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MEDICAL POLICY – 7.01.596

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

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Select a hyperlink below to be directed to that section.

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RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | HISTORY

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Introduction

The esophagus is the muscular tube that allows food to pass from the throat to the stomach. Barrett's esophagus (BE) is a condition where the cells that line the lower part of the esophagus change and look like the cells in the intestines. Barrett's esophagus can lead to a condition called esophageal dysplasia. This is when the abnormal cells become pre-cancerous. These two conditions are diagnosed and monitored with an upper endoscopy and biopsy. An endoscopy uses a thin, flexible tube with a camera to look for problems in the digestive system. During an endoscopy, a tissue sample is taken (a biopsy) to check for changes in the cells. Another type of biopsy is called wide-area transepithelial sampling with three-dimensional analysis, or WATS3D. WATS3D uses a computer system to examine tissue samples. The use of WATS3D is unproven (investigational). More studies are needed to see if this testing improves health outcomes.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a

service may be covered.

Policy Coverage Criteria

Test	Investigational
Wide-area transepithelial sampling with three-dimensional computer-assisted analysis (WATS3D)	**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.**
TissueCypher and Esopredict	**TissueCypher and Esopredict are considered investigational for assessing the risk of progression to high-grade dysplasia or esophageal adenocarcinoma in individuals with Barrett esophagus.**

Coding

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. (used to report TissueCypher Barrett's Esophagus Assay from Cernostics Lab)
0398U	Gastroenterology (Barrett esophagus), P16, RUNX3, HPP1, and FBN1 DNA methylation analysis using PCR, formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as risk score for progression to high-grade dysplasia or cancer (Esopredict Barrett's Esophagus Risk Classifier Assay))
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

Code	Description
	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

Related Information

NA

Evidence Review

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.

Background

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 individuals 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, the 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 individual.[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 the 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 individuals with high-grade dysplasia on biopsy are found to have associated carcinoma in the resection specimen.[7]

For individuals 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 individuals 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]

Summary of Evidence

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

For individuals with non-dysplastic, indefinite dysplasia, or low-grade dysplasia BE who undergo standard screening with adjunctive TissueCypher, the evidence includes multiple clinical validity studies and physician impact studies. Relevant outcomes are test validity, overall survival, disease-specific survival, change in disease status, and quality of life. Clinical validity studies have reported sensitivities ranging from 29% to 71% and specificities between 79% to 95% for predicting progression to high-grade dysplasia or esophageal adenocarcinoma. Hazard ratios for high-risk versus low-risk groups ranged from 3.23 to 5.26, indicating increased progression risk for individuals classified as high-risk by TissueCypher. The assay showed improved risk stratification compared to expert pathologist reviews in several studies. Clinical utility studies have focused on the impact of TissueCypher results on patient management decisions. One author found that TissueCypher results influenced more than half of management decisions, leading to both upstaging and downstaging of treatment approaches. Another study reported that incorporating TissueCypher results significantly increased the percentage of individuals receiving guideline-appropriate management compared to pathology review alone. A randomized trial using simulated individuals found that physicians with access to TissueCypher results were more likely to correctly assess progression risk and offer guideline-concordant treatment. However, these studies primarily relied on simulated cases or management decision

changes, and long-term patient outcomes resulting from TissueCypher-guided management have not been directly assessed. The use of adjunct TissueCypher is intended to classify individuals with BE based on their risk of progression to high-grade dysplasia or esophageal adenocarcinoma, this can change patient management decisions regarding the initiation of treatment such as esophageal eradication therapy or enhanced surveillance. Therefore, direct evidence of improvement in health outcomes is required. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

Ongoing and Unpublished Clinical Trials

Some currently ongoing and 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,	500	June 2024 (recruiting)

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Previously Undiagnosed Barrett's Esophagus and/or Esophageal Adenocarcinoma		
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	June 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			
NCT02988934[a]	The WATS3D (Wide Area Transepithelial Sample Biopsy with 3-Dimensional Computer-Assisted Analysis) US Registry	3173/10000	Feb 2023 (terminated)

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

Practice Guidelines and Position Statements

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

Guidelines or position statements will be considered for inclusion 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 BE based on 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 immunohistochemistry (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 (NDBE)." 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 manufacturerfunded. 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 individuals with BE, the utility and accuracy of WATS3D for detecting high-grade dysplasia and adenocarcinoma in individuals 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."US Preventive Services Task Force Recommendations.

No US 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.

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 US Food and Drug Administration has chosen not to require any regulatory review of this test.

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History

Date	Comments
02/04/22	New policy, approved October 12, 2021, effective for dates of service on or after February 4, 2022, following 90-day provider notification. Policy created with literature review through July 2, 2021. Wide-area transepithelial sampling with three-

Date	Comments
	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.
01/01/23	Annual review, approved December 12, 2022. Policy updated with literature review through July 8, 2022; references added. Policy statements unchanged. Changed the wording from "patient" to "individual" throughout the policy for standardization.
10/01/23	Annual review, approved September 25, 2023. Policy updated with literature review through June 28, 2023; references added. Policy statements unchanged.
01/01/25	Policy renumbered from 7.01.167 Adjunctive Techniques for Screening and Surveillance of Barrett Esophagus and Esophageal Dysplasia to 7.01.596 Adjunctive Techniques for Screening, Surveillance and Risk Classification of Barrett Esophagus and Esophageal Dysplasia, approved December 10, 2024, effective for dates of service on or after April 6, 2025, following 90-day provider notification. Policy statement "TissueCypher and Esopredict are considered investigational for assessing the risk of progression to high-grade dysplasia or esophageal adenocarcinoma in individuals with Barrett esophagus" was added. Added CPT code 0108U for TissueCypher. Policy updated with literature review through June 26, 2024; references added. Added CPT code 0398U (moved from policy 10.01.533 for Esopredict).

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.