Anthem

Clinical UM Guideline

Subject: Testing for Oral and Esophageal Cancer
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Description

This document addresses the use of oral brush biopsies or esophageal brush biopsies for the detection of precancerous or cancerous lesions.

Clinical Indications

Not Medically Necessary:

Oral or esophageal brush biopsies for the diagnosis, screening, or surveillance of precancerous or cancerous lesions are considered **not medically necessary.**

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Not Medically Necessary:
For the procedure and diagnosis codes listed below.

CPT	
40899	Unlisted procedure, vestibule of mouth [when specified as a brush biopsy of oral mucosa]
43191	Esophagoscopy, rigid, transoral; diagnostic, including collection of specimen(s) by brushing or washing when performed (separate procedure) [when specified as brush biopsy of esophagus]
HCPCS	
D7288	Brush biopsy – transepithelial sample collection
ICD-10 Diagnosis	
K22.70-K22.719	Barrett's esophagus
Z12.10	Encounter for screening for malignant neoplasm of intestinal tract, unspecified
Z12.81	Encounter for screening for malignant neoplasm of oral cavity

Discussion/General Information

Oral Brush Biopsy

The oral brush biopsy, such as the OralCDx® Brush Biopsy (CDx Diagnostics, Suffern, NY), was developed as a painless screening method to evaluate oral lesions that could be precancerous or cancerous. The OralCDx system uses a specially designed brush to collect cells from three layers of the epithelium. Once collected, the specimen is prepared and sent to a specialty laboratory for evaluation. If the specimen is suspected to be precancerous or cancerous, the lesion can then be removed by traditional scalpel biopsy, and the diagnosis can be confirmed by histology.

In 1999, Sciubba and colleagues conducted a large, double-blind, multicenter study on OralCDx. The investigators categorized 945 lesions as either Class I, suspicious lesions evaluated by both OralCDx and scalpel biopsy (n=298), or Class II, unsuspicious lesions evaluated only by OralCDx (n=647). OralCDx detected dysplasia or carcinoma in all lesions that were found abnormal by scalpel biopsy and histology (n=131). Of 196 lesions that were found negative by scalpel biopsy and histology, the OralCDx reported 182 as negative and 14 as atypical. The authors concluded that OralCDx has a sensitivity and specificity of 100% (92.9% for atypical results); however, the majority of lesions in the study were not directly compared to scalpel biopsy/histology thus rendering the data incomplete and making the results inconclusive. Additionally, the number of inadequate OralCDx samples was 7%. The authors noted that while OralCDx has potential value, it cannot replace traditional scalpel biopsy and histology.

In a 2013 Cochrane Review, Brocklehurst and colleagues evaluated oral cancer screening methods. They noted a lack of randomized controlled trials and a high risk of bias in the available studies. In addition, they stated that there was not enough evidence to support a general screening for oral cancer. The authors concluded that there is no evidence that adjunct technology, including brush biopsy, decreases oral cancer mortality. Likewise, in a 2015 Cochrane Review, Macey and colleagues evaluated the accuracy of index tests, including oral cytology brush biopsies, for detecting oral cancer. They also noted a lack of high-quality studies available. The authors concluded that no adjunctive test can be recommended as a replacement for scalpel biopsy and histological assessment.

Alsarraf and colleagues (2018) performed a systematic review on the utility of oral brush cytology compared to scalpel biopsy for the early detection of oral malignancy. They included 36 peer-reviewed studies (4302 samples) that included liquid-based cytology (LBC) or exfoliative cytology. The most commonly used oral brushes were a cytobrush (LBC or exfoliative cytology), the OralCDx brush (conventional exfoliative cytology), the Orcellex® brush (LBC; Netherlands), and a baby toothbrush (LBC or conventional exfoliative cytology; India). For the OralCDx brush, the authors found that several studies reported a wide range of sensitivity (71%-100 %, or not reported) and specificity (32%-100%, or not reported). Many studies had heterogeneous sampling techniques and lacked validated protocols for evaluation and surveillance. The authors concluded that LBC brush biopsies, possibly with molecular testing, have more advantages than exfoliative cytology. However, they recommended well-designed, longitudinal studies with clear criteria and accurate cyto-histopathological correlation.

In 2020, Velleuer and colleagues enrolled 279 individuals with Fanconi anemia (FA) (associated with 500-fold to 700-fold elevated risk

of oral squamous cell carcinoma [SCC]). In total, 1233 evaluable brush biopsies were collected from 279 individuals; 86 lesions were identified. Of these individuals, 63% (19 of 30 individuals) were diagnosed in the desired early stages of disease with high-grade oral epithelial dysplasia, including SCC classified as Tis (in situ) (11 individuals) or T1 (8 individuals). This small prospective cohort study provides supporting evidence that oral brush biopsy-based cytology may enhance diagnostic accuracy of SCC in this high-risk population. Further investigation is warranted in larger trials demonstrating a sustained, reproducible effect.

Since the oral brush biopsy was introduced to the market in 1999, there have been a number of nonrandomized studies with varying results. In 2004, Poate and colleagues performed a retrospective analysis of 112 suspicious lesions and found that the OralCDx had a sensitivity of 71.4% (95% confidence interval [CI], 52.1% to 90.9%) and a specificity of 32% (95% CI, 14.8% to 49.4%). In a 2009 prospective study, Hohlweg-Majert and colleagues compared brush biopsy to synchronous histological biopsy in 75 suspicious lesions. The sensitivity rate for OralCDx was 52% with a specificity of 29% (CI not reported). In a 2011 study, Mehrotra and colleagues performed a prospective study in which 79 minimally suspicious lesions were tested with OralCDx immediately followed by scalpel biopsy. The authors found that OralCDx had a sensitivity of 96.3% (95% CI, 87% to 100%) and a specificity of 100% (95% CI, 93% to 100%).

In a 2013 statement on screening for oral cancer, the U.S. Preventive Services Task Force (USPSTF) stated that “screening and adjunct tests have not been adequately tested in primary care nondental settings,” and that “the current evidence is insufficient to assess the balance of benefits and harms of screening for oral cancer in asymptomatic adults.”

In a 2021 Physician Data Query (PDQ) on oral cavity and oropharyngeal cancer screening, the National Cancer Institute (NCI) stated that adjunctive screening methods “have not been shown to have superior sensitivity and specificity for visual examination alone or to yield better health outcomes.” They also note that screening for oral cancer can lead to the following:

- Unnecessary treatment of lesions that would not have progressed (overdiagnosis)
- Psychologic consequences of false-positive tests
- Misdiagnosis due to variability in assessment of biopsies.

Studies on oral brush biopsies have shown inconsistent results, and the evidence does not support use in accordance with generally accepted standards of medical practice.

Esophageal Brush Biopsy

An esophageal brush biopsy, such as the wide area transepithelial sampling (WATS)$^{3D®}$ System (CDx Diagnostics, Suffern, NY), has been proposed as an adjunct to traditional four-quadrant forceps biopsy (FB) for screening and surveillance of individuals with Barrett’s esophagus (BE). The intent of the computer-assisted WATS^{3D} brush biopsy sampling system is to test additional random tissue that may be potentially missed by standard FB sampling. The WATS^{3D} system uses a specialized brush that attaches to an endoscope and collects a wide area, transepithelial specimen of the full-thickness esophageal mucosa. The sample is prepared and sent to a specialty laboratory where it is analyzed by specially trained pathologists using three-dimensional software. The adjunct esophageal brush biopsy proposes to increase the size of the biopsy sample, thereby potentially increasing accuracy in the diagnosis of precancerous or cancerous esophageal disease.

The first-generation WATS^{3D} system was formerly known as EndoCDx®. In a multicenter trial, Johanson and colleagues (2011) compared FB to EndoCDx esophageal brush biopsy for 1266 subjects who were being screened for BE. The authors found that brush biopsy increased the detection of BE by 39.8% (95% CI, 32% to 48%). A total of 139 subjects were found to have BE by brush biopsy that were not found by FB; however, 166 subjects were found to have BE only with FB. Likewise, brush biopsy revealed 14 subjects with dysplasia not found by FB, but FB found 11 subjects with dysplasia not found with brush biopsy. The authors concluded that the adjunctive use of brush biopsy improves detection of BE and dysplasia in a screening population.

In a study evaluating EndoCDx (first-generation WATS^{3D}), Anandasabapathy and colleagues (2011) compared forceps and EndoCDx brush biopsies in 151 subjects with a known history of BE and dysplasia. The brush biopsy was able to detect dysplasia of any kind (that is, low grade dysplasia, high grade dysplasia or carcinoma) in 16 subjects not found by FB alone, reporting a number needed to treat (NNT) of 9.4 (95% CI, 5.6 to 16.6). FB found 23 cases of dysplasia not found by brush biopsy. The authors concluded that esophageal brush biopsy may be a valuable adjunct for high-risk subjects with BE.

In a prospective, randomized, multicenter study, Vennalaganti and colleagues (2018) compared the second-generation WATS^{3D} brush biopsy to FB in 160 subjects with BE. Subjects either received FB followed by WATS^{3D} or WATS^{3D} followed by FB. WATS^{3D} detected 23 cases of high-grade dysplasia/esophageal adenocarcinoma (HGD/EAC) not found initially with FB (absolute increase 14.4%; 95% CI, 7.5% to 21.2%). Among these 23 cases, 11 were classified by biopsy as non-dysplastic BE, and 12 as low-grade dysplasia (LGD)/indeterminate; the majority (n=21; 91.7%) had a prior dysplasia history. Subsequent follow-up was available for 9 of the 23 WATS^{3D} classified HGD/EAC cases: 2 had HGD, 2 had EAC, 3 had LGD and 2 had no dysplasia. WATS^{3D} missed one case of HGD/EAC found by FB. The authors noted that the study may not be generalizable to a low-risk BE surveillance population. The authors concluded that WATS^{3D} increased the detection of HGD/EAC in a high-risk surveillance population and “may be a useful addition to standard endoscopic surveillance programs for the diagnosis of BE neoplasia.”

In a prospective evaluation of 12,899 individuals (18-93 years of age), Smith and colleagues (2019) reported that FB identified 88 cases (0.68% of the total population) of ED or neoplasia and an additional 213 cases were detected using WATS^{3D} that were not detected on FB; an absolute increase of 1.65%, raising the yield from 0.68% to 2.33%. Study authors conclude that adding WATS^{3D} to the random 4- quadrant FB protocol increased the overall detection of dysplasia by 242%.

In a systematic review with meta-analysis, Kumar and colleagues (2020) compared the detection rates of BE and esophageal dysplasia (ED) using either FB alone or FB with WATS^{3D} as an adjunct. All of the studies that met inclusion criteria were non-randomized and open-label. Combined data from 20,392 screening endoscopies showed an increase in the absolute and relative detection rates. A total of 6643 lesions were identified using WATS^{3D} in conjunction with FB compared to 3310 with FB alone. The absolute increase in detection of BE using WATS^{3D} as an adjunct to FB was 16% (measured as risk difference -0.16, 95% CI, 0.10 to 0.22, p<0.00001) with a relative increase of 1.62 times (measured as risk ratio -1.62, 95% CI, 1.28 to 2.05, p<0.0001) and a number needed to test of 6.1. The absolute increase in detection of ED using WATS^{3D} combined with FB was 2% (risk difference 0.02, 95% CI, 0.01 to 0.03, p=0.001) with a relative increase in detection of 2.05 times (risk ratio 2.05, 95% CI, 1.42 to 2.98, p=0.0001) and a number needed to test of 50. The results showed that while there was a significant increase in diagnostic yield for both BE and ED, the increase in detection of ED was marginal and possibly attributable to the fewer number of total cases with respect to BE. It was also noted that Smith and colleagues (2019) contributed approximately more than 60% of the data for this review.

A multicenter prospective trial screened 4203 individuals with suspected BE and those with known BE undergoing surveillance. In total, 594 cases of BE were diagnosed using FB alone, and an additional 493 cases of BE were detected by adding WATS^{3D}; an overall increase in detection of BE of 83% (95% CI, 74%–93%). The authors concluded that adjunctive use of WATS^{3D} significantly improved the detection of both BE and ED when using FB. The study results are promising and further investigation is warranted to validate replication of results (Gross, 2018).

In 2019, an observational cohort study was published with data from January 2017 to December 2018, of 138 consecutive subjects who underwent a clinical examination that included high-definition white light endoscopy (HDWLE), narrow-band imaging (NBI), volumetric laser endomicroscopy (VLE), and Seattle protocol (SP) biopsies (collectively termed HDWLE-NBI-VLE-SP examination). Raised lesions were removed by endoscopic resection. Areas suspicious for dysplasia on NBI and VLE were biopsied, followed by random biopsies and WATS3^{3D} brush biopsies. A total of 35 cases (25%) were identified as some degree of dysplasia on the HDWLE-NBI-VLE-SP examination. Adjunctive use of WATS^{3D} yielded an additional 12 new cases of dysplasia, for an added yield of 34.3% (95% CI, 14.6-62.2). Authors conclude that the addition of WATS^{3D} may increase the detection of dysplasia (Raphael, 2019).

In a retrospective study, Kaul and colleagues (2020) investigated the clinical utility of WATS^{3D} as an adjunct to the Seattle protocol and its impact on clinical management and health care outcomes of individuals when BE or dysplasia was detected by WATS^{3D}, but not by FB. The study included 432 individuals diagnosed with either non-dysplastic BE (n=317), LGD (n=98), or HGD (n=17) by WATS^{3D} and negative by FB. WATS^{3D} results impacted clinical management in 97.8% of individuals diagnosed with BE and 94.9% and 94.1% of individuals with LGD and HGD, respectively. Follow-up data was available for individuals in the BE, LGD, and HGD groups who did not undergo ablation and subsequently underwent follow-up endoscopy with WATS^{3D} and FB. Of the 149 individuals in the BE group, 6 individuals were subsequently diagnosed with LGD by WATS^{3D}, which was missed again by FB. There 28 individuals in the LGD group, 3 of which developed into HGD identified by WATS^{3D} alone. In the HGD group (n=4), 1 individual developed EAC which was identified by WATS^{3D} and FB. The study was limited by the lack of a comparison group. This study did not investigate the ability of WATS^{3D} to guide therapy in a way that improved patient-centered health outcomes.

In 2022 Karmakar and colleagues published the results of a retrospective case series involving 36 subjects with Stage II-IV esophageal carcinoma treated with either concurrent chemo-radiotherapy or neo-adjuvant chemotherapy followed by chemo-radiotherapy who also underwent PET-CT and brush cytology at time of endoscopy. Using clinical follow-up as the gold standard, the authors reported the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of PET-CT plus brush cytology to be 75%, 90%, 85.7% and 81.8% respectively. This study did not investigate the ability of brush cytology to guide therapy in a way that improved patient-centered health outcomes.

DeMeester (2022) reported a study involving 1002 subjects with foregut symptoms undergoing upper endoscopy. FB sampling was conducted in 505 subjects and WATS^{3D} sampling was done in 497. Intestinal metaplasia was found in 19.6% of the FB subjects and 21% of the WATS^{3D} group (p=0.2). The authors reported no overall difference in detection of dysplasia between the FB and WATS^{3D} groups. However, in subjects with no history of intestinal metaplasia (n=439), WATS^{3D} found significantly more intestinal metaplasia compared to FB when a columnar-lined esophagus was present (32.4% in the WATS^{3D} group vs. 15.2% in the FB group, p=0.004). In 184 subjects with known BE, FB and WATS^{3D} found intestinal metaplasia with similar frequency (38.5% vs. 41.9% respectively, p=0.6). Additional prospective data is needed to assess the clinical relevance of intestinal metaplasia detected by WATS^{3D}.

Shaheen (2022) reported on the results of a retrospective case series study involving 151,224 consecutive WATS^{3D} tests in the WATS3D clinical database of subjects undergoing screening or surveillance procedures. The objective was to assess the risk of progression of WATS^{3D}-reported nondysplastic BE, crypt dysplasia, and LGD with HGD or EAC. All subjects had no prior history of dysplasia or ablative therapy. A total of 4545 subjects met the study criteria and were the study group. Both baseline WATS^{3D} samples and FB sampling data were available for analysis in 55% of study subjects, A total of 50 subjects were diagnosed with crypt dysplasia on WATS^{3D} testing vs. none by FB. Of these 50 subjects, 45 were diagnosed with nondysplastic BE and 5 with LGD. Overall, FB samples detected 15 subjects with progression and WATS^{3D} detected 16 subjects with progression. Three progressors detected by WATS^{3D} were not detected by FB and 2 progressors detected by FB were not detected on WATS^{3D}. Of the 16 progressors detected by WATS^{3D}, 11 had no visible abnormality, 3 had esophagitis with no ulceration, and 2 had esophagitis with ulceration at baseline endoscopy. Histologically, of the 16 progressors, all 16 also had baseline FB sampling with 9 having nondysplastic BE, 3 being indefinite for dysplasia, and 4 with low grade dysplasia. Nine of 16 subjects with baseline FB findings of nondysplastic BE had the same findings on WATS^{3D}. All 3 indefinite dysplasia FB cases had crypt dysplasia on WATS^{3D}, and of the 4 subjects with LGD on biopsy, 3 had the same finding on WATS^{3D} testing. The last subject had crypt dysplasia with WATS^{3D}. When considering FB-confirmed progression, the crude progression rates per patient-year for nondysplastic BE, crypt dysplasia, and LGD were 0.08%, 1.42%, and 5.79%, respectively. For overall progression detected by WATS^{3D}, crude progression rates per patient-year were 0.10%, 1.89%, and 3.47%, respectively. Comparison of the progression rates among the 3 groups was statistically significant between nondysplastic BE and crypt dysplasia and between nondysplastic BE and LGD in both progression analyses (pairwise $p<0.01$) and significant between crypt dysplasia and LGD for biopsy-detected progression. Progression to either crypt dysplasia and LGD was also recorded for the nondysplastic BE group and progression to LGD was recorded for the crypt dysplasia group. In the nondysplastic BE group, 136 subjects (3.10%) progressed to crypt dysplasia and 28 subjects (0.64%) progressed to LGD. In the crypt dysplasia group, 10 subjects (7.81%) progressed to LGD on follow-up. The difference in progression to LGD between nondysplastic BE group and crypt dysplasia group was highly significant ($p<0.001$). Overall, 0.33% of subjects progressed to HGD/EAC as diagnosed by biopsy. The authors concluded that nondysplastic BE found on WATS^{3D} has a very low risk of progression. Crypt dysplasia found on WATS^{3D} appears to be a neoplastic precursor lesion with a risk of progression significantly higher than nondysplastic BE but lower than LGD. They also note that WATS^{3D} has a unique ability to detect crypt dysplasia, a diagnosis frequently missed on biopsy. This study included a relatively low number of progressions, leading to relatively wide confidence intervals. Additional study is needed to assess the clinical relevance of crypt dysplasia detected by WATS^{3D}, as well how detection guides therapy in a way that improved patient-centered health outcomes.

van Munster (2023) reported the results of a prospective, multicenter, double blinded, randomized clinical trial (RCT) involving 172 subjects with known BE and a recent history of dysplasia or adenocarcinoma scheduled for regular imaging endoscopy. Subjects had a BE length of <2 cm in circumferential extent or >10 cm maximum extent. All received both four-quadrant forceps biopsy and WATS^{3D} sampling, and were randomized to receive biopsy first followed by WATS^{3D} or the reverse procedure. Each WATS^{3D}

sample involved 2 brushings per 5 cm segment of BE. The first brushing was smeared on a slide and fixed for PAP staining before the bristles were clipped and placed in a vial for pathological analysis. The slide samples underwent computer-assisted 3-D tissue analysis. The second brush went directly into a vial for pathological analysis without slide preparation. A total of 25 subjects (14.5%) were excluded from the final analysis due to inadequate WATS^{3D} specimen (n=23) or biopsy (n=2). The WATS^{3D} sample exclusions were due to air drying artefact or poor PAP stain technique. The biopsy samples were rejected due to insufficient specimen size. Discrepancy between the onsite and central pathologist decisions occurred in 30 (17%) of biopsy samples and 2 (1%) of WATS^{3D} samples. No significant differences were reported between biopsy and WATS^{3D} in the detection of high-grade dysplasia in either the intent-to-treat or per-protocol analyses (p=0.36 and p=0.12, respectively). The absolute increase in high-grade dysplasia/esophageal adenocarcinoma was 10% and relative increase was 55% (p<0.001 for both). The detection rate increased from 19% to 30%. No procedure-related complications were reported in this study. These results are promising and indicate that WATS^{3D} may significantly improve diagnostic yield. Since all participants in this study already had a dysplasia diagnosis, these results may not apply to screening of individuals without known dysplasia. The authors acknowledge that this study was not designed to nor was it powered to demonstrate noninferiority of WATS^{3D} compared to FB.

A number of additional cohort studies have been published as peer-reviewed studies (Kaul, 2020; Mariano, 2019; Shaheen, 2018). In a retrospective observational cohort study, Agha and colleagues (2021) 21 cases of BE missed by FB alone in 108 individuals who underwent WATS^{3D} and FB at the same time for screening of BE. In this study, the addition of WATS^{3D} to FB alone demonstrated a sensitivity of 96.9% and a specificity of 52.3%.

Fatima (2022) reported a retrospective cohort study of 75 subjects presenting for post-endoscopic ablation surveillance endoscopy with both biopsy and WATS^{3D}. The authors reported an absolute increase in yield of biopsy plus WATS^{3D} was 26.9% for non-dysplastic BE and 6.4% for dysplasia/neoplasia. Relative increase in yield of biopsy plus WATS^{3D} was 100% and 167%, respectively. The unblinded, retrospective, single-center design of this trial limits generalizability to prospective use in general community practice.

Zhao (2022) reported a retrospective cohort study involving 109 subjects who had received biopsy plus WATS^{3D}-determined diagnosis. There were 59 BE cases determined by biopsy alone, 72 by WATS^{3D} alone, and 77 with the combined procedure. For WATS^{3D} alone, there was a strong concordance with biopsy (p<0.001). The same diagnosis for BE and dysplasia was reported in 75 (68.8%) cases. When compared to biopsy, WATS^{3D} was reported to be more sensitive for finding intestinal metaplasia (p<0.01), with 22% increase in detection. However, the authors noted that WATS^{3D} "could not clearly discriminate low-grade dysplasia from indefinite for dysplasia and tended to classify low-grade dysplasia as indefinite for dysplasia". WATS^{3D} combined with biopsy diagnosed 77 cases BE, which was a significantly increased detection rate (30.5%, p<0.01) compared with biopsy sampling alone. This study is promising, but is hampered by low numbers of participants, including those with high grade dysplasia or intramucosal carcinoma.

The American Society for Gastrointestinal Endoscopy ([ASGE], 2019) published a guideline on screening and surveillance of BE with graded recommendations for the use of WATS^{3D} in this setting. ASGE recommends using WATS^{3D} in addition to routine endoscopy with Seattle protocol biopsy sampling in individuals with known or suspected BE (which includes both screening and surveillance). This recommendation was graded as "conditional" and based upon "low quality of evidence."

In 2020, the Society of American Gastrointestinal and Endoscopic Surgeons' (SAGES) Technology and Value Assessment Committee (TAVAC) published a safety and efficacy analysis of the WATS^{3D}. The publication reported that no significant morbidity or mortality was associated with use of the technology and that, on average, it increased the diagnostic yield by 38–150% for BE, 40–150% for LGD; and 420% for HGD; when compared to use of FB alone. The SAGES assessment does not cite any studies not listed elsewhere in this document and does not provide an analytic or systematic review of clinical outcomes (Docimo 2020).

In 2020 the American Gastroenterology Association (AGA) published a guideline on the recommendations of management of BE. While there is no mention of brush biopsy for detection and surveillance, 4-quadrant FB is highlighted as the current best practice in the following statement:

> BEST PRACTICE ADVICE 9: Barrett's endoscopic therapy [BET] should be continued until there is an absence of columnar epithelium in the tubular esophagus on high-definition white-light endoscopy and preferably optical chromoendoscopy. In case of complete endoscopic eradication, the neosquamous mucosa and the gastric cardia are sampled by 4-quadrant biopsies.

In a 2021 PDQ on Esophageal Cancer Screening, the NCI stated, "Based on fair evidence, screening would result in no (or minimal) decrease in mortality from esophageal cancer in the U.S. population."

In 2022 the American College of Gastroenterology published an update to their 2016 guideline addressing the diagnosis and management of BE (ACG, Shaeen, 2022). In this updated document they state the following:

> Recommendation 12: ". We could not make a recommendation on the use of wide-area transepithelial sampling with computer-assisted 3-dimensional (WATS-3D) analysis in patients undergoing endoscopic surveillance of BE."
>
> "Given our recommendation that patients with BE undergoing routine endoscopic surveillance should have both chromoendoscopy and white light endoscopy for dysplasia detection, and with the additional factors noted above, the panel could not make a recommendation on the use of WATS-3D in BE surveillance at this time. We include recommendation 12 to document that this recommendation went through the formal GRADE review process with consideration by the authoring panel and to provide the data underpinning this decision."

Finally, the National Comprehensive Cancer Network (NCCN) clinical practice guidelines® on Esophageal and Esophagogastric Junction Cancers (2022) considers WATS^{3D} a "relatively new sampling technique" and does not routinely recommend its use as a screening technique. The CPG states, "the utility and accuracy of WATS for detecting HGD/adenocarcinoma in patients with Barrett's esophagus needs to be evaluated in larger phase III randomized trials." However, they additionally state, "Cytologic brushings or washings are rarely adequate in the initial diagnosis, but can be useful in confirming persistent disease following treatment."

Current evidence does not support the routine use of WATS^{3D}. At present, there is insufficient evidence to determine the clinical role of this diagnostic technique, as well as its contribution to management of BE, in conjunction with generally accepted standards of medical practice.

The EsoGuard test and the EsoCheck device (Lucid Diagnostics, Inc., New York, NY) have been proposed as a screening kit for the detection of BE. The EsoCheck is a specimen collection device in the form of a vitamin-sized, encapsulated balloon. The device is

swallowed and surface textures on the balloon collect a gentle brushing of the esophageal mucosa. The balloon is collapsed to protect the collected specimen and drawn back out through the upper esophagus and mouth. The specimen is submitted to a laboratory for EsoGuard testing. The EsoGuard uses next generation sequencing bisulfate converted DNA to detect the presence of Vimentin and CyclinA1 methylation signatures at 31 sites within those genes to identify the presence of BE. The EsoCheck device has received a 510(k) clearance from the FDA while the EsoGuard was granted a breakthrough device designation. Use of the EsoGuard test for detection of BE is not considered in accordance with generally accepted standards of medical practice.

Definitions

Barrett's Esophagus (BE): a condition in which the lining of the esophagus is damaged by stomach acid. People with BE have an increased risk for cancer in the area involved. However, cancer is not common.

References

Peer Reviewed Publications:

1. Agha YH, Srinivasan S, Hyder J, Wuthnow C, Taleb A, Tofteland N, Kilgore W, Salyers W. WATS3D versus forceps biopsy in screening for Barrett's esophagus: experience in community endoscopy centers. Ann Gastroenterol. 2021; 34(2):164-168.
2. Alsarraf A, Kujan O, Farah CS. The utility of oral brush cytology in the early detection of oral cancer and oral potentially malignant disorders: a systematic review. J Oral Pathol Med. 2018; 47(2):104-116.
3. Anandasabapathy S, Sontag S, Graham DY, et al. Computer-assisted brush-biopsy analysis for the detection of dysplasia in a high-risk Barrett's esophagus surveillance population. Dig Dis Sci. 2011; 56(3):761-766.
4. Codipilly DC, Krishna Chandar A, Wang KK, et al. Wide-area transepithelial sampling for dysplasia detection in Barrett's esophagus: a systematic review and meta-analysis. Gastrointest Endosc. 2022; 95:51-59.e7.
5. DeMeester S, Smith C, Severson P, et al; Hawaii Esophageal Course Study Group. Multicenter randomized controlled trial comparing forceps biopsy sampling with wide-area transepithelial sampling brush for detecting intestinal metaplasia and dysplasia during routine upper endoscopy. Gastrointest Endosc. 2022; 95(6):1101-1110.e22021: S0016-5107(21)01875-7.
6. Fatima H, Wajid M, Hamade N, et al. Retrospective, observational, cross-sectional study of detection of recurrent Barrett's esophagus and dysplasia in post-ablation patients with adjunctive use of wide-area transepithelial sample (WATS-3D). Ann Gastroenterol. 2022; 35(2):113-118.
7. Gross SA, Smith MS, Kaul V.; US Collaborative WATS3D Study Group. Increased detection of Barrett's esophagus and esophageal dysplasia with adjunctive use of wide-area transepithelial sample with three-dimensional computer-assisted analysis (WATS). United European Gastroenterol J. 2018; 6(4):529-535.
8. Hohlweg-Majert B, Deppe H, Metzger MC, et al. Sensitivity and specificity of oral brush biopsy. Cancer Invest. 2009; 27(3):293-297.
9. Johanson JF, Frakes J, Eisen D. Computer-assisted analysis of abrasive transepithelial brush biopsies increases the effectiveness of esophageal screening: a multicenter prospective clinical trial by the EndoCDx Collaborative Group. Dig Dis Sci. 2011; 56(3):767-772.
10. Kaul V, Gross S, Corbett FS, Malik Z, Smith MS, Tofani C, Infantolino A. Clinical utility of wide-area transepithelial sampling with three-dimensional computer-assisted analysis (WATS3D) in identifying Barrett's esophagus and associated neoplasia. Dis Esophagus. 2020;33(12):doaa069.
11. Karmakar S, Mummudi N, Ghosh-Laskar S, et al. Incremental value of endoscopic brush cytology in response assessment after chemo-irradiation for Esophageal cancer. J Gastrointest Cancer. 2022; 53(1):122-129.
12. Kujan O, Huang G, Ravindran A, et al. CDK4, CDK6, cyclin D1 and Notch1 immunocytochemical expression of oral brush liquid-based cytology for the diagnosis of oral leukoplakia and oral cancer. J Oral Pathol Med. 2019; 48(7):566-573.
13. Mariano VS, Pastrez PRA, Mafra Costa A, et al. Impact of brush cytology analysis for the diagnosis of esophageal squamous cell carcinoma: the quality of liquid-based preparation of cytological slides. Acta Cytol. 2019; 63(3):240-246.
14. Mehrotra R, Mishra S, Singh M, Singh M. The efficacy of oral brush biopsy with computer-assisted analysis in identifying precancerous and cancerous lesions. Head Neck Oncol. 2011; 3:39.
15. Poate TW, Buchanan JA, Hodgson TA, et al. An audit of the efficacy of the oral brush biopsy technique in a specialist oral medicine unit. Oral Oncol. 2004; 40(8):829-834.
16. Raphael KL, Stewart M, Sejpal DV, et al. Adjunctive yield of wide-area transepithelial sampling for dysplasia detection after advanced imaging and random biopsies in Barrett's esophagus. Clin Transl Gastroenterol. 2019; 10(12):e00107.
17. Sciubba JJ. Improving detection of precancerous and cancerous oral lesions. computer-assisted analysis of the oral brush biopsy. U.S. Collaborative OralCDx Study Group. J Am Dent Assoc. 1999; 130(10):1445-1457.
18. Shaheen NJ, Smith M, Goldblum J, et al. Progression of Barrett's esophagus (BE) and dysplasia detected by wide area transepithelial sampling with computer-assisted 3D analysis (WATS3D) confirms the clinical significance of crypt dysplasia. Am J Gastroenterol. 2018; 113:s172.
19. Shaheen NJ, Smith MS, Odze RD. Progression of Barrett's esophagus, crypt dysplasia, and low-grade dysplasia diagnosed by wide-area transepithelial sampling with 3-dimensional computer-assisted analysis: a retrospective analysis. Gastrointest Endosc. 2022; 95(3):410-418.e1.
20. Smith MS, Ikonomi E, Bhuta R, et al. Wide-area transepithelial sampling with computer-assisted 3-dimensional analysis (WATS) markedly improves detection of esophageal dysplasia and Barrett's esophagus: analysis from a prospective multicenter community-based study. Dis Esophagus. 2019; 32(3):doy099.
21. Suresh Kumar VC, Harne P, Patthipati VS, et al. Wide-area transepithelial sampling in adjunct to forceps biopsy increases the absolute detection rates of Barrett's oesophagus and oesophageal dysplasia: a meta-analysis and systematic review. BMJ Open Gastroenterol. 2020; 7(1):e000494.
22. van Munster SN, Leclercq P, Haidry R, et al. Wide-area transepithelial sampling with computer-assisted analysis to detect high grade dysplasia and cancer in Barrett's esophagus: a multicenter randomized study. Endoscopy. 2023; 5(4):303-310.
23. Velleuer E, Dietrich R, Pomjanski N, et al. Diagnostic accuracy of brush biopsy-based cytology for the early detection of oral cancer and precursors in Fanconi anemia. Cancer Cytopathol. 2020; 128(6):403-413.
24. Vennalaganti PR, Kaul V, Wang KK, et al. Increased detection of Barrett's esophagus-associated neoplasia using wide-area trans-epithelial sampling: a multicenter, prospective, randomized trial. Gastrointest Endosc. 2018; 87(2):348-355.
25. Zhao CL, Hossein-Zadeh Z, Dabiri B, et al. The concordance between wide-area transepithelial sampling with computer-assisted 3-dimensional analysis (WATS-3D) and standard endoscope biopsy in the detection of Barrett's esophagus and esophageal dysplasia. Ann Diagn Pathol. 2022; 60:151982.

Government Agency, Medical Society, and Other Authoritative Publications:

1. American Society for Gastrointestinal Endoscopy Standards of Practice Committee, Qumseya B, Sultan S, et al. ASGE guideline on screening and surveillance of Barrett's esophagus. Gastrointest Endosc. 2019; 90(3):335-359.
2. Brocklehurst P, Kujan O, O'Malley LA, et al. Screening programmes for the early detection and prevention of oral cancer.

Cochrane Database Syst Rev. 2013;(11):CD004150.
3. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determination (LCD): MolDX: Molecular Testing for Detection of Upper Gastrointestinal Metaplasia, Dysplasia, and Neoplasia.
   - LCD L39256. Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=39256&ver=5&keyword=Esophageal%20Cancer&keywordType=starts&areaId=all&docType=F&contractOption=all&sortBy=relevance&bc=1. Accessed on November 2, 2023.
   - LCD L39262. https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=39262&ver=5&keyword=Esophageal%20Cancer&keywordType=starts&areaId=all&docType=F&contractOption=all&sortBy=relevance&bc=1. Available at: Accessed on November 2, 2023.
   - LCD L39264. https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=39264&ver=5&keyword=Esophageal%20Cancer&keywordType=starts&areaId=all&docType=F&contractOption=all&sortBy=relevance&bc=1. Available at: Accessed on November 2, 2023.
   - LCD L39276. Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=39276&ver=4&keyword=Esophageal%20Cancer&keywordType=starts&areaId=all&docType=F&contractOption=all&sortBy=relevance&bc=1. Accessed on November 2, 2023.
   - LCD L39356. Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=39356&ver=3&keyword=Esophageal%20Cancer&keywordType=starts&areaId=all&docType=F&contractOption=all&sortBy=relevance&bc=1. Accessed on November 2, 2023.
4. Docimo S Jr, Al-Mansour M, Tsuda S. SAGES TAVAC safety and efficacy analysis WATS^{3D} (CDx Diagnostics, Suffern, NY). Surg Endosc. 2020; 34(9):3743-3747.
5. Macey R, Walsh T, Brocklehurst P, et al. Diagnostic tests for oral cancer and potentially malignant disorders in patients presenting with clinically evident lesions. 2015;(5):CD010276.
6. Muthusamy VR, Wani S, Gyawali CP, et al.; CGIT Barrett's Esophagus Consensus Conference Participants. AGA clinical practice update on new technology and innovation for surveillance and screening in Barrett's Esophagus: Expert Review. Clin Gastroenterol Hepatol. 2022; 20(12):2696-2706.e1.
7. National Cancer Institute. Esophageal Cancer Screening (PDQ®)–Health Professional Version. Bethesda, MD. Updated September 9, 2022. Available at: https://www.cancer.gov/types/esophageal/hp/esophageal-screening-pdq. Accessed on April 27, 2023.
8. National Cancer Institute. Oral Cavity and Oropharyngeal Cancer Screening (PDQ®)–Health Professional Version. Bethesda, MD. Updated June 15, 2021. Available at: https://www.cancer.gov/types/head-and-neck/hp/oral-screening-pdq. Accessed on April 27, 2023.
9. National Comprehensive Cancer Network (NCCN), Inc. NCCN Clinical Practice Guidelines in Oncology® 2023. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on April 27, 2023.
   - Esophageal and Esophagogastric Junction Cancers (V5.2022). Revised December 22, 2022.
10. Shaheen NJ, Falk GW, Iyer PG, et al. Diagnosis and Management of Barrett's Esophagus: An Updated ACG Guideline. Am J Gastroenterol. 2022; 117(4):559-587.
11. Sharma P, Shaheen NJ, Katzka D, Bergman JJ.; American Gastroenterology Association (AGA). Clinical practice update on endoscopic treatment of Barrett's Esophagus with dysplasia and/or early cancer: Expert Review. Gastroenterology. 2020; 158(3):760-769.
12. U.S. Preventive Services Task Force. Final update summary: oral cancer: screening. November 13, 2013. Available at: https://www.uspreventiveservicestaskforce.org/uspstf/document/RecommendationStatementFinal/oral-cancer-screening. Accessed on June 14, 2023.

Websites for Additional Information

1. American Cancer Society. Can esophageal cancer be found early? Last revised March 20, 2020. Available at: https://www.cancer.org/cancer/esophagus-cancer/detection-diagnosis-staging/detection.html. Accessed on April 27, 2023.
2. American Cancer Society. Can oral cavity and oropharyngeal cancers be found early? Last revised March 23, 2021. Available at: https://www.cancer.org/cancer/oral-cavity-and-oropharyngeal-cancer/detection-diagnosis-staging/detection.html. Accessed on April 27, 2023.

Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
	04/01/2024	Revised Coding section; removed 88104 and note, no longer applicable; also removed 0114U, other criteria is available.
	12/06/2023	Revised References section.
Reviewed	05/11/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Discussion/General Information, References, and Websites sections.
Reviewed	05/12/2022	MPTAC review. Updated Discussion/General Information, References, Websites and Index sections. Updated Coding section to add CPT PLA code 0114U.
Reviewed	08/12/2021	MPTAC review. Discussion/General Information, References, and Websites sections updated
Reviewed	08/13/2020	MPTAC review. Discussion/General Information, References, and Websites sections updated. Reformatted Coding section.
Reviewed	02/20/2020	MPTAC review. Discussion/General Information, References, and Websites sections updated. Updated Coding section; added D7288.

Reviewed	03/21/2019	MPTAC review.
Reviewed	03/20/2019	Hematology/Oncology Subcommittee review. Discussion/General Information, References, and Websites sections updated.
New	05/03/2018	MPTAC review.
New	05/02/2018	Hematology/Oncology Subcommittee review. Initial document development.

Federal and State law, as well as contract language, and Medical Policy take precedence over Clinical UM Guidelines. We reserve the right to review and update Clinical UM Guidelines periodically. Clinical guidelines approved by the Medical Policy & Technology Assessment Committee are available for general adoption by plans or lines of business for consistent review of the medical necessity of services related to the clinical guideline when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the member's card.

Alternatively, commercial or FEP plans or lines of business which determine there is not a need to adopt the guideline to review services generally across all providers delivering services to Plan's or line of business's members may instead use the clinical guideline for provider education and/or to review the medical necessity of services for any provider who has been notified that his/her/its claims will be reviewed for medical necessity due to billing practices or claims that are not consistent with other providers, in terms of frequency or in some other manner.

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