Endoscopic Radiofrequency Ablation or Cryoablation for Barrett’s Esophagus

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Oncologic Applications of Photodynamic Therapy, Including Barrett’s Esophagus is addressed in medical policy 00234.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:
- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider radiofrequency ablation (RFA) for treatment of Barrett’s esophagus (BE) with either high-grade dysplasia (HGD) or low-grade dysplasia (LGD) to be eligible for coverage.

When Services are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers radiofrequency ablation (RFA) for treatment of Barrett’s esophagus (BE) in the absence of dysplasia to be investigational.*

Based on review of available data, the Company considers cryoablation for Barrett’s esophagus (BE), with or without dysplasia to be investigational.*

Background/Overview
Barrett’s Esophagus and the Risk of Esophageal Carcinoma
The esophagus is normally lined by squamous epithelium. Barrett’s esophagus is a condition in which the normal squamous epithelium is replaced by specialized columnar-type epithelium, known as intestinal metaplasia, in response to irritation and injury caused by gastroesophageal reflux disease (GERD). Barrett’s esophagus occurs in the distal esophagus, may be of any length, may be focal or circumferential, and can be visualized by the endoscopist as being a different color than the background squamous mucosa. Confirmation of BE requires biopsy of the columnar epithelium and microscopic identification of intestinal metaplasia.

Intestinal metaplasia is a precursor to esophageal adenocarcinoma, and esophageal adenocarcinoma is thought to result from a stepwise accumulation of genetic abnormalities in the specialized epithelium, which results in the phenotypic expression of histologic features of LGD to HGD to carcinoma. Two large epidemiologic studies published in 2011 reported the risk of progression to cancer in patients with BE. One
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A study reported the rate of progression to cancer in more than 8,000 patients with a mean duration of follow-up of 7 years (range 1-20 years). The de novo progression to cancer from BE at one year was 0.13%. The risk of progression was reported as 1.4% per year in patients with LGD and 0.17% per year in patients without dysplasia. This incidence translates into a risk of 10-11 times that of the general population. The other study identified over 11,000 patients with BE and, after a median follow-up of 5.2 years, reported that the annual risk of esophageal adenocarcinoma was 0.12%. Detection of LGD on index endoscopy was associated with an incidence rate for adenocarcinoma of 5.1 cases per 1,000 person-years, and the incidence rate among patients without dysplasia was 1.0 case per 1,000 person-years. Risk estimates for patients with HGD were slightly higher.

The reported risk of progression to cancer in BE in older studies was much higher, with an annual incidence of risk of 0.4-0.5% per year, with risk estimated at 30-40 times the general population. It is upon these higher risk estimates that current surveillance recommendations have been based.

Management of Barrett’s Esophagus
The current management of BE includes treatment of GERD and surveillance endoscopy to detect progression to HGD or adenocarcinoma. The finding of HGD or early-stage adenocarcinoma warrants mucosal ablation or resection (either endoscopic mucosal resection [EMR] or esophagectomy).

Endoscopic mucosal resection, either focal or circumferential, provides a histologic specimen for examination and staging (unlike ablative techniques). A study provided long-term results for EMR in 100 consecutive patients with early Barrett’s-associated adenocarcinoma (limited to the mucosa). The 5-year overall survival (OS) was 98% and metachronous lesions were observed in 11% of patients after a mean of 36.7 months. In a recent review by Pech and Ell, the authors state that circumferential EMR of the entire segment of Barrett’s leads to a stricture rate of 50%, and recurrences occur at a rate of up to 11%.

Ablation Techniques
Mucosal ablation techniques that are available consist of one of several thermal (multipolar electrocoagulation [MPEC], argon plasma coagulation [APC], heater probe, Nd:YAG laser, KTP-YAG laser, diode laser, argon laser, and cryoablation) or nonthermal (5-aminolevulinic acid [5-ALA] and photofrin photodynamic therapy [PDT]) techniques. Photodynamic therapy has been the only therapy shown in a randomized Phase III trial to significantly decrease the risk of carcinoma in BE.

The CryoSpray Ablation system uses a low-pressure spray for spraying liquid nitrogen through an upper endoscope. Cryotherapy allows for treatment of uneven surfaces; however, a disadvantage is the uneven application inherent in spraying the cryogen.

The HALO system uses radiofrequency (RF) energy and consists of 2 components: an energy generator and an ablation catheter. The generator provides rapid (ie, <1 second) delivery of a predetermined amount of RF energy to the catheter. The HALO90 or the HALO360 is inserted into the esophagus with an endoscope, using standard endoscopic techniques. The HALO90 catheter is plate-based and used for focal ablation of areas of BE up to 3 cm. The HALO360 uses a balloon catheter that is sized to fit the individual’s esophagus and is inflated to allow for circumferential ablation.
Ablation with RF affects only the most superficial layer of the esophagus (ie, the mucosa), leaving the underlying tissues unharmed. Measures of efficacy for the procedure are eradication of intestinal metaplasia, without leaving behind microscopic (or “buried”) foci, and postablation regrowth of the normal squamous epithelium. Reports of the efficacy of the HALO system in ablating BE have been as high as 70% (comparable with alternative methods of ablation [eg, APC, MPEC]), and even higher in some reports. The incidence of leaving behind buried foci of intestinal metaplasia has been reported to be between 20% and 44% with APC and 7% with MPEC; studies using the HALO system have reported 0%. Another potential advantage to the HALO system is that because it is an automated process, it eliminates operator-dependent error that may be seen with APC or MPEC.

The risk of treating HGD or mucosal cancer solely with ablative techniques is undertreatment for approximately 10% of patients with undetected submucosal cancer, in whom esophagectomy would have been required.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

In 2005, the HALO360 (now Barrx™ 360 RFA Balloon Catheter) was cleared for marketing by the FDA through the 510(k) process and, in 2006, the HALO90 (now Barrx 90 RFA Focal Catheter) received clearance. FDA-labeled indications are for use in coagulation of bleeding and nonbleeding sites in the gastrointestinal tract, and include the treatment of BE. FDA product code: GEI.

In December 2007, the CryoSpray Ablation™ System (formerly the SprayGenix Cryo Ablation system; CSA Medical, Lutherville, MD) was cleared for marketing by FDA through the 510(k) process for use as a “cryosurgical tool for destruction of unwanted tissue in the field of general surgery, specifically for endoscopic applications.” FDA product code: GEH.

In July 2002, the Polar Wand® device (Chek Med Systems, Willington, CT), a cryosurgical device that uses compressed carbon dioxide, was cleared for marketing by FDA through the 510(k) process. Indications for use are, “ablation of unwanted tissue in the fields of dermatology, gynecology, general surgery, urology, and gastroenterology.”

Rationale/Source

This evidence review has been updated periodically with literature review. The most recent update covers the period through October 5, 2016.

Radiofrequency Ablation versus Surgical Resection for Barrett Esophagus

Radiofrequency ablation has been accepted as a less invasive alternative to surgical mucosal resection or esophagectomy, based on the results of randomized and non-randomized trials. Early single-arm trials reported high rates of success in eradication of dysplastic and metaplastic tissue, with low rates of adverse effects.
Systematic Reviews
In 2014, Chadwick et al reported on a systematic review that compared RFA and complete endoscopic mucosal resection (EMR) for treatment of BE. Twenty studies (22 articles) were reviewed, including 2 randomized controlled trials (RCTs), 10 cohort studies on EMR and 8 cohort studies on RFA. The only study that compared RFA and EMR was the RCT by van Vilsteren et al; the other RCT was by Shaheen et al (see below). The studies were heterogeneous in design. A total of 1087 (532 EMR, 555 RFA) patients with HGD or intramucosal carcinoma were included in the studies reviewed. The median number of resections or RFA sessions required for the eradication of BE was 2. Complete EMR and RFA eradicated BE dysplasia in 95% and 92% of patients, respectively. Eradication was maintained in 95% of EMR patients at a median follow-up of 23 months and in 94% of RFA patients at a median follow-up of 21 months. Fewer RFA patients experienced short-term adverse effects (2.5%) than those who received complete EMR (12%). Esophageal strictures requiring additional treatment occurred in 4% of RFA patients and 38% of complete ER patients.

In 2013, Orman et al reported on a systematic review and meta-analysis of 24 studies with a total of 4342 patients treated with RFA for BE dysplasia and intestinal metaplasia. Included in this review were the studies by van Vilsteren et al and Shaheen et al. The studies reviewed were heterogeneous in design and contained a mix of nondysplastic and LGD and HGD. The use of EMR varied in the studies and ranged from 0% to 96%. Patients were followed for a median of 20.5 months (range, 12-31 months). For patients treated with RFA, complete eradication of dysplasia occurred in 91% (95% confidence interval [CI], 87% to 95%), and complete eradication of intestinal metaplasia occurred in 78% (95% CI, 70% to 86%). Intestinal metaplasia recurred in 13% (95% CI, 9% to 18%) after eradication. In patients with complete eradication of intestinal metaplasia, 0.2% and 0.7% progressed to cancer during treatment and after treatment, respectively. The most frequent adverse event observed was esophageal stricture, which occurred in 5% of patients (95% CI, 3% to 7%).

Semlitsch et al reported a systematic review of this evidence for RFA of BE based on a total of 9 observational studies and 429 patients. Inclusion criteria for the systematic review required that studies include patients with BE and metaplasia or dysplasia for which RFA was the intervention (with or without endoscopic mucosal resection) and have a minimum follow-up period of 12 months. In 7 of the studies, patients were treated with circumferential ablation followed by focal ablation, whereas 2 studies used only the circumferential method. The maximum number of ablations performed was reported in 7 studies and ranged from 2 to 5. Complete eradication of BE with dysplasia and BE with metaplasia was achieved in 71% to 100% and 46% to 100% of patients, respectively. Six cases of esophageal stenosis and 1 case of buried intestinal metaplasia were reported among all patients.

Randomized Controlled Trials
Van Vilsteren et al reported on the results of a multicenter, randomized trial that compared the safety of stepwise radical endoscopic resection (SRER) versus focal EMR followed by RFA for complete eradication of BE ≤5 cm containing HGD/early cancer. Patients in the SRER group underwent piecemeal ER of 50% of BE followed by serial EMR. Patients in the ER/RFA group underwent focal EMR for visible lesions followed by serial RFA. Follow-up endoscopy with biopsies (4-quadrant/2 cm BE) was performed at 6 and 12 months and then annually. The main outcome measures were: stenosis rate; complications; complete histologic
response for neoplasia (CR-neoplasia); and complete histologic response for intestinal metaplasia (CR-IM). CR-neoplasia was achieved in 25 of 25 (100%) SRER and in 21 of 22 (96%) ER/RFA patients. CR-IM was achieved in 23 (92%) SRER and 21 (96%) ER/RFA patients. The stenosis rate was significantly higher with SRER (88%) versus ER/RFA (14%; p<0.001), resulting in more therapeutic sessions in SRER (6 vs 3; p<0.001), due to dilations. After a median follow-up of 24 months, 1 SRER patient had recurrence of early cancer, requiring endoscopic resection. This study confirmed that both techniques achieve comparably high rates of CR-IM and CR-neoplasia but found that SRER was associated with a higher number of complications and therapeutic sessions.

Noncomparative Studies
Since publication of the systematic reviews described above, individual noncomparative studies have described outcomes after use of combined EMR with RFA to treat BE with HGD and any early cancer, if any present. In 2016, Phoa et al reported on a prospective, single-arm interventional study with 132 subjects that evaluated the use of combined EMR with RFA for BE with HGD and/or early cancer. At baseline endoscopy, all visible abnormalities were removed at a single endoscopic resection for histologic staging. After 2 mapping endoscopies, patients underwent the first RFA treatment for circumferential or focal ablation, after which they underwent RFA treatment every 3 months until visible BE was cleared. Complete eradication of neoplasia (absence of all HGD and early cancer on biopsy and endoscopic clearance of BE) and complete eradication of intestinal metaplasia were achieved in 92% (95% CI, 83% to 93%) and 87% (95% CI, 80% to 92%), respectively, of all patients who began the study in intention-to-treat (ITT) analysis.

Section Summary: Radiofrequency Ablation vs Surgical Resection for Barrett’s Esophagus With Dysplasia
RFA is a less-invasive alternative to EMR and/or esophagectomy for BE with dysplasia. The available research indicates that RFA results in similar efficacy for disease that has not extended into the submucosa, with fewer complications.

Radiofrequency Ablation Versus Surveillance Alone in Barrett’s Esophagus RFA for Dysplastic BE
One randomized multi-center, sham-controlled trial has been published that compares RFA to surveillance alone in BE with dysplasia. This trial included patients with both HGD and LGD. A total of 127 patients with dysplastic BE were randomized in a 2:1 ratio to receive RFA or a sham procedure. The groups were randomly assigned according to the grade of dysplasia (low-grade [n=64] or high-grade [n=63]) and length of the BE (<4 cm or 4-8 cm). Patients in the RFA group could receive up to 4 ablation sessions, performed at baseline and at 2, 4, and 9 months. Primary outcomes were the proportion of patients who had complete eradication of dysplasia at 12 months and the proportion of all patients who had complete eradication of intestinal metaplasia at 12 months. The proportion of patients who had progression of dysplasia was a secondary outcome, this included progression of LGD to HGD or cancer, and the progression of HGD to cancer. This trial was included in the 2010 Technology Evaluation Center (TEC) Assessment and was rated fair on formal quality assessment according to the U.S. Preventive Services Task Force system. The only obstacles to a good rating were missing details about random sequence generation and concealment of allocation.
Overall, complete eradication of intestinal metaplasia was 77.4% in the ablation group compared with 2.3% of the control group (p<0.001). Patients who did not receive RFA were more likely to have disease progression (16.3%) than those who received RFA (3.6%; p=0.03). Three serious adverse events occurred in the RFA group, including 1 episode of upper GI hemorrhage, which was treated endoscopically, one overnight hospitalization for new-onset chest pain 8 days after RFA, and 1 night of hospitalization for an episode of chest discomfort and nausea immediately after RFA. No adverse events were observed in the control group. No esophageal perforations or procedure-related deaths occurred. Among patients in the RFA group, esophageal stricture developed in 5 patients (6%), all of whom successfully underwent dilated endoscopy.

In 2011, 2- and 3-year results of this trial were reported. Subjects were followed for a mean time of 3.05 years, with 106/127 (83%) patients included in the analysis. Outcomes included eradication of dysplasia or intestinal metaplasia after 2 and 3 years, durability of response, disease progression, and adverse events. After 2 years, 101 of 106 patients had complete eradication of all dysplasia (95%) and 99 of 106 had eradication of intestinal metaplasia (93%). Serious adverse events occurred in 4 of 119 subjects (3.4%). No perforations or procedure-related deaths occurred. The rate of esophageal stricture was 7.6%. The rate of esophageal adenocarcinoma was 1 per 181 patient-years (0.55%/patient-years); there was no cancer-related morbidity or mortality. The annual rate of any neoplastic progression was 1 per 73 patient-years (1.37%/ patient-years). The authors concluded that, for patients with dysplastic BE, RFA is durable and associated with a low rate of disease progression for up to 3 years.

Section Summary: RFA for Dysplastic BE
The most direct evidence related to the efficacy of RFA for BE with dysplasia comes from 1 small-to-moderate, reasonably well-designed RCT comparing RFA with surveillance only in patients with both LGD and HGD. Radiofrequency ablation was associated with a lower risk of disease progression compared with surveillance.

Radiofrequency Ablation for High-Grade Dysplasia
In patients diagnosed with BE with HGD, risk of progression to cancer is relatively high and esophageal adenocarcinoma is associated with poor morbidity and a 5-year survival rate of 13% or less. Therefore, intervention with esophagectomy or RFA may be strongly indicated.

The Shaheen RCT reported that RFA was successful in eradicating HGD, with complete eradication achieved in 81% of the ablation group versus 19% in the control group (p<0.001) at 12 months. This trial also confirmed a high risk of progression to cancer in patients with HGD and established that this progression was significantly reduced in patients treated with RFA. Among 63 patients with HGD in that trial, 19% in the control group progressed to cancer versus 2.4% in the RFA group (p=0.04). This represented a nearly 90% relative risk reduction for progression to cancer (relative risk [RR]: 0.1, 95% confidence interval [CI]: 0.01-1.0, p=0.04), and a number needed to treat of 6.0 to prevent one case of cancer over a one-year period.

Longer-term follow-up at 2-3 years reported that complete eradication of dysplasia was maintained in most participants with initial HGD. For 54 patients with HGD available for follow-up, all dysplasia was eradicated.
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in 50 of 54 (93%), and all intestinal metaplasia was eradicated in 48 of 54 (89%). After 3 years, dysplasia was eradicated in 55 of 56 of subjects (98%), and all intestinal metaplasia was eradicated in 51 of 56 (91%). More than 75% of high-grade patients remained free of intestinal metaplasia with a follow-up of longer than 3 years, with no additional therapy.

RFA may be used alongside focal endoscopic resection. In the ITT analysis of a prospective interventional study that included 132 subjects with BE and HGD or early cancer treated with endoscopic resection followed by RFA, complete eradication of neoplasia and complete eradication of intestinal metaplasia occurred in 92% and 87% of subjects, respectively.22 At a median follow-up of 27 months, neoplasia or intestinal metaplasia had recurred in 4% and 8% of subjects, respectively.

Barret et al retrospectively analyzed a prospectively enrolled cohort including 40 patients with early BE who had a visible lesion and required EMR for the visible early neoplasia lesion, followed by RFA for the residual BE, which was done at the same procedure. Follow-up was available for 34 patients at a median of 19 months. For the study's primary outcome (complete remission of dysplasia), in the ITT analysis, remission was achieved in 85% of cohort participants; complete remission of intestinal metaplasia was achieved in 82.5% of cohort participants.

Section Summary: RFA for HGD
For patients who have BE with HGD, there is a relatively high risk of progression to cancer, and interventions to prevent progression are warranted. RFA results in high rates of complete eradication of dysplasia that is durable for at least 2 years. One RCT demonstrated that, following RFA, progression from HGD to cancer is reduced by approximately 90%, with rates of esophageal strictures of 6%.

Radiofrequency Ablation for Low-Grade Dysplasia
In 2014, Almond et al reported results of a meta-analysis of studies using endoscopic therapy for the treatment of BE with LGD. The analysis included 37 studies, 9 of which evaluated RFA alone, including the Shaheen et al RCT. Most studies were small, with the Shaheen et al RCT representing the largest study (52 with LGD treated with RFA). For patients treated with RFA, the pooled incidence of cancer or HGD was 10.77 per 1000 patient-years (95% CI, 2.22 to 31.48 per 1000 patient-years). For RFA-treated patients, pooled rates of complete eradication of intestinal metaplasia and complete eradication of dysplasia were 87.2% (95% CI, 76.2% to 93.5%) and 90.6% (95% CI, 81.0% to 95.6%), respectively.

A 2010 TEC Assessment on the use of RFA plus surveillance versus surveillance alone in the treatment of nondysplastic and low-grade dysplastic BE included the Shaheen et al. randomized trial and 4 single-arm studies; it determined that the evidence was insufficient to permit conclusions for the use of RFA for patients with nondysplastic or LGD BE.

Since the TEC Assessment and the 2014 Almond et al systematic review, an RCT of RFA versus surveillance in patients with LGD has been published by Phoa et al. This trial randomized 140 patients with BE and confirmed LGD; 4 patients were excluded after randomization for not meeting study inclusion criteria at further review, leaving a total of 136 patients in the modified intention-to-treat analysis. “Confirmed” LGD was defined as a diagnosis of LGD by the local pathologist with confirmation by a
centralized expert panel of pathologists convened for the trial. The primary outcome measure was the occurrence of either HGD or adenocarcinoma up to 3 years following randomization. Secondary outcomes were complete eradication of dysplasia, the absence of intestinal metaplasia, and adverse events.

The study was terminated early due to interim analysis that determined superiority of RFA. At the time of termination, all patients had reached the 24-month follow-up time point, and the median follow-up was 36 months. The occurrence of adenocarcinoma was significantly lower in the RFA group (1.5%) compared with the surveillance group (8.8%, p<0.03), and the occurrence of HGD was also significantly lower for the RFA group (1.5%) compared with the surveillance group (26.5%, p<0.001). For patients treated with RFA, complete eradication of dysplasia during follow-up was 98.4% and the absence of metaplasia was 90.0%. There were 3 serious adverse events in 2 patients who received RFA (1 abdominal pain requiring hospitalization, 1 bleeding episode, 1 episode of fever/chills following dilation for stricture), and a total of 12 other adverse events (8 strictures requiring dilation, 3 mucosal lacerations, 1 retrosternal pain).

In the Shaheen RCT, there were 64 patients with LGD. At 12 months follow-up, the dysplasia was completely eradicated in 90.5% of those in the RFA group, compared with 22.7% of those in the control group (p<0.001). There were no patients in the LGD group that progressed to cancer over the initial 12 months. Progression to HGD was noted in 2/42 (5%) of patients in the RFA group, compared to 3/22 (14%) in the control group. The difference in rates of progression to HGD did not reach statistical significance (RR: 0.3, 95% CI: 0.1-1.9, p=0.33). After 2 years, there were 52 subjects available who had initial LGD treated with RFA. Progression from LGD to HGD or cancer occurred in one patient, for an estimated rate of 2.0% per patient per year. In patients with initial LGD, all dysplasia was eradicated in 51 of 52 (98%), and all intestinal metaplasia was eradicated in 51 of 52 (98%).

Selection of Patients With LGD

There are challenges in diagnostically differentiating between nondysplastic BE and BE with LGD; they are important in the consideration of treatment for LGD. Both sampling bias and interobserver variability have been shown to be problematic. Therefore, analysis of progression to carcinoma in BE with intestinal metaplasia versus LGD is difficult. Initial diagnosis of BE can also be a challenge with respect to histologic grading because inflammation and LGD can share similar histologic characteristics.

One approach to risk-stratify patients with an initial diagnosis of LGD has been to use multiple pathologists, including experts in GI histopathology, to confirm the initial diagnosis of LGD. There is a high degree of interobserver variability among the pathology readings of LGD versus inflammatory changes, and the resultant variability in pathology diagnosis may contribute to the variable rates of progression of LGD reported in the literature. Kerkhof et al reported that, in patients with an initial pathologic diagnosis of LGD, review by an expert pathologist will result in the initial diagnosis being downgraded to nondysplasia in up to 50% of cases. Curvers et al tested this hypothesis in 147 patients with BE who were given an initial diagnosis of LGD. All pathology slides were read by 2 expert GI pathologists with extensive experience in BE: any disagreements among experts in the readings were resolved by consensus. Once this process was completed, 85% of initial diagnoses of LGD were downgraded to nondysplasia, leaving 22 (15%) of 147 patients with a confirmed diagnosis of LGD. All patients were followed for a mean of 5.1 years for
progression to HGD or cancer. For patients with confirmed LGD, the rate of progression was 13.4%,
compared with 0.5% for patients who had been downgraded to nondysplasia.

The strategy of having LGD confirmed by expert pathologists is supported by the results of the Phoa RCT,
which required confirmation of LGD by a central expert panel following initial diagnosis by a local
pathologist.25 Of 511 patients with an initial diagnosis of LGD, 264 (52%) were excluded because the
central expert panel reassigned classification of LGD, most often from LGD to indefinite or nondysplasia.
These findings were further confirmed in a retrospective cohort study of 293 BE cases with LGD diagnosed
over an 11-year period and submitted for expert panel review.31 In this sample, 73% of subjects were
downstaged.

Section Summary: RFA for LGD
The risk of progression from LGD to cancer is not well-defined, with highly variable rates reported in the
published literature. Evidence from randomized and nonrandomized studies has established that RFA can
achieve complete eradication of dysplasia in patients with LGD that is durable for at least 2 years. One RCT
of 136 subjects reported a lower rate of progression to HGD or adenocarcinoma for patients who had
confirmed LGD treated with RFA. This trial supports the strategy of selecting a population that has a higher
risk of progression by subjecting the initial pathologic diagnosis of LGD to review by an expert in GI
pathology. Expert review has reduced the number of patients diagnosed with LGD by 50% to 75%,
presumably by reducing the number of patients with inflammatory changes who are miscategorized as
having LGD.

Radiofrequency Ablation for Non-Dysplastic Barrett’s Esophagus
There are no RCTs that evaluate treatment of non-dysplastic BE with RFA. The evidence on this question
consists of single arm trials that report outcomes of RFA. This evidence can provide useful data on the
success in eradicating dysplasia, but cannot provide high-quality evidence on the comparative efficacy of
RFA versus surveillance alone. Progression to cancer in non-dysplastic BE is lower than that for LGD or
HGD, with rates in the literature ranging from 0.05-0.5%.

Fleischer and colleagues reported the 5-year follow-up of a single-arm study of patients with non-dysplastic
BE treated with RFA. The original study included 70 patients who underwent circumferential RFA and
complete-response-intestinal metaplasia (CR-IM); defined as complete eradication of nondysplastic BE,
CR-IM was seen in 70% of patients at 1-year follow-up; patients with persistent BE underwent focal RFA. At
the 2.5 year follow-up, CR-IM was found in 60 of 61 patients (98%). At 5 year follow-up, 4-quadrant biopsies
were obtained from every 1 cm of the original extent of BE and the authors reported the proportion of
patients demonstrating CR-IM. If nondysplastic BE was identified at the 5-year follow-up, focal RFA was
performed 1 month later and re-biopsy 2 months after to assess histologic response. Primary outcomes
were the proportion of patients demonstrating CR-IM at 5-year biopsy or after single session focal RFA. For
the 5-year follow-up, there were 60 eligible patients, 50 (83%) of whom were willing to participate. Forty-six
of 50 patients (92%) showed CR-IM at the 5-year biopsy visit. The four patients found to have BE at 5 years
underwent a single session of RFA 1 month after biopsy, and all were found to have CR-IM at subsequent
re-biopsy 2 months after RFA. No strictures were noted. The authors concluded that this first report of 5-
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year CR-IM outcomes lends support to the safety, efficacy, cost-utility, and reduction in neoplastic progression in treating non-dysplastic BE with RFA.

Section Summary: RFA for Nondysplastic BE
Non-dysplastic BE has a relatively low rate of progression to cancer. Although available research reports that non-dysplastic metaplasia can be eradicated by RFA, the risk/benefit ratio and the net effect on health outcomes is uncertain.

Radiofrequency Ablation Versus Photodynamic Therapy for BE
In 2013 Ertan et al reported on a series of 86 consecutive patients treated with either photodynamic therapy (PDT) or RFA by a single investigator. RFA was administered to 47 patients with LGD and 6 patients with HGD. PDT was administered to 33 patients with HGD. Average time from ablative therapy to follow-up biopsy was 33 months (range, 24-48 months) for RFA and 44 months (range, 24-60 months) for PDT. Radiofrequency ablation resulted in significantly more complete eradication of dysplasia than PDT (88.7% vs 54.5%, respectively, p=0.001). However, interpretation of this study is limited by its nonrandomized nature and differences in the type of dysplasia between groups.

In a retrospective observational study of BE patients with HGD or adenocarcinoma, David et al compared several endovascular therapies, including RFA, endoscopic mucosal resection plus RFA, and PDT. Of the 342 patients included, 98 underwent endoscopic mucosal resection plus RFA, 119 had RFA alone, and 125 received PDT. Patients treated with PDT were typically older, had more advanced stages of BE, and more comorbidities. In multivariable analysis, complete remission of intestinal metaplasia was more likely in those patients who received PDT than those treated with endoscopic mucosal resection plus RFA (RR=2.69; p<0.001) or RFA alone (RR=4.47; p<0.001). However, the multivariable analysis did not adjust for a history of esophageal cancer, esophagectomy, or warfarin use. Among 121 patients who had at least 1 follow-up visit after complete remission of intestinal metaplasia was established, the disease recurrence rate was 32.2%, which did not differ across treatment groups.

Section Summary: Radiofrequency Ablation Versus Photodynamic Therapy for BE
There is limited evidence to compare RFA with PDT for treatment of BE and no controlled trials. Evidence from nonrandomized studies have mixed findings about the comparative efficacy of RFA compared with PDT.

Cryoablation of Barrett’s Esophagus
Published efficacy data for cryoablation in BE are limited. Johnston and colleagues conducted a prospective, single-center pilot study in 11 men with BE and degrees of dysplasia ranging from none to multifocal HGD. The mean length of Barrett’s was 4.6 cm (range: 1–8 cm). After 6 month follow-up, complete histologic eradication of BE was achieved in 7 of the 9 patients (78%), completing the protocol.

An open-label, single-center, prospective, nonrandomized cohort study assessed the safety of cryoablation as a treatment option for BE with HGD or early cancer (intramucosal carcinoma). Thirty patients who were either deemed high-risk surgical candidates or who refused esophagectomy underwent cryoablation. Twenty-seven patients (90%) had downgrading of pathology stage after treatment. After a median follow-up
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period of 12 months, elimination of cancer or downgrading of HGD was 68% for HGD and 80% for intramucosal cancer.

Greenwald and colleagues reported the safety, tolerability, and efficacy of low-pressure liquid nitrogen spray cryotherapy in 77 patients from multiple institutions who underwent a total of 377 procedures for BE with HGD (58.4%), intramucosal carcinoma (16.9%), invasive carcinoma (13%), BE without dysplasia (9.1%), and severe squamous dysplasia (2.6%). The main outcome measurement was the incidence of serious adverse events and side effects from treatments. No side effects were reported by 28.6% of patients. The most common side effects were chest pain (18%), dysphagia (13%), odynophagia (12.1%), and sore throat (9.6%). Esophageal stricture occurred in 3 patients, all of which were successfully treated with dilation, and gastric perforation occurred in one patient. Complete response (CR) for HGD, all dysplasia, intestinal metaplasia, and cancer were assessed in patients completing therapy during the study period and having at least 1 follow-up endoscopy with biopsy for assessment of histologic regression of the underlying lesion (n=23). For patients with HGD (n=17), CR of the HGD, any dysplasia, and intestinal metaplasia was 94%, 88% and 53%, respectively. For patients with intramucosal carcinoma (n=4), 100% had CR of the cancer, HGD, and any dysplasia, and 75% had CR of intestinal metaplasia. For the patients with invasive cancer (n=3), 100% had CR of the cancer, HGD, and any dysplasia, and 67% of intestinal metaplasia.

Shaheen and colleagues reported a multicenter, retrospective cohort study of 98 consecutive patients with BE with HGD treated with spray cryotherapy to assess the safety and efficacy. A total of 333 treatments (mean 3.4 per patient) were performed, and cryotherapy was performed with the intent to eradicate all BE. Sixty patients completed all planned cryotherapy treatments and were assessed for efficacy with follow-up endoscopy sessions with 4 quadrant biopsies performed every 1-2 cm. Fifty-eight patients (97%) had complete eradication of HGD, 52 (87%) had complete eradication of all dysplasia with persistent nondysplastic intestinal metaplasia, and 34 (57%) had complete eradication of all intestinal metaplasia. There were no esophageal perforations, and esophageal stricture occurred in 3 patients. The authors noted the limitations of the study as it was nonrandomized, retrospective without a control group, lacked centralized pathology, used surrogate outcomes for decreased cancer risk, and had a short follow-up (10.5 months).

In 2015, Canto et al reported on a retrospective, single-center study that evaluated a carbon dioxide cryosurgery device for treatment of patients with neoplasia or HGD who were treatment-naive or who had persistent or recurrent neoplasia after initial treatment. The study’s analysis included 68 patients who were offered treatment with cryoablation for either initial therapy (n=21) or after previous therapy with any ablative technique (n=47). At 1 year, CR for dysplasia was 89% (57/64) overall and 95% (19/20) and 86% (38/44) in treatment-naive and previously treated patients, respectively. Over a median follow-up of 4.2 years, the differences in CR for HGD at 3 years or study end was not statistically significant between treatment-naive and previously treated patients (100% for treatment-naive, 84% for previously treated; p=0.08).

Also in 2015, a retrospective, single-center study by Sengupta et al evaluated cryoablation among 16 patients who failed RFA. The cohort of 16 patients was derived from an original cohort of 121 patients who underwent RFA for BE with LGD, HCD, or IC. After a median of 3 treatments with RFA, 91 subjects had
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complete eradication of dysplasia. Of 21 patients offered cryotherapy, 16 underwent cryotherapy and had adequate follow-up. Fourteen of those who did not have complete eradication and 2 patients who had recurrence of dysplasia underwent salvage cryotherapy. Over a median follow-up of 2.5 months, and with a median of 3 cryotherapy treatments, 12 patients (75%) had complete eradication of dysplasia after cryotherapy and 14 (88%) had some improvement in pathology after cryotherapy.

Section Summary: Cryoablation of BE
There are no controlled trials evaluating cryoablation for the treatment of BE. The evidence from uncontrolled studies has reported high rates of success in eradicating dysplasia, with low rates of complications. These data are not sufficient to determine the comparative efficacy of cryoablation and RFA.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td>Clinical and Medico-economic Evaluation of Radiofrequency Ablation Versus Oesophagectomy in the Treatment of High Grade Dysplasia in Barrett’s Oesophagus</td>
<td>250</td>
<td>Nov 2018</td>
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<tr>
<td>Unpublished</td>
<td>Prospective Randomized Trial Comparing Radiofrequency Ablation (Barrx) and Cryotherapy (truFreeze™) for the Treatment of Barrett’s Esophagus With High-Grade Dysplasia and/or Early Adenocarcinoma</td>
<td>50</td>
<td>Feb 2016 (unknown)</td>
</tr>
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</table>

NCT: national clinical trial.

Summary of Evidence
For individuals who have BE with HGD who receive endoscopic RFA, the evidence includes 1 RCT comparing radical endoscopic resection with focal endoscopic resection followed by RFA, RCT comparing RFA with surveillance alone, and a number of observational studies, some of which compared RFA with other endoscopic treatment modalities. Relevant outcomes are overall survival, change in disease status, morbid events, and treatment-related morbidity and mortality. The available evidence has shown that using RFA to treat BE with HGD is at least as effective in eradicating HGD as other ablative techniques, with a lower progression rate to cancer, and may be considered an alternative to esophagectomy. Evidence from at least 1 RCT has demonstrated higher rates of eradication than surveillance alone. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have BE with LGD who receive endoscopic RFA, the evidence includes at least 2 RCTs comparing RFA with surveillance alone, a number of observational studies, and systematic reviews of these studies. Relevant outcomes are overall survival, change in disease status, morbid events, and treatment-related morbidity and mortality. For patients confirmed to have LGD, evidence from 1 RCT has suggested that RFA reduces progression to HGD and adenocarcinoma. Challenges exist in differentiating between
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nondysplastic BE and BE with LGD; making the correct diagnosis has important implications for LGD treatment decisions. One of the available RCTs required that LGD be confirmed by an expert panel, which supports the use of having a gastrointestinal pathologist confirm LGD before treatment of BE with LGD can begin. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have BE without dysplasia who receive endoscopic RFA, the evidence include single-arm studies reporting outcomes after RFA. Relevant outcomes are overall survival, change in disease status, morbid events, and treatment-related morbidity and mortality. The available studies have suggested that nondysplastic metaplasia can be eradicated by RFA. However, the risk-benefit ratio and the net effect of RFA on health outcomes are unknown. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have BE with or without dysplasia who receive endoscopic cryoablation, the evidence includes noncomparative studies reporting outcomes after cryoablation. Relevant outcomes include overall survival, change in disease status, morbid events, and treatment-related morbidity and mortality. These studies have generally demonstrated high rates of eradication of dysplasia. However, the available evidence does not compare cryoablation to surgical care or RFA. The evidence is insufficient to determine the effects of the technology on health outcomes.

References
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Policy History

| Original Effective Date | 06/16/2010 |
| Current Effective Date | 01/18/2017 |
| 06/03/2010 | Medical Policy Committee approval |
| 06/16/2010 | Medical Policy Implementation Committee approval. New policy. |
| 05/05/2011 | Medical Policy Committee approval |
| 05/18/2011 | Medical Policy Implementation Committee approval. No change to coverage. |
| 04/12/2012 | Medical Policy Committee review |
| 04/25/2012 | Medical Policy Implementation Committee approval. Radiofrequency ablation for treatment of Barrett's esophagus with low-grade dysplasia was changed from investigational to eligible for coverage when the initial diagnosis of low-grade dysplasia is confirmed by a second pathologist who is an expert in GI pathology. Added that treatment of Barrett's esophagus with low-grade dysplasia in any other situation is investigational. |
| 03/04/2013 | Coding revised |
| 04/04/2013 | Medical Policy Committee review |
| 04/24/2013 | Medical Policy Implementation Committee approval. No change to coverage. |
| 06/25/2013 | Medical Policy Implementation Committee approval. Retired medical policy. |
| 01/09/2014 | Medical Policy Committee review |
| 01/15/2014 | Medical Policy Implementation Committee approval. “Based on review of available data, the Company considers radiofrequency ablation for treatment of Barrett’s esophagus in the absence of dysplasia” was changed from investigational to not medically necessary. Dropped the requirement of a second pathologist from coverage section. Brought back from retired status. |
| 01/08/2015 | Medical Policy Committee review |
| 01/21/2015 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 08/03/2015 | Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed. |
| 01/07/2016 | Medical Policy Committee review |
| 01/22/2016 | Medical Policy Implementation Committee approval. RFA for treatment of BE in the absence of dysplasia is considered investigational. |
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01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
01/05/2017 Medical Policy Committee review
01/18/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date: 01/2018

Coding
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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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<tr>
<th>Code Type</th>
<th>Code</th>
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<tr>
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<td>43229, 43257, 43270</td>
</tr>
<tr>
<td>HCPCS</td>
<td>No codes</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>D13.0, K22.70, K22.710, K22.711, K22.719</td>
</tr>
</tbody>
</table>

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association TEC or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:
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A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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