BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Adjunctive Techniques for Screening and Surveillance of Barrett Esophagus and Esophageal Dysplasia

Policy #: 743
Latest Review Date: August 2022
Category: Medical

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Blue Advantage will treat **wide-area transepithelial sampling with three-dimensional computer-assisted analysis (WATS3D)** as a **non-covered benefit** and as **investigational** for all indications, including but not limited to the screening and surveillance of Barrett esophagus and esophageal dysplasia.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

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.

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.

KEY POINTS:

This evidence review was created in August 2021 with a search of the PubMed database. The most recent literature update was performed through July 8, 2022.

Summary of Evidence

For individuals with a history of BE who receive standard surveillance with adjunctive WATS3D, the evidence includes 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. Relative diagnostic yields for BE and various categories of dysplasia have ranged from 18.8% to 73% and 42.1% to 428.6%, 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% confidence interval [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 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 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. Relative diagnostic yields for BE and dysplasia have ranged from 75% to 213% and 88.5% to 274%, 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.

Practice Guidelines and Position Statements

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.

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.2.2022) 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:

- "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.

KEY WORDS:
Wide-area transepithelial sampling with three-dimensional computer-assisted analysis, WATS3D

APPROVED BY GOVERNING BODIES:
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). The WATS3D (CDx Diagnostics), formerly known as EndoCDx, is 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.

BENEFIT APPLICATION:
Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

CURRENT CODING:
CPT Codes:

88104	Cytopathology, fluids, washings or brushings, except cervical or vaginal; smears with interpretation
88305	Level IV - Surgical pathology, gross and microscopic examination
88312	Special stain including interpretation and report; Group I for microorganisms (eg, acid fast,

	methenamine silver)
88361	Morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; using computer-assisted technology

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POLICY HISTORY:

Adopted for Blue Advantage, August 2021
Medical Policy Group, August 2021
Medical Policy Group, August 2022
