

## Adjunctive Techniques for Screening, Surveillance, and Risk Classification of Barrett Esophagus and Esophageal Dysplasia

**Policy # 00757**

Original Effective Date: 11/08/2021

Current Effective Date: 01/01/2025

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

*Note: Endoscopic Radiofrequency Ablation or Cryoablation for Barrett Esophagus is addressed separately in medical policy 00261.*

### Services Are Considered Investigational

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers wide-area transepithelial sampling with three-dimensional computer-assisted analysis (WATS3D) for all indications, including but not limited to the screening and surveillance of Barrett esophagus (BE) and esophageal dysplasia to be **investigational**.\*

Based on review of available data, the Company considers TissueCypher for assessing the risk of progression to high-grade dysplasia or esophageal adenocarcinoma in individuals with Barrett esophagus to be **investigational**.\*

### Background/Overview

#### **Barrett Esophagus**

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

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## ***Cancer Risk and Management***

Intestinal metaplasia is a precursor to esophageal adenocarcinoma, and patients with BE are at a 40-fold increased risk for developing this disease compared to the general population.

However, there are few data to guide recommendations about management and surveillance, and many issues are controversial. Guidelines from the American College of Gastroenterology (ACG) and a consensus statement from an international group of experts (Benign Barrett's and Cancer Taskforce) on the management of BE are published. The ACG recommendations for surveillance are stratified by the presence and grade of dysplasia.

When no dysplasia is detected, ACG has reported the estimated risk of progression to cancer ranges from 0.2% to 0.5% per year and endoscopic surveillance every 3 to 5 years is recommended. For low-grade dysplasia, the estimated risk of progression is 0.7% per year, and endoscopic therapy is preferred; however, endoscopic surveillance every 12 months is considered an acceptable alternative. It is recommended that both options are discussed with the patient. Precise estimates of cancer risk are not available for individuals with low-grade dysplasia due to large disparities among studies on its natural history. Interobserver variability in the diagnosis of low-grade dysplasia with standard biopsy may be responsible, with expert pathologists commonly downgrading initial diagnoses made by community pathologists.

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

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

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

## **FDA or Other Governmental Regulatory Approval**

### **U.S. Food and Drug Administration (FDA)**

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). TissueCypher (Castle BioSciences) and WATS3D



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(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/Source**

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

## **Description**

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. 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.

## **Summary of Evidence**

For individuals with a history of Barrett esophagus (BE) who receive standard surveillance with adjunctive WATS3D, the evidence includes a meta-analysis of studies of diagnostic yield, a randomized controlled trial, a physician impact study, a decision analytic model, and a retrospective analysis of the manufacturer database. Relevant outcomes are test validity, overall survival, disease-specific survival, change in disease status, and quality of life. A meta-analysis reported incremental diagnostic yields of 6.9% and 2.4% for any dysplasia or esophageal adenocarcinoma (EAC) or high-grade dysplasia (HGD)/EAC, respectively. These studies are limited by heterogeneity in classification and reporting of test results and selection bias stemming from the enrichment of patients with a prior history of dysplasia. It is also unclear to what extent results obtained from academic centers are generalizable to community-based settings, where adherence to endoscopic biopsy guidelines is poor. In discordant cases where BE or dysplasia were identified only by WATS3D, significant physician management changes included initiation of invasive treatments. Health outcomes stemming from management changes were not reported, and risks associated with overdiagnosis and overtreatment require elucidation. Follow-up data on disease progression in these patients are limited. 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 low-grade dysplasia diagnoses via WATS3D sampling; however, study interpretation is limited as only 16 cases (0.33%) of progression defined as high-grade dysplasia or esophageal adenocarcinoma on follow-up forceps biopsy were identified. A RCT enrolling patients with a recent history of dysplasia



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reported an absolute increase of 10% in the diagnostic yield of HGD/EAC but did not report on long-term disease progression or mortality outcomes. No direct evidence of clinical utility was identified. Because combined use of WATS3D with standard surveillance is intended to replace the current standard of care for guiding patient management decisions regarding initiation of treatment or surveillance, direct evidence of clinical utility is required. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals at increased risk of BE who undergo standard screening with adjunctive WATS3D, the evidence includes a meta-analysis of studies of diagnostic yield, a physician impact study, a decision analytic model, and a retrospective analysis of the manufacturer database. Relevant outcomes are test validity, overall survival, disease-specific survival, change in disease status, and quality of life. A meta-analysis reported incremental diagnostic yields of 7.2% and 2.1% for any dysplasia/EAC or HGD/EAC, respectively. However, available studies have incomplete descriptions of selection criteria, and it is unclear whether study patients are at increased risk as defined by guideline recommendations for screening. In fact, 2 studies were enriched with women in whom screening is generally not recommended by society guidelines. These studies also 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. In discordant cases where BE or dysplasia were identified only by WATS3D, significant physician management changes included initiation of invasive treatments. Health outcomes from management changes were not reported, and risks associated with overdiagnosis and overtreatment require elucidation. Follow-up data on disease progression in these patients are limited. 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 low-grade dysplasia diagnoses via WATS3D sampling; however, study interpretation is limited as only 16 cases (0.33%) of progression defined as high-grade dysplasia or esophageal adenocarcinoma on follow-up forceps biopsy were identified. No direct evidence of clinical utility was identified. Because combined use of WATS3D with standard screening is intended to replace the current standard of care for guiding patient management decisions regarding initiation of treatment or surveillance, direct evidence of clinical utility is required. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with non-dysplastic, indefinite dysplasia, or low-grade dysplasia BE who undergo standard screening with adjunctive TissueCypher, the evidence includes multiple clinical validity studies and physician impact studies. Relevant outcomes are test validity, overall survival, disease-specific survival, change in disease status, and quality of life. Clinical validity studies have reported sensitivities ranging from 29% to 71% and specificities between 79% to 95% for predicting progression to high-grade dysplasia or esophageal adenocarcinoma. Hazard ratios for high-risk versus low-risk groups ranged from 3.23 to 5.26, indicating increased progression risk for individuals classified as high-risk by TissueCypher. The assay showed improved risk stratification compared to expert pathologist reviews in several studies. Clinical utility studies have focused on the impact of TissueCypher results on patient management decisions. One author found that



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TissueCypher results influenced more than half of management decisions, leading to both upstaging and downstaging of treatment approaches. Another study reported that incorporating TissueCypher results significantly increased the percentage of patients receiving guideline-appropriate management compared to pathology review alone. A randomized trial using simulated patients found that physicians with access to TissueCypher results were more likely to correctly assess progression risk and offer guideline-concordant treatment. However, these studies primarily relied on simulated cases or management decision changes, and long-term patient outcomes resulting from TissueCypher-guided management have not been directly assessed. The use of adjunct TissueCypher is intended to classify individuals with BE based on their risk of progression to high-grade dysplasia or esophageal adenocarcinoma, this can change patient management decisions regarding the initiation of treatment such as esophageal eradication therapy or enhanced surveillance. Therefore, direct evidence of improvement in health outcomes is required. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

## **Supplemental Information**

### **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. 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, 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.



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### ***American Gastroenterological Association***

In 2022, the American Gastroenterological Association issued a clinical practice update addressing new technology and innovation for surveillance and screening in BE. 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. 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 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.

### ***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. 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.

### ***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. Expert panel statements regarding the safety, efficacy, and value of WATS3D included:

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- "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
<i>Ongoing</i>			
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)

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NCT04312633 <sup>a</sup>	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)
<i>Unpublished</i>			
NCT02988934 <sup>a</sup>	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.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

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10/07/2021	Medical Policy Committee review
10/13/2021	Medical Policy Implementation Committee approval. New policy.
12/15/2021	Coding Update
03/10/2022	Coding update
10/06/2022	Medical Policy Committee review
10/11/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/05/2023	Medical Policy Committee review
10/11/2023	Medical Policy Implementation Committee approval. Esophageal brush biopsy tests (e.g., EsoGuard) added to the policy in the investigational statement. Background information added to detail research on other screening methods. Information on EsoCheck added to the FDA section. Detail added to Rationale section to support the policy. References updated.
05/02/2024	Medical Policy Committee review
05/08/2024	Medical Policy Implementation Committee approval. Removed esophageal brush biopsy tests (e.g., EsoGuard) from the investigational statement and references to EsoGuard throughout the policy (see Carelon Guidelines for dates of service 7/1/2024 and beyond).
12/05/2024	Medical Policy Committee review
12/11/2024	Medical Policy Implementation Committee approval. Title changed from "Adjunctive Techniques for Screening and Surveillance of Barrett Esophagus and Esophageal Dysplasia" to "Adjunctive Techniques for Screening, Surveillance, and Risk Classification of Barrett Esophagus and Esophageal Dysplasia".



# Adjunctive Techniques for Screening, Surveillance, and Risk Classification of Barrett Esophagus and Esophageal Dysplasia

Policy # 00757

Original Effective Date: 11/08/2021

Current Effective Date: 01/01/2025

Added investigational statement for TissueCypher for assessing the risk of progression to high-grade dysplasia or esophageal adenocarcinoma in individuals with Barrett esophagus.

Next Scheduled Review Date: 12/2025

## **Coding**

*The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2023 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.*

*The responsibility for the content of Louisiana Blue Medical Policy Coverage Guidelines is with Louisiana Blue and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Louisiana Blue Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Louisiana Blue Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.*

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	88104, 88305, 88312, 88361 Delete code effective 07/01/2024: 0114U Add code effective 01/01/2025: 0108U
HCPCS	No codes
ICD-10 Diagnosis	All related Diagnoses

\*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and

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whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
1. Consultation with technology evaluation center(s);
  2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
  3. Reference to federal regulations.

‡ Indicated trademarks are the registered trademarks of their respective owners.

**NOTICE:** If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

**NOTICE:** 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 eligibility for coverage.

