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## Endoscopic Radiofrequency Ablation or Cryoablation for Barrett's Esophagus

### Description

Barrett's esophagus (BE) is a condition in which the normal squamous epithelium is replaced by specialized columnar-type epithelium, known as intestinal metaplasia. Intestinal metaplasia is a precursor to adenocarcinoma and may be treated with mucosal ablation techniques such as radiofrequency ablation or cryoablation.

### Background

#### BE and the Risk of Esophageal Carcinoma

The esophagus is normally lined by squamous epithelium. BE 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). BE occurs in the distal esophagus, may be of any length, 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 low-grade dysplasia (LGD) to high-grade dysplasia (HGD) to carcinoma. Two large epidemiologic studies published in 2011 reported the risk of progression to cancer in patients with BE. One 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 Barrett's esophagus and, after a median follow-up of 5.2 years, reported that the annual risk of esophageal adenocarcinoma was 0.12%. Detection of low-grade dysplasia 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

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high-grade dysplasia 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 BE**

The current management of BE includes treatment of GERD and surveillance endoscopy to detect progression to HGD or adenocarcinoma. The finding of LGD typically warrants only follow-up and surveillance biopsies, whereas the finding of HGD or early-stage adenocarcinoma warrants mucosal ablation or resection (either endoscopic mucosal resection [EMR] or esophagectomy).

EMR, 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 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. PDT has been the only therapy shown in a randomized Phase III trial to significantly decrease the risk of carcinoma in BE. PDT therapy for BE is discussed in a separate policy No. 8.01.06.

The CryoSpray Ablation™ System (formerly the SprayGenix™ Cryo Ablation System, CSA Medical, Inc.) uses a low-pressure spray for spraying liquid nitrogen through an upper endoscope. Cryotherapy allows for treatment of uneven surfaces; however, disadvantages include the uneven application inherent in spraying the cryogen.

The HALO System from Barrx™ Medical, Inc. (Sunnyvale, Calif.-acquired by Covidien in 2012 and now known as the Barrx line of products) uses radiofrequency (RF) energy and consists of 2 components: an energy generator and an ablation catheter. The generator provides rapid (i.e., less than 1 second) delivery of a predetermined amount of RF energy to the catheter. Both the HALO90 and HALO360 are 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 Barrett's esophagus up to 3 cm. The HALO360 uses a balloon catheter that is sized to fit the individual esophagus and is inflated to allow for circumferential ablation.

Ablation with RF affects only the most superficial layer of the esophagus (the mucosa), leaving the underlying tissues unharmed. Efficacy measures of the procedure include eradication of

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intestinal metaplasia without leaving behind microscopic (or “buried”) foci and post-ablation regrowth of the normal squamous epithelium. Reports of the efficacy of the HALO system in ablating Barrett's esophagus have been as high as 70% (comparable to alternative methods of ablation [e.g., APC and MPEC]), and even higher in some reports. The incidence of leaving behind “buried” foci of intestinal metaplasia has been reported to be 20–44% with APC and 7% with MPEC; reports using the HALO system have been 0%. Another potential advantage to the HALO system is that because it is automated, it eliminates operator-dependent error that may be seen with APC and MPEC.

Treating HGD or mucosal cancer solely with ablative techniques risks undertreating the approximately 10% of patients who have undetected submucosal cancer, in whom esophagectomy would have been required.

### Regulatory Status

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

The CryoSpray Ablation™ System received FDA 510(k) marketing clearance in December 2007 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.”

### Related Policies

2.01.87 Confocal Laser Endomicroscopy

8.01.06 Oncologic Applications of Photodynamic Therapy, Including Barrett's Esophagus

### Policy

*\*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.*

Radiofrequency ablation may be considered **medically necessary** for treatment of Barrett's esophagus with high-grade dysplasia. (See Policy Guidelines)

Radiofrequency ablation may be considered **medically necessary** for treatment of Barrett's esophagus with low-grade dysplasia, when the initial diagnosis of low-grade dysplasia is confirmed by two physicians. (See Policy Guidelines)

Radiofrequency ablation is considered **investigational** for treatment of Barrett esophagus when the

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above criteria are not met, including but not limited to Barrett esophagus in the absence of dysplasia.

Cryoablation is considered **investigational** for Barrett's esophagus, with or without dysplasia.

### Policy Guidelines

Radiofrequency ablation for BE with high-grade dysplasia may be used in combination with endoscopic mucosal resection of nodular/visible lesions. The diagnosis of HGD should be confirmed by two pathologists before RFA.

There is considerable interobserver variability in the diagnosis of low-grade dysplasia (LGD), and the potential exists for overdiagnosis of LGD by nonexpert pathologists. This is due primarily to the difficulty in distinguishing inflammatory changes from LGD. There is literature evidence that expert gastrointestinal (GI) pathologists will downgrade a substantial portion of biopsies that are initially read as LGD by nonexperts (Curvers et al, 2010; Kerkhof et al, 2007). As a result, it is ideal that 2 experts in GI pathology agree on the diagnosis to confirm LGD; this may result in greater than 75% of initial diagnoses of LGD being downgraded to nondysplasia (Curvers et al, 2010). A review by a single expert GI pathologist will also result in a large number of LGD diagnoses being downgraded, although probably not as many downgrades as achieved using 2 expert pathologists (Kerkhof et al, 2007).

### Rationale

#### Literature Review

#### RFA versus surgical resection for Barrett's Esophagus

Radiofrequency ablation (RFA) 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 which compared RFA and complete endoscopic resection (ER) for Barrett esophagus (BE). Twenty studies (22 articles) were reviewed including 2 randomized controlled trials (RCT), 10 cohort studies on ER and 8 cohort studies on RFA. The only study that compared RFA and ER was the RCT by van Vilsteren (described next). The other RCT was by Shaheen et al (also described next). The studies were heterogeneous in design. A total of 1087 (532 ER and 555 RFA) patients with high-grade dysplasia (HGD) or intramucosal cancer were included in the studies reviewed. The median number of resections or RFA sessions required for BE eradication was 2. Complete ER and RFA eradicated BE dysplasia in 95% and 92%, respectively. Eradication was maintained in 95% of ER 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%) versus complete ER (12%). Esophageal strictures requiring additional treatment occurred in 4% of RFA patients and 38% of complete ER patients.

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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 the review were the van Vilsteren and Shaheen studies. The studies were heterogeneous in design and contained a mix of nondysplastic and LGD and HGD. The use of ER varied in the studies with a range of 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% 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 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, the 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 metaplasia was achieved in 71-100% and 46-100% of patients, respectively. Six cases of esophageal stenosis and one 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 which compared the safety of stepwise radical endoscopic resection (SRER) versus focal endoscopic resection (ER) followed by RFA for complete eradication of BE  $\leq$ 5 cm containing HGD/early cancer. Patients in the SRER group underwent piecemeal ER of 50% of BE by serial ER. Patients in the ER/RFA group underwent focal ER 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. Main outcome measures were: stenosis rate, complications, complete histological response for neoplasia (CR-neoplasia); and complete histological response for intestinal metaplasia (CR-IM). CR-neoplasia was achieved in 25/25 (100%) SRER and in 21/22 (96%) ER/RFA patients. CR-IM was achieved in 23 (92%) SRER and 21 (96%) ER/RFA patients. The stenosis rate was significantly higher in 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 median follow-up of 24 months, one 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 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

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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 Esophagus With Dysplasia**

RFA is a less-invasive alternative to surgical mucosal resection (SMR) and/or esophagectomy. Available research supports that RFA results in similar efficacy for disease that has not extended into the submucosa, with fewer complications.

#### **RFA versus Surveillance Alone in BE**

##### **RFA for Dysplastic BE**

One randomized multi-center, sham-controlled trial has been published that compares RFA to surveillance alone in BE with dysplasia. (17). 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 TEC Assessment and was rated fair on formal quality assessment according to the U.S. Preventive Services Task Force system (USPSTF). 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 gastrointestinal hemorrhage, which was treated endoscopically, 1 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

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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. RFA was associated with lower risk of disease progression, compared with surveillance.

### **RFA for HGD**

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% CI: 0.01-1.0,  $p = 0.04$ ), and a number needed to treat of 6.0 to prevent 1 case of cancer over a 1-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 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. 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

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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 with BE and 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. Evidence from 1 RCT reports that progression from HGD to cancer is reduced by approximately 90% following RFA, with rates of esophageal strictures of 6%.

### **RFA for LGD**

In 2014, Almond et al reported results of a meta-analysis of studies of endoscopic therapy in 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 LGD BE included the Shaheen et al randomized trial and 4 single-arm studies and 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 due to 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 to the surveillance group (8.8%,  $p < 0.03$ ), and the occurrence of high-grade dysplasia was also significantly lower for the RFA group (1.5%) compared to 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 three serious adverse events in 2 patients who received RFA (one abdominal pain requiring hospitalization, one bleeding episode, one episode of fever/chills following dilation for stricture), and a total of 12 other adverse events (8

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strictures requiring dilation, 3 mucosal lacerations, 1 retrosternal pain).

In the Shaheen RCT, there were 64 patients with LGD for which subgroup analysis was reported. At 12-month follow-up, 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 who progressed to cancer over the initial 12 months. Progression to HGD was noted in 2 of 42 (5%) of patients in the RFA group, compared with 3 of 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 to 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 1 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 diagnostic differentiation between nondysplastic BE and BE with LGD that 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 a challenge. Initial diagnosis of BE can 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 low-grade dysplasia has been to use multiple pathologists, including experts in gastrointestinal (GI) histopathology, to confirm the initial diagnosis of LGD. There is a high degree of intraobserver variability in pathologists' reading of LGD versus inflammatory changes, and this 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 pathological diagnosis of LGD, review by an expert pathologist will result in downgrading the initial diagnosis to non-dysplasia 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 then read by 2 expert GI pathologists with extensive experience in BE, with disagreements among experts resolved by consensus. After review by expert pathologists, 85% of initial diagnoses of LGD were downgraded to non-dysplasia, leaving a total of only 22/147 patients (15%) 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 a rate of 0.5% for patients who had been downgraded to non-dysplasia.

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. 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. In this sample, 73% of subjects were downstaged.

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**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 patients reported a lower rate of progression to HGD or adenocarcinoma for patients treated with RFA who had confirmed LGD. 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 been reported to reduce the number of patients diagnosed with LGD by 50% to 75%, presumably by reducing the number of patients with inflammatory changes who are mislabeled as having LGD.

**RFA for Non-Dysplastic BE**

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%. (1, 2)

Fleischer et al reported the 5-year follow-up of a single-arm study of patients with non-dysplastic Barrett's esophagus treated with RFA. The original study included 70 patients who underwent circumferential RFA and 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 fifty patients (92%) showed CR-IM at the 5-year biopsy visit. The 4 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-year CR-IM outcomes lends support to the safety, efficacy, cost-utility, and reduction in neoplastic progression in treating nondysplastic BE with RFA.

**Section Summary: RFA for Mpdysplastic BE**

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

**RFA versus PDT for BE**

In 2013 Ertan et al reported on a series of 86 consecutive patients treated with either 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) for RFA and 44 months (range, 24-60) for PDT. RFA resulted

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in significantly more complete eradication 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: RFA vs 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 et al 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 BE was 4.6 cm (range: 1–8 cm). After 6 months' 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 Barrett's esophagus 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 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%), Barrett's esophagus 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 1 patient. Complete response for HGD, all dysplasia, intestinal metaplasia,

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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), complete response (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 complete response of intestinal metaplasia. For the patients with invasive cancer (n=3), 100% had complete response of the cancer, HGD, and any dysplasia, and 67% of intestinal metaplasia.

Shaheen et al reported a multicenter, retrospective cohort study of 98 consecutive patients with Barrett's esophagus 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, HGD, or IC. After a median of 3 treatments with RFA, 91 subjects had 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 report high rates of success in eradicating dysplasia, with low rates of

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complications. These data are not sufficient to determine the comparative efficacy of cryoablation compared with RFA.

## Practice Guidelines and Position Statements

### American College of Gastroenterology

In 2016, the American College of Gastroenterology (ACG) issued guidelines for the diagnosis and management of Barrett esophagus (BE), which makes statements about endoscopic therapies in general, as outlined in Table 1.<sup>42</sup>

**Table 1: American College of Gastroenterology Guidelines**

Guidelines	Recommendation Strength	Level of Evidence
Patients with nodularity in the BE segment should undergo endoscopic mucosal resection of the nodular lesion(s) as the initial diagnostic and therapeutic maneuver.... Histologic assessment of the EMR specimen should guide further therapy. In subjects with EMR specimens demonstrating HGD, or IMC, endoscopic ablative therapy of the remaining BE should be performed.	Strong	High
In patients with EMR specimens demonstrating neoplasia at a deep margin, residual neoplasia should be assumed, and surgical, systemic, or additional endoscopic therapies should be considered	Strong	Low
Endoscopic ablative therapies should not be routinely applied to patients with nondysplastic BE because of their low risk of progression to EAC. Endoscopic eradication therapy is the procedure of choice for patients with confirmed LGD, and confirmed HGD, as noted above	Strong	Very low
In patients with T1a EAC, endoscopic therapy is the preferred therapeutic approach, being both effective and well tolerated	Strong	Moderate
In patients with T1b EAC, consultation with multidisciplinary surgical oncology team should occur before embarking on endoscopic therapy. In such patients, endoscopic therapy may be an alternative strategy to esophagectomy, especially in those with superficial (sm1) disease with a well-differentiated neoplasm lacking lymphovascular invasion, as well as those who are poor surgical candidates	Strong	Low
Routine staging of patients with nodular BE with EUS or other imaging modalities before EMR has no demonstrated benefit. Given the possibility of over- and understaging, findings of these modalities should not preclude the performance of EMR to stage-early neoplasia	Strong	Moderate
In patients with known T1b disease, EUS may have a role in assessing and sampling regional lymph nodes, given the increased prevalence of lymph node involvement in these patients compared with less advanced disease	Strong	Moderate
In patients with dysplastic BE who are to undergo endoscopic ablative therapy for nonnodular disease, radiofrequency ablation is currently the preferred endoscopic ablative therapy	Strong	Moderate

BE: Barrett esophagus; EAC: esophageal adenocarcinoma; EMR: endoscopic mucosal resection; EUS: endoscopic ultrasound; HGD: high grade dysplasia; IMC: intramucosal carcinoma; LGD: low- grade dysplasia.

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### British Society of Gastroenterology

In 2014, the British Society of Gastroenterology published guidelines on the diagnosis and management of BE, which made the following recommendations on management of dysplasia and early cancer (see Table 2).<sup>43</sup>

**Table 2: British Society of Gastroenterology Guidelines**

Guidelines	Recommendation
Management of low-grade dysplasia (LGD) is unclear in view of limited data about the natural history. It is essential that the diagnosis is confirmed by two pathologists, and patients should be surveyed endoscopically at 6 monthly intervals. Currently, ablation therapy cannot be recommended routinely until more data are available	C
For HGD and Barrett's-related adenocarcinoma confined to the mucosa, endoscopic therapy is referred over oesophagectomy or endoscopic surveillance	B
In the presence of HGD or intramucosal cancer without visible lesions (flat HGD/intramucosal cancer), these should be managed with an endoscopic ablative technique	A
There are few comparative data among ablative techniques, but RFA currently has a better safety and side-effect profile and comparable efficacy	C
Eradication of residual Barrett's esophagus after focal ER reduces the risk of metachronous neoplasia and is recommended	B

ER: endoscopic resection; HGD: high-grade dysplasia; RFA: radiofrequency ablation.

### American Society for Gastrointestinal Endoscopy

In 2012, the American Society for Gastrointestinal Endoscopy issued guidelines on the role of endoscopy in BE and other premalignant conditions of the esophagus.<sup>44</sup> These guidelines made the following recommendations on ablative therapies (see Table 3).

**Table 3: British American Society for Gastrointestinal Endoscopy Guidelines**

Guidelines	Evidence Quality <sup>a</sup>
We suggest that ablation be considered in select patients with LGD. Appropriate surveillance intervals after ablation are unknown	Low
We recommend that endoscopic resection of nodular dysplastic BE be performed to determine the stage of dysplasia before considering other ablative endoscopic therapy	Moderate
We suggest that local staging with EUS ± FNA is an option in select patients being considered for endoscopic ablative therapy	Very low
We recommend that eradication with endoscopic resection or RFA be considered for flat HGD in select cases because of its superior efficacy (compared with surveillance) and side effect profile (compared with esophagectomy)	Moderate

BE: Barrett esophagus; EUS: endoscopic ultrasound; FNA: fine needle aspiration; HGD: high-grade dysplasia; LGD: low-grade dysplasia; RFA: radiofrequency ablation.

<sup>a</sup> Quality assessed using GRADE system.

### American Gastroenterological Association

In 2015, the American Gastroenterological Association (AGA) published consensus recommendations for the management of BE, dysplasia, and esophageal adenocarcinoma.<sup>45</sup>

Statements with 80% or higher consensus agreement but generally low-quality evidence relevant to radiofrequency ablation (RFA) for BE included:

- In patients with BE undergoing endoscopic therapy, endoscopic resection of more than two-thirds of the circumference is not generally recommended due to the risk of stricture. (Agreement 83%, strongly agree 13%, agree 70%, neither 17%).

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- Radiofrequency ablation is an acceptable treatment option for BE patients with flat mucosa containing HGD without any visible lesions confirmed by high-resolution, high-definition endoscopy. (Agreement 87%, strongly agree 35%, agree 52%, neither 13%).

Statements with consensus agreement below 80% relevant to RFA for BE included:

- In patients with BE, all cases of possible dysplasia (indefinite, low grade, high grade) should be reviewed by at least 2 additional pathologists with specific expertise in Barrett's pathology. (Agreement 60.8%, neither 8.7%, disagree 26.1%, strongly disagree 4.3%)

A 2011 AGA medical position statement on the management of BE recommended endoscopic eradication therapy with RFA, photodynamic therapy, or endoscopic mucosal resection rather than surveillance for treatment of patients with confirmed high-grade dysplasia (HGD) within BE. AGA also stated that:

“Although endoscopic eradication therapy is not suggested for the general population of patients with Barrett's esophagus in the absence of dysplasia, we suggest that RFA, with or without EMR, should be a therapeutic option for select individuals with non-dysplastic Barrett's esophagus who are judged to be at increased risk for progression to high-grade dysplasia or cancer but that specific criteria that identify this population have not been fully defined at this time.”

“Endoscopic eradication therapy with RFA should also be a therapeutic option for treatment of patients with confirmed low-grade dysplasia in Barrett's esophagus.”

The current literature is inadequate to recommend endoscopic eradication therapy with cryotherapy for patients with confirmed low-grade dysplasia (LGD) or HGD within BE or patients judged to be at high risk for progression to HGD or esophageal carcinoma. Further studies are needed to assess whether reversion to squamous epithelium can persist long-term after cryotherapy.<sup>46</sup>

### Society of American Gastrointestinal and Endoscopic Surgeons

In 2010, the Society of American Gastrointestinal and Endoscopic Surgeons published guidelines on the surgical treatment of gastroesophageal reflux disease, which included recommendations for the treatment of BE (see Table 4).<sup>47</sup>

**Table 4: Society of American Gastrointestinal and Endoscopic Surgeons Guidelines**

Guidelines	Grade
HGIN and IMC can be effectively treated with endoscopic therapy including PDT, EMR, and RFA, alone or in combination	B
Antireflux surgery may be performed in a patient with non-neoplastic IM, IND, or LGIN, with or without endoscopic therapy to eradicate the Barrett's tissue. Specifically, RFA has been shown to be safe, clinically effective, and cost-effective in these disease states and may be performed in eligible patients before, during, or after antireflux surgery	B

EMR: endoscopic mucosal resection; HGIN: high-grade dysplasia; IM: intestinal metaplasia; IMC: intramucosal carcinoma; IND: indeterminate dysplasia; LGIN: low-grade dysplasia; PDT: photodynamic therapy; RFA: radiofrequency ablation.

### National Comprehensive Cancer Network

National Comprehensive Cancer Network guidelines (v.2.2016) for esophageal cancer make the following recommendations about early-stage esophageal adenocarcinomas (see Table 5).<sup>48</sup>

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**Table 5: National Comprehensive Cancer Network Guidelines**

Guidelines	Category
For pTis stage disease (high-grade dysplasia): endoscopic therapies (ER, ablation, or ER followed by ablation) are preferred	2A
For pT1a stage disease (tumor invades lamina propria or muscularis mucosa): endoscopic therapies (ER or ER followed by ablation) are preferred	2A
For superficial pT1b stage disease (tumor invades submucosa): endoscopic resection (ER followed by ablation) or esophagectomy is recommended ER: endoscopic resection.	2A

The recommendations state that endoscopic resection of focal nodules in early-stage disease should be performed.

For posttreatment surveillance, the guidelines state that ablation of residual flat or recurrent HGD and LGD using RFA or cryoablation should be considered. Ablation of nondysplastic BE is not recommended.<sup>48</sup>

### U.S. Preventive Services Task Force Recommendations

Not applicable.

### Summary of Evidence

The evidence for the use of endoscopic RFA for the treatment of patients who have BE with high-grade dysplasia (HGD) includes 1 randomized controlled trial (RCT) comparing radical endoscopic resection with focal endoscopic resection followed by RFA; 1 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 evidence available indicates that RFA of HGD in BE has been shown to be at least as effective in eradicating HGD as other ablative techniques, with a lower progression rate to cancer, and may be considered as an alternative to esophagectomy. Evidence from at least 1 RCT demonstrates higher rates of eradication than surveillance alone. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for the use of endoscopic RFA for the treatment of patients who have BE with low-grade dysplasia (LGD) 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 suggests that RFA reduces progression to HGD and adenocarcinoma. Challenges exist in differentiating between nondysplastic BE and BE with LGD; making the correct diagnosis has important implications for treatment decisions for LGD. 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 qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for the use of RFA for the treatment of patients who have BE without dysplasia 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 suggest that nondysplastic metaplasia can be eradicated by RFA. However, the risk/benefit ratio and

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the net effect of RFA on health outcomes are unknown. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for the use of cryoablation in patients who have BE (with or without dysplasia) 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 generally demonstrate high rates of eradication of dysplasia. However, the available evidence does not allow comparisons with surgical care or RFA. The evidence is insufficient to determine the effects of the technology on health outcomes.

### Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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### Policy History

Date	Action	Reason
December 2011	New Policy	
June 2013	Update Policy	Policy update with literature search, reference numbers 1, 2, 9, 10, 16, 18, 19, 21, 22, 30, 31 added others renumbered. Policy statement updated to include RFA for treatment of Barrett's esophagus with low-grade dysplasia (LGD), when the initial diagnosis of LGD is confirmed by a second pathologist who is an expert in GI pathology, as medically necessary.
June 2014	Update Policy	Policy updated with literature review. No changes to policy statements. References 15, 19, 23, & 28 added.
June 2015	Update Policy	Policy updated with literature review through March 6, 2015. References 22-23 added. Statement added to policy statements to clarify that radiofrequency ablation for Barrett esophagus is considered investigational for all cases in which the medically necessary criteria do not apply. Policy statements otherwise unchanged.
June 2016	Update Policy	Policy updated with literature review through October 7, 2015; references 32 and 37-41 added. Policy statements unchanged.
March 2017	Update Policy	Policy updated with literature review through October 5, 2016; references 19, 22, 31, and 42 added. Policy statements unchanged.

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## Keywords

Barrett's Esophagus, Radiofrequency  
Ablation Cryosurgical Ablation, Esophagus  
Radiofrequency Ablation, Esophagus  
CryoSpray  
HALO  
HALO360  
HALO90

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**This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 17, 2017 and is effective April 15, 2017.**

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