where BE or dysplasia was identified only by WATS3D, significant physician management changes included initiation of invasive treatments. Health outcomes stemming from these management changes were not reported, and risks associated with overdiagnosis and overtreatment require elucidation.

A 5-year prospective study addressing the clinical utility of WATS3D is currently recruiting patients (see Table 1).

Section Summary: Screening and Surveillance of Barrett Esophagus and Esophageal Dysplasia with WATS3D

Direct evidence of clinical utility for the adjunctive use of WATS3D was not identified in neither screening nor surveillance populations. Indirect evidence of clinical utility includes a decision analytic model, a physician impact study with incomplete follow-up reporting on disease progression, and a retrospective manufacturer database analysis of disease progression. Because significant management changes in the physician impact study included invasive treatments such as ablation, endoscopic mucosal resection, and antireflux surgery, risks associated with overdiagnosis and overtreatment require further elucidation. A retrospective analysis of the manufacturer database found a disease progression rate of 5.79% per patient-year (95% CI, 1.02% to 10.55%) for baseline LGD diagnoses via WATS3D sampling; however, study interpretation is limited as only 16 cases (0.33%) of progression defined as HGD or esophageal adenocarcinoma on follow-up forceps biopsy were identified. Adjunctive, concurrent use of WATS3D with standard biopsy techniques for screening and surveillance of BE is intended to replace the current standard of care for guiding patient management decisions regarding initiation of treatment or surveillance, and guideline-based recommendations for the clinical management of discordant results are not presently available.

Therefore, direct evidence of improvement in health outcomes is required. A 5-year prospective study addressing the clinical utility of WATS3D is currently recruiting patients (Table 1).

Screening of Barrett Esophagus and Esophageal Dysplasia with EsoCheck and EsoGuard

Clinical Context and Test Purpose

The American Gastroenterological Association has defined Barrett Esophagus (BE) as the replacement of normal epithelium at the distal esophagus by intestinal metaplasia, which predisposes to malignancy.[1,] Early detection of BE is dependent on performing esophagogastroduodenoscopy and has not been recommended in the general population which results in many cases of esophageal adenocarcinoma where the antecedent status of BE is unknown.[25,]

The purpose of EsoCheck® is to provide an office-based alternative tissue sampling methodology for use in concert with the EsoGuard® esophageal DNA test to determine if epigenetic changes consistent with BE or esophageal adenocarcinoma (EAC) are present.

The following PICOs are proposed to select literature to inform this review.

Populations

The relevant screening population includes individuals at increased risk of BE. The American College of Gastroenterology recommends consideration of screening in men with chronic (>5 years) and/or frequent (weekly or more) symptoms of gastroesophageal reflux disease (GERD) and 2 or more risk factors for BE or esophageal adenocarcinoma (EAC), including:[3,]

- Age > 50 years
- Caucasian race
- Central obesity: waist circumference >102 cm or waist-to-hip ratio >0.9
- Current or past history of smoking
- Confirmed first-degree relative with a history of BE or EAC

Given the significantly lower risk of EAC in women with chronic GERD symptoms, screening in women is not recommended but may be *considered* in individual cases with 2 or more risk factors, including:[3,]

- Age > 50 years
- Caucasian race
- Chronic and/or frequent GERD
- Central obesity: waist circumference >88 cm or waist-to-hip ratio >0.8
- Current or past history of smoking
- Confirmed first-degree relative with a history of BE or EAC

Interventions

The test being considered combines Esocheck, a non-endoscopic, swallowable, balloon capsule catheter designed for non-invasive distal esophageal mucosal cell sampling, with the EsoGuard 2 methylated DNA biomarker panel (Lucid Diagnostics) for screening of BE or EAC. After swallowing, the balloon inflates and is withdrawn to swab the esophagus, then deflates to protect collected cells within the capsule as it's removed, allowing for subsequent analysis with EsoGuard at a CAP-accredited, CLIA-certified laboratory. According to the company website, the mucosal cell sample undergoes bisulfite conversion to demarcate unmethylated sites. Subsequently, two genes, *VIM* and *CCNA1*, encompassing 31 methylation sites associated with esophageal precancer and cancer, are amplified via PCR and analyzed through NGS. Algorithms then evaluate the sequencing data, quantifying the methylation status of the 31 target sites and generating a binary EsoGuard result.[26,]

EsoCheck and EsoGuard are intended to be used as a screening tool; positive results generally lead to confirmatory endoscopy and biopsy and are aimed at addressing the challenge of detecting BE/EAC earlier in more patients.

Comparators

The comparators of interest are other non-invasive screening methods in addition to standard esophageal screening or surveillance only. Standard screening is defined as random four-quadrant forceps biopsy during white-light endoscopy with grading of dysplasia. Biopsy samples are typically obtained at 1-cm intervals in patients with prior dysplasia and 2-cm intervals in patients without dysplasia. This biopsy sampling procedure is also known as the Seattle protocol. Due to high interobserver variability in the interpretation of dysplasia of any grade, guidelines recommend review by 2 pathologists, at least 1 of whom has specialized training in gastrointestinal pathology. Evidence-based guidelines note that there is no direct evidence on the effectiveness of surveillance or screening for BE with traditional forceps biopsy. Screening for BE is recommended by medical societies based on the assumption that detection of BE will lead to enrollment in surveillance programs.[1,] The overall certainty in the evidence for the association between endoscopic surveillance and EAC-related mortality is considered low to very low by the American Society for Gastrointestinal Endoscopy.[12,]

Outcomes

The outcomes of interest for diagnostic accuracy include test validity. Beneficial outcomes of a true test result are the initiation of appropriate treatment or surveillance or avoidance of unnecessary procedures or surveillance. Harmful outcomes from a false-positive test result include unnecessary treatments and/or surveillance and negative psychosocial sequelae. Harmful outcomes from a false-negative test result include failure to receive timely and appropriate treatment or surveillance. The primary outcomes of interest for clinical utility are overall survival, disease-specific survival, change in disease status (i.e., progression to cancer), and quality of life.

The timing of follow-up for screening and surveillance is weeks for diagnosis to years for survival outcomes. In patients with non-dysplastic BE, the risk of progression to cancer ranges from 0.2% to 0.5% per year and endoscopic surveillance every 3 to 5 years is generally recommended.[3,]

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes (length of life, quality of life, and ability to function) for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- The study was conducted on the marketed version of the technology;
- To assess direct evidence of clinical utility, controlled studies that have compared health outcomes for patients managed with and without the test were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

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, more effective therapy, or avoid unnecessary therapy or testing.

Review of Evidence

Clinical Validity

Greer et al (2024) conducted a prospective study to evaluate the diagnostic accuracy, tolerance, and acceptability of EsoGuard and EsoCheck for non-endoscopic screening of BE and EAC in a population of at-risk veterans.[27,] The study recruited 130 veterans who met the American College of Gastroenterology (ACG) guideline criteria for BE and EAC screening at a VA medical center. Participants underwent EsoCheck sampling without sedation followed by sedated upper endoscopy (UE). Six individuals did not receive both tests and were excluded from analysis. Based on UE findings the prevalence of BE or EAC was 12.9% (16/124). EsoGuard demonstrated a sensitivity of 92.9% (95% CI, 66.1% to 99.8%) and specificity of 72.2% (95% CI, 62.1% to 80.8%) for UE detected BE and EAC. The positive predictive value (PPV) and negative predictive values (NPV) were 32.5% (95% CI, 18.6% to 49.1%) and 98.6% (95% CI, 92.4% to 100%), respectively. The authors also assessed the acceptability of non-endoscopic sample collection with the EsoCheck device and found a mean post-procedure acceptability score of 7.23 out of 10 (Standard deviation [SD], 2.45).

Moinova et al (2024) conducted a multicenter, prospective evaluation of the performance of EsoCheck sampling coupled with EsoGuard testing in a cohort of 243 individuals, including 88 cases with either BE, dysplasia (LGD or high-grade dysplasia), or EAC and 155 controls (no evidence of BE or intestinal metaplasia on any biopsy).[25,] The study reported an overall sensitivity of 85% (95% CI, 0.78% to 0.93%) and specificity of 85% (95% CI, 0.79% to 0.90%) for detecting BE and BE-related neoplasia. Notably, the test demonstrated 100% sensitivity for EAC detection. The sensitivity for NDBE was 84%, while the sensitivity for high-grade dysplasia was 78%. The authors noted several challenges in EsoCheck device administration and sample recovery, with 17% of subjects failing to swallow the device and 14% of samples yielding insufficient DNA. However, most individuals (94%) who participated in esophageal balloon testing considered it acceptable on a procedure tolerability survey (Likert scale scores ≤ 7 on a 10-point scale).

Clinical Utility

No direct evidence of clinical utility was identified, as published studies comparing health outcomes in screening populations managed with standard of care compared to screening with EsoGuard and EsoCheck are not available.

Englehardt et al (2023) conducted a multicenter, prospective registry study to evaluate the real-world experience and clinical utility of EsoGuard and EsoCheck as a triage test for BE and esophageal adenocarcinoma (EAC) screening.[28,] The study included 517 subjects enrolled from April 14 to August 16, 2023, with a mean age of 47.9 years. Of these, 63.8% met American Gastroenterological Association (AGA) criteria for BE screening, and 81.2% met "AGA positive" criteria when firefighting was included as an additional risk factor. The EsoCheck cell collection procedure was successfully completed in 99.6% of subjects; however, in 29 (6.1%) participants, the result was not able to be evaluated, lacked sufficient DNA quantity for analysis, or had other administrative or sample issues. The EsoGuard positivity rate was 14.1% (67/476), with 79.8% (380/476) testing negative. Among 437 subjects with both binary EsoGuard results and physician decisions on UE referral, the positive agreement between EsoGuard results and UE referral was 100%, while the negative agreement between EsoGuard negative results and non-referral for UE was 99.4%. The overall concordance between EsoGuard results and UE referral decisions was 97.9%.

Hamblin et al (2023) conducted a retrospective analysis of prospectively collected data on the use of EsoGuard and EsoCheck for BE/EAC screening in on-duty firefighters during two health fairs in Texas in January 2023.[29,] A total of 388 firefighters deemed at high risk for BE/EAC by evaluating physicians underwent EG/EC testing. The successful EsoCheck cell collection rate was 99.22%

(385/388), with a median participant age of 41.5 years and 93% male. The study found that 96.6% (372/385) of samples had successful EsoGuard analysis, with 7.3% (28/372) testing positive and 89.35% (344/372) testing negative. All 28 EsoGuard positive firefighters were referred for confirmatory UE by the ordering physician, while no EsoGuard negative subjects were referred for additional testing. The results of this UE testing and the concordance with EsoGuard results were not reported by the authors.

Lister et al (2023) conducted a multicenter, observational trial to evaluate the clinical utility of EsoGuard as a triage test for UE in the diagnosis of BE in real-world use. [30,] The study included 275 subjects enrolled across 4 centers between February and July 2023. Participants underwent non-endoscopic cell sampling using the EsoCheck device, followed by EsoGuard testing. The primary endpoints were positive and negative agreement between EsoGuard results and endoscopy referral patterns. The study found that 96.3% of subjects successfully completed EsoCheck cell collection, 8 (3.4%) individuals had insufficient DNA quantity for EsoGuard analysis, and 4 (1.7%) samples were unevaluable due to contamination. Of 232 subjects with documented EsoGuard results, 29.3% were positive, and 65.5% were negative. The positive agreement between EsoGuard results and endoscopy referral was 100%, while the negative agreement was 99.3%. Overall concordance between EsoGuard results and endoscopy referral was 98.8%. Notably, all subjects with positive EsoGuard results were referred for confirmatory endoscopy, while only one subject with a negative result was referred.

Section Summary: Screening of Barrett Esophagus and Esophageal Adenocarcinoma with EsoCheck and EsoGuard

Direct evidence of clinical utility for the use of EscoCheck and EsoGuard for screening of Barrett Esophagus (BE) and esophageal adenocarcinoma (EAC) was not identified. Indirect evidence of clinical utility includes studies focused on the use of EsoGuard and EsoCheck as triage tests for upper endoscopy (UE) referral. One observational study reported a 97.9% concordance between EsoGuard results and UE referral decisions in a real-world setting. Another study found a 7.3% EsoGuard positivity rate among high-risk firefighters, with all positive cases referred for confirmatory UE. Another study observed a 98.8% overall concordance between EsoGuard results and endoscopy referral patterns. While these studies demonstrate high agreement between EsoGuard results and UE referral decisions, they lack comprehensive follow-up data on the outcomes of confirmatory endoscopies for EsoGuard-positive cases, which is crucial for fully establishing the clinical utility of the test in BE and EAC screening and management. Several observational studies have evaluated the diagnostic accuracy and acceptability of EsoGuard and EsoCheck for non-endoscopic screening of BE and EAC. One author reported a sensitivity of 92.9% and specificity of 72.2% for EsoGuard in detecting BE and EAC in at-risk veterans. Another study found an overall sensitivity and specificity of 85% for detecting BE and BE-related neoplasia in a multicenter trial, with 100% sensitivity for EAC detection. Studies evaluating the acceptability of the EsoCheck device for tissue sampling found that swallowing the device caused issues in some patients and necessitated multiple attempts, but nearly all participants were able to complete sampling, with most rating the procedure as acceptable. The use of EsoCheck and Esoguard for screening is intended to triage patients to more invasive confirmatory testing with UE and change the current standard of care for guiding patient management decisions regarding the initiation of treatment or surveillance. Therefore, direct evidence of improvement in health outcomes is required. Several ongoing trials are currently recruiting patients to assess the clinical utility of EsoGuard (Table 1).

Risk Stratification with Adjunctive TissueCypher

Clinical Context and Test Purpose

The American Gastroenterological Association has defined Barrett esophagus as replacement of normal epithelium at the distal esophagus by intestinal metaplasia, which predisposes to malignancy.[1,] Although grading of dysplasia in mucosal biopsies is the current standard for assessing the risk of malignant transformation, esophageal inflammation may mimic or mask dysplasia, and

interobserver variability may yield inconsistent risk classifications.[10,] Additional prognostic information, therefore, may be potentially useful.

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

Populations
The relevant population of interest is individuals with non-dysplastic, indefinite dysplasia, or low-grade dysplasia Barrett Esophagus.

Interventions
The test being considered is TissueCypher as an adjunct to standard prognostic practices; TissueCypher is a test to help identify individuals at a high risk of progression to high-grade dysplasia or esophageal adenocarcinoma for enhanced surveillance or treatment (e.g. endoscopic eradication therapy).

The CastleBiosciences website describes TissueCypher as a multi-analyte assay with algorithmic analysis that uses proprietary automated image analysis of formalin-fixed parafin-embedded tissue sections from endoscopic biopsy specimens. The test quantifies the expression and localization of 9 biomarkers (p16, p53, alpha-methylacylCoA racemase [AMACR], HER2/neu, Cytokeratin-20 [K20], Cyclooxygenase-2 [COX-2], CD68, Hypoxia-inducible factor 1-α [HIF1A], and CD45RO) in the context of tissue morphology. A risk score ranging from 0, the lowest risk, to 10, the highest risk, is calculated which estimates the risk of progression to high-grade dysplasia or esophageal adenocarcinoma in the next 5 years. [31,]

Comparators
The following tests and practices are currently being used to predict progression from non-dysplastic, indefinite dysplasia, or low-grade dysplasia Barrett esophagus to high-grade dysplasia or esophageal adenocarcinoma: 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 affect 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.

Study Selection Criteria
For the evaluation of the clinical validity of the TissueCypher test (including the algorithm), studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the patented TissueCypher technology for classifying patients into prognostic categories for malignancy;
- Included a suitable reference standard (long-term follow-up for malignancy; histopathology from surgically resected lesions);
- Patient and sample clinical characteristics were described;
- Patient and sample selection criteria were described.

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
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.[32,] 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.[33,] 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.[34,] 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).[32,] 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.[35,] 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.[36,] 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.[37,] 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.

Section Summary: TissueCypher

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.

Risk Stratification with Adjunctive BarreGEN

Clinical Context and Test Purpose

The American Gastroenterological Association has defined Barrett esophagus as replacement of normal epithelium at the distal esophagus by intestinal metaplasia, which predisposes to malignancy.[1,] Although grading of dysplasia in mucosal biopsies is the current standard for assessing the risk of malignant transformation, esophageal inflammation may mimic or mask dysplasia, and interobserver variability may yield inconsistent risk classifications.[10,] Additional prognostic information, therefore, may be potentially useful.

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

Populations

The relevant population of interest is individuals with Barrett esophagus. It is unclear what other clinical characteristics would identify candidates for BarreGEN or what previous testing is appropriate before BarreGEN.

Interventions
The test being considered is BarreGEN topographic genotyping in addition to standard prognostic practices.

The Interpace website describes BarreGEN as a molecular based assay that helps resolve the risk of progression of Barrett's Esophagus to esophageal cancer. molecular diagnostic test to "determine the risk of progressing to esophageal cancer in patients with Barrett's Esophagus."[38,]

Comparators
The following tests and practices are currently being used to predict developing Barrett 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 affect 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.

Study Selection Criteria
For the evaluation of the clinical validity of the BarreGEN test (including the algorithm), studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the patented PathFinder Barrett Esophagus or BarreGEN technology for classifying patients into prognostic categories for malignancy;
- Included a suitable reference standard (long-term follow-up for malignancy; histopathology from surgically resected lesions);
- Patient and sample clinical characteristics were described;
- Patient and sample selection criteria were described.

Two studies were excluded from the evaluation of the clinical validity of the BarreGEN test because it was not clear whether the authors used the marketed version of the BarreGEN test.[39,40,]

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
No relevant studies have been identified assessing the clinical validity of the BarreGEN test.

Clinically Useful
A test is clinically useful if the use of the results inform 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.

Review of Evidence
Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No studies assessing the clinical utility of BarreGEN in this population were found.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because evidence for the clinical validity of BarreGEN is lacking, a chain of evidence that would support clinical utility cannot be constructed.

Section Summary: BarreGEN

There is no evidence evaluating the clinical validity of the BarreGEN test for assessing Barrett esophagus thus, there is no evidence that BarreGEN testing for prognosis of Barrett esophagus adds incremental value to current prognostic assessments.

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.

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

In 2016, the American College of Gastroenterology (ACG) published clinical guidelines on the diagnosis and management of Barrett esophagus (BE) on the basis of a systematic literature review.[3,] Guidelines state that "in patients with suspected BE, at least 8 random biopsies should be obtained to maximize the yield of [intestinal metaplasia] on histology. In patients with short (1-2 cm) segments of suspected BE in whom 8 biopsies are unattainable, at least 4 biopsies per cm of circumferential BE, and 1 biopsy per cm in tongues of BE, should be taken (conditional recommendation, low level of evidence)." The guidelines also state that "the role of computer-assisted or wide-field 'brush biopsy' tissue acquisition for increasing the yield of dysplasia is currently under investigation."

In a 2022 guideline update,[41,] the ACG stated that they could not make a recommendation on the use of wide-area transepithelial sampling with three-dimensional computer-assisted analysis (WATS3D) and noted that "it is difficult to know how much of the incremental benefit is truly due to more complete sampling of the mucosa by WATS-3D or better detection of dysplasia by the analysis algorithm and how much might be due to overdiagnosis of dysplasia and false-positive examinations by WATS-3D." Limitations of the existing evidence base were summarized, including a lack of studies on adjunctive use for surveillance when forceps biopsies are guided both by white light and chromoendoscopy, a lack of studies reproducing results using pathologists not employed by the manufacturer, and limited stratification of results by grade of dysplasia. The ACG also proved recommendations on the use of minimally invasive, office-administered BE detection tests (e.g. Cytosponge, EsoCheck, and EsophaCap) and stated 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." This was given a conditional strength of recommendation due to the very low quality evidence base assessed by the authors. The guideline discusses TissueCypher but could not make a recommendation on its use: "For patients with BE and a diagnosis of no, indefinite, or LGD, the prevalence-adjusted sensitivity and specificity of TissueCypher at 5 years for the 3-tiered classification system were 29% and 86%, respectively. 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." The BarreGEN test was not addressed in the guidelines.

American Gastroenterological Association

In 2022, the American Gastroenterological Association (AGA) issued a clinical practice update addressing new technology and innovation for surveillance and screening in BE.[42,] Best practice

advice statements were issued based on a review of existing literature and expert opinion. However, statements were not formally rated based on quality of evidence or strength of recommendation. The update states that WATS3D may be used as an adjunctive technique to sample the suspected or established BE segment in addition to the Seattle biopsy protocol. The update also suggests that nonendoscopic cell-collection devices (e.g. Cytosponge, EsoCheck, and EsophaCap) may be considered as an option to screen for BE. For TissueCypher, the guideline suggests it "may be utilized for risk stratification of patients with nondysplastic BE." The authors note TissueCypher has been "validated and demonstrated to accurately risk stratify patients with NDBE," with studies showing "30.4% sensitivity and 95% specificity for detecting progression in patients with NDBE."

The AGA's Clinical Practice Update provides insights on several emerging technologies for Barrett's esophagus (BE) screening and surveillance. For WATS3D, the guideline suggests it "may be used as an adjunctive technique to sample the suspected or established Barrett's segment," noting a "7.2%" incremental yield for dysplasia detection and "less interobserver variability" in pathologic interpretation. However, they call for further studies comparing WATS3D to the Seattle protocol. The guideline does not mention BarreGen. Regarding nonendoscopic screening tools like EsoGuard and EsoCheck, the update states these "may be considered as an option to screen for BE," highlighting their "excellent tolerability, safety, and sensitivity."

American Society of Gastrointestinal Endoscopy

In 2019, the American Society of Gastrointestinal Endoscopy (ASGE) published guidelines addressing screening and surveillance of BE based on a systematic review and meta-analysis of the literature.[12,] Recommendations were drafted at a meeting of the Standards of Practice Committee. The guidelines state that "in patients with known or suspected BE, we suggest using WATS-3D in addition to [white-light endoscopy] with Seattle protocol biopsy sampling compared with [white-light endoscopy] with Seattle protocol biopsy sampling alone (conditional recommendation, low quality of evidence)." The certainty of the recommendation was downgraded due to risk of bias, inconsistency, and indirectness. Definitions of dysplasia varied across studies, and most studies were manufacturer-funded. The guidelines also note that no recommendation for WATS-3D was made at the initial face-to-face panel meeting. The conditional recommendation was issued following review of additional published literature and a phone conference.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines on esophageal and esophagogastric junction cancers (v.3.2024) state that while WATS3D may help increase the detection of esophageal dysplasia in patients with BE, the utility and accuracy of WATS3D for detecting high-grade dysplasia and adenocarcinoma in patients with BE needs to be evaluated in larger phase III randomized trials.[43,]

Society of American Gastrointestinal and Endoscopic Surgeons

The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) Technology and Value Assessment Committee (TVAC) published expert panel recommendations following a safety and efficacy analysis of WATS3D in 2020.[44,] Expert panel statements regarding the safety, efficacy, and value of WATS3D included:

- "No significant morbidity or mortality was reported within the literature associated with the WATS3D technology."
- "WATS3D increases diagnostic yield by 38-150% for Barrett's Esophagus, by 40-150% for Low Grade Dysplasia; and by 420% for High Grade Dysplasia; when compared to forceps biopsy alone."
- "WATS3D technique has very high inter-observer agreement for the pathological diagnosis of non-dysplastic and dysplastic Barrett's Esophagus."
- "Increased detection of pre-malignant diseases of the esophagus by the adjunctive use of WATS3D supports screening and surveillance by the adjunctive use of WATS3D during upper endoscopy in appropriate patients."

The committee also noted that "currently, WATS3D is not recommended as a stand-alone substitute for cold forcep biopsies," as the latter still offers the ability to sample specific areas of concern or visible lesions. Additionally, "further research into the use of the WATS3D system as an independent screening or diagnostic modality may be warranted."

U.S. Preventive Services Task Force Recommendations

No U.S. Preventive Services Task Force (USPSTF) recommendations for the screening or surveillance of BE and esophageal dysplasia were identified.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04295811	A Multicenter Case-Control Study of the Efficacy of EsoGuard on Samples Collected Using EsoCheck, Versus Esophagogastroduodenoscopy, for the Diagnosis of Barrett's Esophagus With and Without Dysplasia, and for Esophageal Adenocarcinoma	470	Dec 2023 (recruiting)
NCT05778851	Clinical Utility of a Non Endoscopic Device EsoCheck and Biomarker EsoGuard as Alternative to Endoscopy for Screening for Barrett's Esophagus in At Risk Population (ASBE)	100	June 2024 (recruiting)
NCT05965999	A Multicenter, Prospective, Open-Label Registry Study of the Utilization of EsoGuard, on Samples Collected Using EsoCheck, in an At-Risk Population Undergoing Standard of Care Screening for, and Management of, Previously Undiagnosed Barrett's Esophagus and/or Esophageal Adenocarcinoma	500	June 2024 (recruiting)
NCT05210049	Non-endoscopic Esophageal Sampling to Detect Barrett's Esophagus and Esophageal Cancer in Veterans	125	Aug 2024 (recruiting)
NCT05056051	Additive Value of Wide-Area Transepithelial Sampling (WATS3D) in Detection of Recurrence of Intestinal Metaplasia Following Endoscopic Eradication Therapy (EET) for Barrett's Esophagus-Related Neoplasia	200	Jun 2025 (recruiting)
NCT04312633[a]	CDx Study 906: The Clinical Utility of WATS3D (Wide Area Transepithelial Sampling with Computer-Assisted 3-Dimensional Analysis): A 5-Year Prospective Registry	90000	Apr 2025 (recruiting)
NCT04880044	Detection of Barrett's Esophagus in Patients Without Gastroesophageal Reflux Disease (GERD) Symptoms	500	Jan 2026 (recruiting)
NCT05530343	A Multicenter Randomized Trial of Seattle Biopsy Protocol Versus Wide-Area Transepithelial Sampling in Patients With Barrett's Esophagus Undergoing Surveillance (The SWAT-BE Study)	2700	Mar 2026 (recruiting)
NCT05642338	A Multicenter Prospective Cohort Study Comparing Random Biopsies Versus Wide-Area Transepithelial Brush-Sampling (WATS) for Surveillance of Barrett's Esophagus, the WATS-EURO2 Study	416	May 2027 (recruiting)
NCT05753748	A Multicenter Randomized Controlled Trial of Surveillance vs. Endoscopic Therapy for Barrett's Esophagus With Low-grade Dysplasia (The SURVENT Trial)	680	Feb 2028 (recruiting)
Unpublished			

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT02988934[a]	The WATS3D (Wide Area Transepithelial Sample Biopsy with 3-Dimensional Computer-Assisted Analysis) U.S. Registry	3173/10000	Feb 2023 (terminated)

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

References

1. 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
2. Hirota WK, Loughney TM, Lazas DJ, et al. Specialized intestinal metaplasia, dysplasia, and cancer of the esophagus and esophagogastric junction: prevalence and clinical data. Gastroenterology. Feb 1999; 116(2): 277-85. PMID 9922307
3. 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
4. Lagergren J, Bergstrom R, Lindgren A, et al. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med. Mar 18 1999; 340(11): 825-31. PMID 10080844
5. 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
6. Curvers WL, ten Kate FJ, Krishnadath KK, et al. Low-grade dysplasia in Barrett's esophagus: overdiagnosed and underestimated. Am J Gastroenterol. Jul 2010; 105(7): 1523-30. PMID 20461069
7. Fayter D, Corbett M, Heirs M, et al. A systematic review of photodynamic therapy in the treatment of pre-cancerous skin conditions, Barrett's oesophagus and cancers of the biliary tract, brain, head and neck, lung, oesophagus and skin. Health Technol Assess. Jul 2010; 14(37): 1-288. PMID 20663420
8. Sinh P, Anaparthy R, Young PE, et al. Clinical outcomes in patients with a diagnosis of "indefinite for dysplasia" in Barrett's esophagus: a multicenter cohort study. Endoscopy. Aug 2015; 47(8): 669-74. PMID 25910065
9. Trindade AJ, Odze RD, Smith MS, et al. Benefit of Adjunctive Wide Area Transepithelial Sampling with 3-Dimensional Computer-Assisted Analysis Plus Forceps Biopsy Based on Barrett's Esophagus Segment Length. Gastrointest Endosc. Apr 04 2023. PMID 37023868
10. Yantiss RK. Diagnostic challenges in the pathologic evaluation of Barrett esophagus. Arch Pathol Lab Med. Nov 2010; 134(11): 1589-600. PMID 21043812
11. CDx Diagnostics. WATS3D. 2024; https://www.cdxdiagnostics.com/wats3d. Accessed June 28, 2024.
12. Qumseya B, Sultan S, Bain P, et al. ASGE guideline on screening and surveillance of Barrett's esophagus. Gastrointest Endosc. Sep 2019; 90(3): 335-359.e2. PMID 31439127
13. DeMeester S, Smith C, Severson P, et al. Multicenter randomized controlled trial comparing forceps biopsy sampling with wide-area transepithelial sampling brush for detecting intestinal metaplasia and dysplasia during routine upper endoscopy. Gastrointest Endosc. Jun 2022; 95(6): 1101-1110.e2. PMID 34902373
14. Codipilly DC, Krishna Chandar A, Wang KK, et al. Wide-area transepithelial sampling for dysplasia detection in Barrett's esophagus: a systematic review and meta-analysis. Gastrointest Endosc. Jan 2022; 95(1): 51-59.e7. PMID 34543648
15. Gross SA, Smith MS, Kaul V. Increased detection of Barrett's esophagus and esophageal dysplasia with adjunctive use of wide-area transepithelial sample with three-dimensional computer-assisted analysis (WATS). United European Gastroenterol J. May 2018; 6(4): 529-535. PMID 29881608

16. Smith MS, Ikonomi E, Bhuta R, et al. Wide-area transepithelial sampling with computer-assisted 3-dimensional analysis (WATS) markedly improves detection of esophageal dysplasia and Barrett's esophagus: analysis from a prospective multicenter community-based study. Dis Esophagus. Mar 01 2019; 32(3). PMID 30541019
17. Anandasabapathy S, Sontag S, Graham DY, et al. Computer-assisted brush-biopsy analysis for the detection of dysplasia in a high-risk Barrett's esophagus surveillance population. Dig Dis Sci. Mar 2011; 56(3): 761-6. PMID 20978843
18. Vennalaganti PR, Kaul V, Wang KK, et al. Increased detection of Barrett's esophagus-associated neoplasia using wide-area trans-epithelial sampling: a multicenter, prospective, randomized trial. Gastrointest Endosc. Feb 2018; 87(2): 348-355. PMID 28757316
19. Corbett FS, Odze RD, McKinley MJ. Utility of wide-area transepithelial sampling with 3-dimensional computer-assisted analysis as an adjunct to forceps biopsy sampling in the surveillance of patients with Barrett's esophagus after endoscopic eradication therapy. iGIE. December 2022; 1(1): 33-43. DOI: 10.1016/j.igie.2022.10.011.
20. van Munster SN, Leclercq P, Haidry R, et al. Wide-area transepithelial sampling with computer-assisted analysis to detect high grade dysplasia and cancer in Barrett's esophagus: a multicenter randomized study. Endoscopy. Apr 2023; 55(4): 303-310. PMID 36150646
21. Shaheen NJ, Odze RD, Singer ME, et al. Adjunctive Use of Wide-Area Transepithelial Sampling-3D in Patients With Symptomatic Gastroesophageal Reflux Increases Detection of Barrett's Esophagus and Dysplasia. Am J Gastroenterol. Apr 18 2024. PMID 38635377
22. Shaheen NJ, Smith MS, Odze RD. Progression of Barrett's esophagus, crypt dysplasia, and low-grade dysplasia diagnosed by wide-area transepithelial sampling with 3-dimensional computer-assisted analysis: a retrospective analysis. Gastrointest Endosc. Mar 2022; 95(3): 410-418.e1. PMID 34537193
23. Singer ME, Smith MS. Wide Area Transepithelial Sampling with Computer-Assisted Analysis (WATS 3D) Is Cost-Effective in Barrett's Esophagus Screening. Dig Dis Sci. May 2021; 66(5): 1572-1579. PMID 32578042
24. Kaul V, Gross S, Corbett FS, et al. Clinical utility of wide-area transepithelial sampling with three-dimensional computer-assisted analysis (WATS3D) in identifying Barrett's esophagus and associated neoplasia. Dis Esophagus. Dec 07 2020; 33(12). PMID 32607543
25. Moinova HR, Verma S, Dumot J, et al. Multicenter, Prospective Trial of Nonendoscopic Biomarker-Driven Detection of Barrett's Esophagus and Esophageal Adenocarcinoma. Am J Gastroenterol. May 21 2024. PMID 38686933
26. Lucid Diagnostics. Lucid Diagnostics Launches Next-Generation EsoGuard Esophageal DNA Test. 2023; https://ir.luciddx.com/2023-11-09-Lucid-Diagnostics-Launches-Next-Generation-EsoGuard-R-Esophageal-DNA-Test-and-Announces-Upcoming-Investor-Day. Accessed June 28, 2024.
27. Greer KB, Blum AE, Faulx AL, et al. Non-endoscopic screening for Barrett's esophagus and Esophageal Adenocarcinoma in at risk Veterans. Am J Gastroenterol. Jul 11 2024. PMID 38989889
28. Englehardt R, Samarasena JB, Bildzukewicz NA, et al. Real world experience and clinical utility of esoguard - interim data from the lucid registry. medRxiv. 2023:2023.2009.2026.23296162. doi:10.1101/2023.09.26.23296162
29. Hamblin R, Lee VT, deGuzman BJ, Verma S, Aklog L. Clinical utility of esoguard as an efficient triage test for diagnosing barretts esophagus in on-duty firefighters. medRxiv. 2023:2023.2008.2016.23294176. doi:10.1101/2023.08.16.23294176
30. Lister D, Fine A, Maheshwari S, et al. Clinical utility study of esoguard on samples collected with esocheck as a triage test for endoscopy to identify barretts esophagus interim data of the first 275 subjects. medRxiv. 2023:2023.2008.2031.23294916. doi:10.1101/2023.08.31.23294916
31. Castle Biosciences. Tissue Cypher Sample Report v2.011/23. 2023; https://castlebiosciences.com/Sample%20Report%20and%20Order%20Form/TC-Sample-Report_watermark.pdf. Accessed June 28, 2024.

32. Davison JM, Goldblum J, Grewal US, et al. Independent Blinded Validation of a Tissue Systems Pathology Test to Predict Progression in Patients With Barrett's Esophagus. Am J Gastroenterol. Jun 2020; 115(6): 843-852. PMID 32079863
33. Frei NF, Konte K, Bossart EA, et al. Independent Validation of a Tissue Systems Pathology Assay to Predict Future Progression in Nondysplastic Barrett's Esophagus: A Spatial-Temporal Analysis. Clin Transl Gastroenterol. Oct 2020; 11(10): e00244. PMID 33108124
34. Khoshiwal AM, Frei NF, Pouw RE, et al. The Tissue Systems Pathology Test Outperforms Pathology Review in Risk Stratifying Patients With Low-Grade Dysplasia. Gastroenterology. Nov 2023; 165(5): 1168-1179.e6. PMID 37657759
35. Diehl DL, Khara HS, Akhtar N, et al. TissueCypher Barrett's esophagus assay impacts clinical decisions in the management of patients with Barrett's esophagus. Endosc Int Open. Mar 2021; 9(3): E348-E355. PMID 33655033
36. Duits LC, Khoshiwal AM, Frei NF, et al. An Automated Tissue Systems Pathology Test Can Standardize the Management and Improve Health Outcomes for Patients With Barrett's Esophagus. Am J Gastroenterol. Nov 01 2023; 118(11): 2025-2032. PMID 37307529
37. Peabody JW, Cruz JDC, Ganesan D, et al. A Randomized Controlled Study on Clinical Adherence to Evidence-Based Guidelines in the Management of Simulated Patients With Barrett's Esophagus and the Clinical Utility of a Tissue Systems Pathology Test: Results From Q-TAB. Clin Transl Gastroenterol. Jan 01 2024; 15(1): e00644. PMID 37767993
38. Interpace Diagnostics. BarreGen Esophageal Cancer Risk Classifier. 2023. https://barregen.com/. Accessed June 25, 2024.
39. Khara HS, Jackson SA, Nair S, et al. Assessment of mutational load in biopsy tissue provides additional information about genomic instability to histological classifications of Barrett's esophagus. J Gastrointest Cancer. Jun 2014; 45(2): 137-45. PMID 24402860
40. Eluri S, Brugge WR, Daglilar ES, et al. The Presence of Genetic Mutations at Key Loci Predicts Progression to Esophageal Adenocarcinoma in Barrett's Esophagus. Am J Gastroenterol. Jun 2015; 110(6): 828-34. PMID 26010308
41. Shaheen NJ, Falk GW, Iyer PG, et al. Diagnosis and Management of Barrett's Esophagus: An Updated ACG Guideline. Am J Gastroenterol. Apr 01 2022; 117(4): 559-587. PMID 35354777
42. Muthusamy VR, Wani S, Gyawali CP, et al. AGA Clinical Practice Update on New Technology and Innovation for Surveillance and Screening in Barrett's Esophagus: Expert Review. Clin Gastroenterol Hepatol. Dec 2022; 20(12): 2696-2706.e1. PMID 35788412
43. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Esophageal and Esophagogastric Junction Cancers (v.3.2024). April 26, 2024; https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf. Accessed June 28, 2024.
44. Docimo S, Al-Mansour M, Tsuda S. SAGES TAVAC safety and efficacy analysis WATS 3D (CDx Diagnostics, Suffern, NY). Surg Endosc. Sep 2020; 34(9): 3743-3747. PMID 32162125

Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for

clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	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
	81479	Unlisted molecular pathology procedure
	88104	Cytopathology, fluids, washings or brushings, except cervical or vaginal; smears with interpretation
	88305	Level IV - Surgical pathology, gross and microscopic examination Abortion - spontaneous/missed Artery, biopsy Bone marrow, biopsy Bone exostosis Brain/meninges, other than for tumor resection Breast, biopsy, not requiring microscopic evaluation of surgical margins Breast, reduction mammoplasty Bronchus, biopsy Cell block, any source Cervix, biopsy Colon, biopsy Duodenum, biopsy Endocervix, curettings/biopsy Endometrium, curettings/biopsy Esophagus, biopsy Extremity, amputation, traumatic Fallopian tube, biopsy Fallopian tube, ectopic pregnancy Femoral head, fracture Fingers/toes, amputation, non-traumatic Gingiva/oral mucosa, biopsy Heart valve Joint, resection Kidney, biopsy Larynx, biopsy Leiomyoma(s), uterine myomectomy - without uterus Lip, biopsy/wedge resection Lung, transbronchial biopsy Lymph node, biopsy Muscle, biopsy Nasal mucosa, biopsy Nasopharynx/oropharynx, biopsy Nerve, biopsy Odontogenic/dental cyst Omentum, biopsy Ovary with or without tube, non-neoplastic Ovary, biopsy/wedge resection Parathyroid gland Peritoneum, biopsy Pituitary tumor Placenta, other than third trimester Pleura/pericardium - biopsy/tissue Polyp, cervical/endometrial Polyp, colorectal Polyp, stomach/small intestine Prostate, needle biopsy Prostate, TUR Salivary gland, biopsy Sinus, paranasal biopsy Skin, other than cyst/tag/debridement/plastic repair Small intestine, biopsy Soft tissue, other than tumor/mass/lipoma/debridement Spleen Stomach, biopsy Synovium Testis, other than tumor/biopsy/castration Thyroglossal duct/brachial cleft cyst Tongue, biopsy Tonsil, biopsy Trachea, biopsy Ureter, biopsy Urethra, biopsy Urinary bladder, biopsy Uterus, with or without tubes and ovaries, for prolapse Vagina, biopsy Vulva/labia, biopsy
	88312	Special stain including interpretation and report; Group I for microorganisms (e.g., acid fast, methenamine silver)
	88361	Morphometric analysis, tumor immunohistochemistry (e.g., Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; using computer-assisted technology
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
01/01/2025	New policy.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must

be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
New Policy **Policy Statement:** **N/A**	**Adjunctive Techniques for Screening, Surveillance, and Risk Classification of Barrett Esophagus and Esophageal Dysplasia 7.01.167** **Policy Statement:** I. Wide-area transepithelial sampling with three-dimensional computer-assisted analysis (WATS3D) is considered **investigational** for all indications, including but not limited to the screening and surveillance of Barrett esophagus and esophageal dysplasia. II. EsoCheck and Esoguard are considered **investigational** for the screening and surveillance of Barrett esophagus and esophageal dysplasia. III. TissueCypher is considered **investigational** for assessing the risk of progression to high-grade dysplasia or esophageal adenocarcinoma in individuals with Barrett esophagus. IV. BarreGen is considered **investigational** for assessing the risk of progression to high-grade dysplasia or esophageal adenocarcinoma in individuals with Barrett esophagus.