**Prior Authorization Review Panel**
**MCO Policy Submission**

A separate copy of this form must accompany each policy submitted for review.
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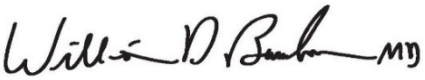
| **Plan: Keystone First Community HealthChoices** | **Submission Date**: October 29, 2020 |
| **Policy Number:** CCP.1472 | **Effective Date:** 11/2020<br>**Revision Date:** October 7, 2020 |
| **Policy Name: WATS-3D brush biopsy for Barrett's esophagus** | |

**Type of Submission – Check all that apply:**

- ☑ **New Policy**
- ☐ **Revised Policy***
- ☐ **Annual Review – No Revisions**
- ☐ **Statewide PDL**

***All revisions to the policy must be highlighted using track changes throughout the document.**

**Please provide any clarifying information for the policy below:**

| **Name of Authorized Individual (Please type or print):** | **Signature of Authorized Individual:** |
|---|---|
| William D. Burnham, MD |  |

Keystone First
Community HealthChoices

# WATS-3D brush biopsy for Barrett's esophagus

Clinical Policy ID: CCP.1472

Recent review date: 10/2020

Next review date: 2/2022

Policy contains: Barrett's esophagus, esophageal cancer, forceps biopsy, WATS-3D brush.

*Keystone First Community HealthChoices has developed clinical policies to assist with making coverage determinations. Keystone First Community HealthChoices' clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Keystone First Community HealthChoices when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Keystone First Community HealthChoices' clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Keystone First Community HealthChoices' clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First Community HealthChoices will update its clinical policies as necessary. Keystone First Community HealthChoices' clinical policies are not guarantees of payment.*

## Coverage policy

WATS-3D brush biopsy for Barrett's esophagus is investigational/not clinically proven and, therefore, not medically necessary.

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

Conventional biopsy.

## Background

Barrett's esophagus is a condition that occurs in the area where the esophagus connects to the stomach. In Barrett's, the esophageal squamous mucosa in the lining of the esophagus is replaced by metaplastic columnar mucosa, similar to the lining of the small intestine. Barrett's esophagus likely develops from chronic inflammation resulting from gastroesophageal reflux disease, affecting those who have had the disease for a long time or developed it at a young age.

About 10% of persons with gastroesophageal reflux disease develop Barrett's esophagus (WebMD, 2020). The prevalence of Barrett's in the U.S. is estimated to be 5.6% (Kuipers, 2011).

A precancerous change in the tissue, called dysplasia, will develop in some cases. In 0.5% (1 in 200) of Barrett's esophagus per year, the dysplasia will become esophageal adenocarcinoma. An endoscopy with biopsy should be performed every three years in patients with dysplasia (American Society for Gastrointestinal Endoscopy, 2010).

The following table presents data on the prevalence and incidence rates of cancer in the Barrett's esophagus population (Thompson Cancer Survival Center, 2020).

| | Cancer | High-Grade Dysplasia | Low-Grade Dysplasia |
|---|---|---|---|
| Prevalence | 6.7% | 3.0% | 7.3% |
| Annual Incidence | 0.5% | 0.9% | 4.3% |

Esophageal adenocarcinoma, for several decades, has had the most rapid increase of incidence of any cancer in the world. It also has a high mortality rate; an estimated 15,450 Americans died from the disease in 2014. In nine U.S. states and metropolitan areas, the average annual incidence for esophageal adenocarcinoma rose 6.1% for men and 5.9% for women from 1975 to 2009. Barrett's is more common in men than in women (Hur, 2013).

A systematic review/meta-analysis of 20 studies (n = 74,943) assessed those risk factors most strongly linked with progression of Barrett's esophagus without dysplasia or with low-grade dysplasia to high-grade dysplasia or esophageal adenocarcinoma. These factors included increasing age, male sex, ever-smoker status, increasing Barrett's segment length, and low-grade (versus no) dysplasia. Alcohol use and obesity did not raise risk (Krishnamoorthi, 2018).

Four-quadrant cold forceps biopsy has traditionally been the technique used to diagnose Barrett's esophagus. These standard and large-capacity forceps are used with a diagnostic endoscope, while jumbo forceps are recommended for use with a therapeutic endoscope with a larger (3.2 millimeter) channel. A study of 436 biopsy samples tested for Barrett's esophagus found that jumbo forceps diagnosed a significantly greater (71%, $P <$ .001) number of cases (Martinek, 2015). In general, standard forceps biopsy is unable to sample large portions of mucosa, and thus undercounts the number of dysplasia cases (Sutton, 2019).

The low number of Barrett's esophagus cases detected with traditional biopsy methods is supported by a study of 2,245 cases with linked endoscopy reports that recorded the disease's length. Adherence to guidelines was observed in 51.2% of cases. Stratified by length, lack of adherence was associated with significantly decreased dysplasia detection (Abrams, 2009).

Diagnosis of esophageal adenocarcinoma from endoscopic surveillance of Barrett's esophagus was associated with a lower mortality compared to carcinomas not detected by surveillance, based on a meta-analysis of eight studies (29% reduction) (Ding, 2018) and a meta-analysis of 12 studies (27% reduction) (Codipilly, 2018). Thus, effectiveness of surveillance is crucial in improving outcomes in esophageal cancer.

WATS-3D brush biopsy (CDx Diagnostics®) is a recent introduction in the identification of Barrett's esophagus. WATS-3D stands for Wide Area Transepithelial Sampling with 3-Dimensional Analysis. It is a brush-based sampling technique combined with a computer-synthesized 3-dimensional image of resultant tissue to fill gaps

from the standard cytology brush. Bristles are more rigid than earlier brushes, and the endoscopist pushes the brush against the epithelium in a zig-zag-like pattern (Smith, 2016).

Mark Rutenberg Ph.D. M.S.E.E., Founder and Chief Scientific Officer of CDx Diagnostics, states that over 10 years, about 250,000 WATS-3D brush biopsy procedures have been performed (CDx Diagnostics, 2019).

## Findings

The American College of Gastroenterology has published a guideline stating patients with nondysplastic Barrett's esophagus should undergo endoscopic surveillance no more frequently than every 3-5 years, due to the small proportion that actually progress to esophageal cancer (Shaheen, 2016). The College's 2011 guideline on diagnosing Barrett's or dysplasia does not address WATS-3D, but states that endoscopy has become standard practice for diagnosis; no updates have been issued by the College since then (Spechler, 2011).

In September 2019, the American Society for Gastrointestinal Endoscopy's Standards of Practice Committee issued a guideline on screening and surveillance of Barrett's esophagus. The panel initially made no recommendation for WATS-3D at the face-to-face meeting. After a complete review of additional published literature (including data on adverse events) and an additional phone conference, the panel made a conditional recommendation for the use of WATS-3D.

The Committee stated "In patients with known or suspected Barrett's esophagus, 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." The decision based on six studies with 6,271 Barrett's endoscopy cases. Of these, white light endoscopy identified 125 dysplasia cases, while WATS-3D also identified the 125, plus 137 more cases (Qumseya, 2019).

The National Comprehensive Cancer Network falls short of recommending WATS-3D, stating that the utility and accuracy of the WATS-3D biopsy for detecting high grade dysplasia/adenocarcinoma in patients with Barrett's esophagus needs to be evaluated in larger phase III randomized trials (National Comprehensive Cancer Network, 2020).

A study of 1,266 persons screened for Barrett's esophagus and esophageal dysplasia found that 363 were diagnosed with Barrett's by forceps biopsy alone, plus 146 additional cases by adding brush biopsy, an increase of 40%. In a subset of 848 patients with gastroesophageal reflux disease and no prior history of Barrett's esophagus, adding brush biopsy increased the number diagnosed with esophageal dysplasia by 87.5% (another 14 in addition to the initial 16). All brush biopsies were conducted by pathologists at CDx laboratories (Johanson, 2011).

A study of 4,203 patients suspected to have Barrett's esophagus revealed 594 were diagnosed by four-quadrant random forceps biopsy, and 493 additional cases were detected by adding WATS-3D, increasing the overall detection rate by 83%. Low-grade dysplasia was diagnosed in 26 patients by biopsy alone, and 23 additional cases were detected by adding WATS-3D, increasing the detection by 89% (Gross, 2018).

A study with 21 participating centers (n = 12,899) patients were enrolled in a study of screening and surveillance for Barrett's esophagus. Forceps biopsy identified 88 cases, and WATS-3D detected an additional 213 cases missed by forceps biopsy, an increase in detection of 142%, or more than double. Combined random and targeted forceps biopsy identified 1,684 cases of Barrett's esophagus, plus an additional 2,570 detected by WATS-3D, an increase of 153% (Smith, 2019).

The following tables illustrate findings of the prior three studies:

| | # screened for Barrett's | Cases found by standard biopsy | Other cases found by WATS-3D | % Additional Cases by WATS-3D |
|---|---|---|---|---|
| Johanson, 2011 | 1,266 | 363 | 146 | + 40% |
| Gross, 2018 | 4,203 | 594 | 493 | + 83% |
| Smith, 2019[1] | 12,899 | 88 | 213 | +142% |
| Smith, 2019[2] | 12,899 | 1,684 | 2,570 | +153% |

[1]From forceps biopsy; [2]From random and targeted forceps biopsy

| | # tested for dysplagia | Cases found by standard biopsy | Other cases found by WATS-3D | % Additional Cases by WATS-3D |
|---|---|---|---|---|
| Johanson, 2011 | 848 | 16 | 14 | + 88% |
| Gross, 2018 | 4,203 | 26 | 23 | + 89% |
| Smith, 2019 | Not tested for dysplagia | | | |

A survey of 33 users of WATS-3D (all but one of whom were gastroenterologists), represented 4,881 total WATS-3D kits, 25.9% of the 18,828 used at that time. Serious adverse effects were reported in only .06% (3 of 4,881) of the kits (Smith, 2014).

A study of slides obtained using the WATS-3D method from 149 patients with Barrett's esophagus (109 with no dysplasia, the other 40 with low-grade dysplasia, high-grade dysplasia, or esophageal adenocarcinoma) were evaluated by four blinded pathologists. The agreement between pathologists for all slides was high (mean kappa value = 0.86) (Vennalaganti, 2015).

## References

On August 14, 2020, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were "Barrett's esophagus," "esophageal cancer," "forceps biopsy," and "WATS-3D brush." We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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## Policy updates

10/2020: initial review date and clinical policy effective date: 11/2020