05-87000-01

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Reviewed: 10/24/24

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

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

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.

Summary and Analysis of Evidence: Patients with a history of BE who receive standard surveillance with adjunctive WATS3D, the evidence includes several studies, meta-analysis of studies of diagnostic yield, randomized controlled trials, physician impact study, decision analytic model, and retrospective analysis of the manufacturer database. 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 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. Patients at increased risk of BE who undergo standard screening with adjunctive WATS3D, the evidence includes several studies, meta-analysis of studies of diagnostic yield, physician impact study, a decision analytic model, and retrospective analysis of the manufacturer database. 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. The American Gastroenterological Association (AGA) Clinical Practice Update on New Technology and Innovation for Surveillance and Screening in Barrett's Esophagus: Expert Review (2022) includes, "Wide-area transepithelial sampling (WATS-3D) may be used as an adjunctive technique to sample the suspected or established Barrett's segment (in addition to the Seattle biopsy protocol)". "As such, the recent ASGE [American Society for Gastrointestinal Endoscopy] guidelines supported the use of WATS-3D in addition to Seattle protocol in select patients (eg, indeterminate for dysplasia or clinically high-risk NDBE) undergoing surveillance. Further prospective studies directly comparing WATS-3D and Seattle protocol are needed to understand if WATS-3D sampling might be as or more effective". The National Comprehensive Cancer Network (NCCN) Esophageal and Esophagogastric Junction Cancers guideline (V4.2024) includes, "The use of wide-area transepithelial sampling with computer-assisted 3-dimensional analysis (WATS3D), a relatively new sampling technique combining an abrasive brush biopsy of the Barrett esophagus mucosa with computer-assisted pathology analysis to highlight abnormal cells, may help increase the detection of esophageal dysplasia in patients with Barrett esophagus. In a multicenter prospective trial, patients with Barrett esophagus (n = 160) were randomized to receive biopsy sampling in conjunction with WATS or biopsy sampling alone. Results showed that the addition of WATS to biopsy sampling was feasible and yielded an additional 23 cases of HGD/esophageal adenocarcinoma (absolute increase, 14.4%). Two other studies have reported similar results. However, the utility and accuracy of WATS for detecting HGD/adenocarcinoma in patients with Barrett esophagus needs to be evaluated in larger phase III randomized trials". Patients 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. Patients 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. Clinical validity studies have reported sensitivities ranging from 29% to 71% and specificities between 79% to 95% for predicting progression to high-grade dysplasia or esophageal adenocarcinoma. Hazard ratios for high-risk versus low-risk groups ranged from 3.23 to 5.26, indicating increased progression risk for individuals classified as high-risk by TissueCypher. The assay showed improved risk stratification compared to expert pathologist reviews in several studies. Clinical utility studies have focused on the impact of TissueCypher results on patient management decisions. One

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

POSITION STATEMENT:

Wide-area transepithelial sampling with three-dimensional computer-assisted analysis (WATS3D) is considered **experimental or investigational** for all indications, including but not limited to the screening and surveillance of Barrett's esophagus and esophageal dysplasia. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

EsoCheck and Esoguard are considered **experimental or investigational** for the screening and surveillance of Barrett esophagus and esophageal dysplasia. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

TissueCypher is considered **experimental or investigational** for assessing the risk of progression to high-grade dysplasia or esophageal adenocarcinoma in members with Barrett esophagus. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

BarreGen is considered **experimental or investigational** for assessing the risk of progression to high-grade dysplasia or esophageal adenocarcinoma in members with Barrett esophagus. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

BILLING/CODING INFORMATION:

There is no specific CPT or HCPCS code to report WATS3D. It may be billed using multiple codes such as 88104, 88305, 88312, and 88361.

CPT Coding:

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 (**Investigational**)
0114U	Gastroenterology (Barrett's esophagus), VIM and CCNA1 methylation analysis, esophageal cells, algorithm reported as likelihood for Barrett's esophagus (**Investigational**)

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage products: The following were reviewed on the last guideline reviewed date: ocal Coverage Determination (LCD) Molecular Pathology Procedures (L34519); Billing and Coding: Molecular Pathology Procedures (A57451); Billing and Coding: Molecular Pathology and Genetic Testing (A58918) located at fcso.com.

DEFINITIONS:

No guideline specific definitions apply.

RELATED GUIDELINES:

Endoscopic Radiofrequency Ablation or Cryosurgical Ablation for Barrett's Esophagus, 01-91000-10

Molecular Testing for the Management of Pancreatic Cysts and Solid Pancreaticobiliary Lesions, 05-86000-27

OTHER:

None applicable.

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detection of Barrett's esophagus and esophageal dysplasia. Ann Diagn Pathol. 2022 Oct;60:151982. PMID: 35667232.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Medical Policy and Coverage Committee on 10/24/24.

GUIDELINE UPDATE INFORMATION:

06/15/22	New Medical Coverage Guideline.
10/15/23	Review: Position statement maintained and references updated.
11/15/24	Review: Position statements, coding, description, policy title, and references updated.