



# BlueCross BlueShield of Louisiana

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## Transesophageal Endoscopic Therapies for Gastroesophageal Reflux Disease

**Policy #** 00123

**Original Effective Date:** 06/24/2002

**Current Effective Date:** 04/23/2014

*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.*

### **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 transesophageal endoscopic gastroplasty (e.g., the EndoCinch™, NDO Plicator™, or EsophyX™ procedures)<sup>†</sup> as a treatment of gastroesophageal reflux disease (GERD) to be **investigational**.\*

Based on review of available data, the Company considers endoscopic submucosal implantation of a prosthesis or injection of a bulking agent (e.g., biocompatible liquid polymer, polymethylmethacrylate [PMMA] beads, zirconium oxide spheres) as a treatment of gastroesophageal reflux disease (GERD) to be **investigational**.\*

### **Background/Overview**

Transesophageal endoscopic therapies are being developed for the treatment of GERD. A variety of procedures are being evaluated, including devices for fundoplication, application of RF energy, and injection/implantation of prosthetic devices or bulking agents.

Due in part to the prevalence of GERD, there has been interest in creating a minimally invasive transesophageal therapeutic alternative to open or laparoscopic fundoplication or chronic medical therapy. Three types of procedures have been investigated:

1. Transesophageal endoscopic gastroplasty (gastroplication or fundoplication) is an outpatient procedure. During this procedure, suture(s) are placed in the lower esophageal sphincter. The sutures are designed to strengthen and lengthen the sphincter to decrease reflux.

Currently, three endoscopic suturing devices have received U.S. Food and Drug Administration (FDA) 510(k) marketing clearance for use in the treatment of GERD:

1. EndoCinch (CR Bard, Murray Hill, NJ) is a suture technique for partial-thickness plication, approved January 2001
  2. NDO Plicator (Ethicon Endo-Surgery, Chicago, IL) for full-thickness plication, approved May 2003
  3. EsophyX (EndoGastric Solutions, Redmond, WA) for full-thickness plication, approved September 2007
2. Submucosal injection or implantation of a prosthetic or bulking agent to enhance the volume of the lower esophageal sphincter has also been investigated.

In one procedure, a biocompatible liquid polymer is injected into the lower esophageal sphincter. On contact with the tissue, the polymer precipitates into a spongy mass. The mechanism of action in reducing reflux is

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not precisely known. One polymer, Enteryx, received FDA approval in 2003 through the premarket approval (PMA) process for the treatment of symptomatic GERD. However, on September 23, 2005, Boston Scientific Corporation issued a recall of Enteryx due to the device polymerizing shortly after injection into a spongy material that cannot be removed. Serious adverse events involved unrecognized transmural injections of Enteryx into structures surrounding the esophagus, potentially resulting in serious injury or death.

Another bulking agent, pyrolytic carbon-coated zirconium oxide spheres (Durasphere®)<sup>‡</sup>, is being evaluated. Durasphere is a bulking agent approved for treatment of urinary and fecal incontinence. Use of this product for esophageal reflux would be considered off-label use. The website of Carbon Medical Technologies states that Durasphere GR is an investigational device in the U.S. "intended to treat problems associated with GERD."

The Gatekeeper Reflux Repair System (Medtronic, Shoreview, MN) utilizes a soft, pliable, expandable prosthesis made of a polyacrylonitrile-based hydrogel. The prosthesis is implanted into the esophageal submucosa, and with time, the prosthesis absorbs water and expands, creating bulk in the region of implantation.

Endoscopic submucosal implantation of PMMA beads into the lower esophageal folds has also been investigated.

### **Rationale/Source**

This policy was based, in part, on a 2003 Technology Evaluation Centers (TEC) Assessment of transesophageal endoscopic treatments for gastroesophageal reflux. The TEC Assessment concluded that data were insufficient to permit conclusions about the effects of transesophageal suturing or transesophageal RF (the Stretta procedure) on GERD. Since the 2003 TEC Assessment, this policy has been updated periodically with literature searches.

Following is a summary of the key literature to date.

A 2005 report of the Agency for Healthcare Research and Quality (AHRQ) on "Comparative Effectiveness of Management Strategies for Gastroesophageal Reflux Disease" found that more efficacy and safety data on new endoscopic approaches were needed. The Comparative Effectiveness Review (CER) evaluated studies on the EndoCinch Suturing System, Stretta, Enteryx, and the NDO Plicator. A 2011 update of the AHRQ report excluded Enteryx and the NDO Plicator, since they were no longer available in the U.S., and added the EsophyX procedure (endoscopic fundoplication), which was commercialized after the 2005 review. The 2011 update reported the following:

- Like the 2005 CER, the update did not identify any study that compared medical treatment with endoscopic therapy. The strength of evidence was rated insufficient.
- The review identified one small nonrandomized study that compared laparoscopic total fundoplication with EndoCinch. This study reported that laparoscopic total fundoplication was more effective than EndoCinch in improving GERD symptoms and decreasing acid exposure. The strength of evidence was rated insufficient.

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- No study directly comparing endoscopic treatments was identified for the update. The strength of evidence was rated insufficient.
- Five cohort studies evaluated the effectiveness of EsophyX. The proportion of patients who were off proton pump inhibitors (PPIs) at the end of follow-up ranged from 47% to 71%. Significant improvement of quality of life as measured by the GERD-Health Related Quality of Life (GERD-HRQL) scale was reported by 2 of the 5 studies. The strength of evidence was rated insufficient.
- Common adverse events after endoscopic suturing included chest or abdominal pain (up to 24%), bleeding (up to 11%), dysphagia (up to 50%), and bloating (up to 19%). None of these quantitative estimates were reliable because of the lack of a standard definition and uniform system of reporting. The strength of evidence was rated low.

The AHRQ report concluded that for the three available endoscopic procedures (EndoCinch, Stretta, EsophyX), effectiveness remains substantially uncertain for the long-term management of GERD. While some clinical benefits were observed in patients who had these procedures, the studies were generally small, of variable quality, and of short duration. In addition, all of these procedures have been associated with complications, including dysphagia, infection/fever, and bloating. Higher quality studies are needed to determine the role and value of endoscopic procedures in the treatment of patients with GERD.

A 2009 systematic review of 33 studies examined 7 endoscopic treatments for GERD (3 of which do not have FDA marketing clearance for use in the U.S.). The review by Chen et al. included sham-controlled and active-controlled studies for the EndoCinch suturing system, the Stretta RF procedure, and the (recalled) Enteryx polymer injection. The authors highlighted the importance of both subjective and objective improvements in GERD studies: To the extent that improved subjective outcomes are mediated by interruption of submucosal sensory fibers from the vagus nerve, ongoing acid reflux may be undetected, leading to adverse consequences. Chen et al. conclude,

“Despite the potential benefits of these procedures, there is insufficient evidence at present to establish their safety and efficacy, particularly in the long-term.”

The review of evidence is divided into 2 separate questions, according to the 2 types of procedures included in this policy review:

1. Does endoscopic plication improve health outcomes for patients with GERD, compared to treatment with PPIs or laparoscopic fundoplication?
2. Does endoscopic Injection/Implantation of prosthetics or bulking agents improve outcomes for patients with GERD, compared to treatment with PPIs or laparoscopic fundoplication?

### Endoscopic Plication

1. Does endoscopic plication improve health outcomes for patients with GERD, compared to treatment with PPIs or laparoscopic fundoplication?

Two early case series reported results of endoscopic plication using non-FDA approved devices. In 1999, Swain reported on a case series of 28 patients with GERD whose symptoms were not controlled with medical therapy. In 2001, Filipi and colleagues reported on a multicenter case series of 64 patients with



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symptoms of GERD. These case series were evaluated by the 2003 TEC Assessment, which concluded that these types of studies were insufficient to permit conclusions about the effects of transesophageal suturing on GERD. Randomized, controlled trials (RCTs) were needed to determine the comparative impact on outcomes compared to alternatives, and long-term follow-up data were needed.

### EndoCinch

The available evidence on this question for EndoCinch consists of 2 randomized, sham-controlled trials, one non-randomized comparative study, and numerous uncontrolled case series.

#### *Controlled Trials*

Montgomery et al. reported on a randomized, double-blind sham trial of 46 patients with GERD who required daily PPI therapy in 2006. In this study, 22 patients had plication (EndoCinch) and 24 had a sham procedure. There were no statistically significant differences between groups for some key measures including acid exposure and discontinuation of PPI. Also, there were no changes in the extent of esophagitis. Also noted was a marked loss of sutures, with 67% remaining at 12 months.

Schwartz et al. reported a single-center study of 60 patients with GERD; 20 patients were randomly assigned to EndoCinch; 20 had a sham procedure; and 20 had observation. At 3-month follow-up, while PPI use decreased more in the active treatment group (compared to sham), there was no difference between the 2 groups in acid exposure time; acid exposure times normalized in 29% of actively treated patients and in 22% of sham patients ( $p = 0.71$ ). During the 12-month follow-up, 29% of those who received suturing were retreated.

In 2006, Mahmood and colleagues reported on a nonrandomized contemporaneous comparative study of 27 patients receiving endoscopic plication with EndoCinch to 24 patients having laparoscopic Nissen fundoplication. Many of those receiving endoscopic procedures were referred to a gastroenterologist, while those having the fundoplication were often referred directly to a surgeon. Patients had GERD symptoms requiring continuous PPI treatment; some had breakthrough symptoms on PPIs. In this small, nonrandomized study, symptom control improved in both groups but was better for the Nissen fundoplication group. Dysphagia was more common after Nissen fundoplication. Ninety-one percent of Nissen fundoplication patients achieved normal esophageal pH compared to 48% in the endoscopic group.

A nonrandomized study comparing transesophageal suturing with the EndoCinch to laparoscopic antireflux surgery was published in 2004. This comparative study showed that suturing was not as effective as antireflux surgery in reducing medication use.

#### *Uncontrolled Studies*

There are numerous uncontrolled case series that report on outcomes of EndoCinch treatment. An example is the publication by Mahmood and colleagues, which reported on a case series of 26 patients treated with EndoCinch in 2003. This trial reported an improvement in a number of outcome measures, including PPI use, reflux episodes, and heartburn symptoms. However, because of the lack of control group, the clinical meaning of these improvements is unclear.



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### *Other Studies*

Radiofrequency has been applied as supplementation to EndoCinch plication to reduce the loss of mucosal sutures seen at 1 year with that procedure. In 2008, Mosler et al. reported a pilot study in 16 GERD patients comparing endoluminal gastroplication with EndoCinch alone to EndoCinch with cautery of mucosal surfaces prior to suturing. After 1 year, 10 of 27 sutures (37%) in 9 patients treated with cautery remained intact, while 3 of 20 sutures (15%) in 7 patients treated with EndoCinch alone remained intact. Initial improvements in heartburn, pH score, and medication use were seen at 12 months but were not sustained at 24 months in either group.

Several papers have been published on laparoscopic Nissen fundoplication following failed transesophageal endoscopic therapies for GERD. In 2010, Furnee and colleagues reported prospectively collected data from 11 consecutive patients who underwent Nissen fundoplication after failure of EndoCinch gastroplication. The 11 patients were from a cohort of 50 (22%) who had been treated with EndoCinch from a randomized trial described above (20 randomized to EndoCinch and 30 controls who crossed over). Two patients had persistence of their primary symptoms after EndoCinch plication, and the other 9 experienced recurrence of symptoms after several months. Upper endoscopy showed disruption of between 1 and 3 of the gastroplications. Nissen fundoplication was performed without major complications at a median of 23 months (range 7-33) after the EndoCinch procedure. After a median follow-up of 31 months (range, 6-61 months), 9 patients (81.8%) reported their preoperative symptoms as resolved or improved. General quality of life improved from 33 to 79 on a visual analog scale (VAS). Three patients (27.3%) had daily complaints of troublesome dysphagia, a rate which compared unfavorably with the 3.6% rate reported after primary Nissen fundoplication. Another patient had troublesome chest pain. Acid exposure times were found to have increased slightly after EndoCinch and decreased after Nissen fundoplication.

### *Section Summary*

Comparative studies with EndoCinch have failed to show an improvement in acid exposure time when compared to sham and suggest inferior results when compared to laparoscopic surgery. There is a high rate of loss of intact sutures at 1-year follow-up, and there are reports that laparoscopic fundoplication is common following failed EndoCinch procedure. A search of the online site [www.clinicaltrials.gov](http://www.clinicaltrials.gov) in October 2013 found no active trials with EndoCinch.

### Plicator

The available evidence on Plicator consists of one RCT and numerous uncontrolled case series.

### *Controlled Trials*

Rothstein et al. reported on use of full-thickness plication (Plicator) with 3-month follow-up in a randomized, sham-controlled multicenter study of 159 patients with GERD requiring maintenance therapy. In this short-term study, complete cessation of PPI therapy was higher among those in the treatment group than in the sham group (50% vs. 24%, respectively). Quality-of-life scores also improved more in the active group. The percent reduction in median percent time the pH was less than 4 was improved more in the active group (7% vs. 10%, respectively) but did not change in the sham group (10% vs. 9%, respectively). The authors noted that the single full-thickness plication normalized the distal esophageal acid contact for less than one-third of the patients and was not effective in healing esophagitis. Also, radiating shoulder pain and



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abdominal pain were more frequent adverse events in the active treatment group (12% vs. 0% and 9% vs. 0%, respectively).

A 2013 trial from Europe randomized 70 patients with GERD to endoscopic gastroplication with the Plicator or to laparoscopic fundoplication. Patients were followed for 3 months, and outcome measures included a variety of physiologic and symptom-based measures. On some outcomes, more effective relief of reflux-related symptoms was obtained after laparoscopic fundoplication, while on others the improvement was similar between groups. The Plicator was found to have a better side-effect profile, with a higher number of serious adverse events reported in the laparoscopic fundoplication group. There were 13 patients in the Plicator group that required additional antireflux procedures due to a lack of adequate improvement in symptoms. Another small randomized trial from Eastern Europe assigned 52 patients in a 2:1 ratio to transoral incisionless fundoplication (TIF) or to laparoscopic Nissen fundoplication. The first 18 patients randomized to TIF were treated with NDO Plicator. After the company terminated production of the NDO Plicator, the next 16 patients randomized to TIF were treated with Esophyx. Results of this study are described below in the section on Esophyx.

### *Uncontrolled Case Series*

Full-thickness fundoplication using the Plicator was assessed in a cohort study of 131 patients variably responsive to PPI therapy. At 12 months, 50 patients (38%) were lost to follow-up or had not yet reached their 12-month follow-up visit. Sixty-six percent of the remaining 81 patients demonstrated a 50% reduction in their GERD-HRQL score, compared to their prefundoplication (off meds) score. No serious adverse events were reported. The lack of a contemporaneous control (comparison) group greatly limits the use of these findings.

Use of multiple Plicator endoscopic suturing devices was studied in a 12-month industry-supported case series of 41 patients with PPI-dependent GERD. At 12-months, 24 of 41 patients (59%) had discontinued daily PPI therapy. Twenty-six of 41 patients (63%) had an improved GERD-HRQL equal to or greater than 50%. Gastroesophageal reflux disease-Health Related Quality of Life scores improved from a median of 25 at baseline *off* PPI to 8 post-treatment, a statistically significant improvement ( $p < 0.001$ ), and from a median of 11 at baseline *on* PPI to 8 post-treatment, a statistically significant improvement ( $p = 0.015$ ). Acid exposure was not measured. All procedure-related adverse events occurred within the first postprocedure week.

A search of online site [www.clinicaltrials.gov](http://www.clinicaltrials.gov) in June 2011 found several studies with the NDO Plicator listed as terminated, since the sponsoring company (NDO Surgical, Inc.) was acquired by Johnson & Johnson and has ceased business operations.

### Esophyx

The available literature on Esophyx fundoplication consists of numerous case series and 1 small non-randomized study with limited follow-up, and results from a multicenter registry.



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### *Controlled Trials*

A small randomized trial assigned 52 patients in a 2:1 ratio to TIF (18 NDO Plicator and 16 Esophyx) or to laparoscopic Nissen fundoplication. Patients were enrolled in the study if they had pathologic esophageal acid exposure confirmed by 24-hour pH measurements, responded at least partially to PPI therapy, showed a deteriorated gastroesophageal junction, and had a small hiatal hernia (< 2 cm). At the 12-month follow-up, there were 26 patients (76%) in the TIF group and 14 patients (78%) in the Nissen fundoplication group. The GERD-HRQL improved to a similar extent in both groups. At 12 months, a similar percentage of patients in the TIF group (79%) and Nissen fundoplication group (73%) improved in the Hill grade by 50% or more, and the percentage of patients who had completely stopped PPI use was not significantly different (50% TIF vs. 71% Nissen). The hospital stay was significantly shorter following TIF group (2.9 days) compared to Nissen fundoplication (6.4 days).

In 2011, Frazzoni et al. reported a small (n = 20) prospective open-label study comparing the EsophyX procedure with laparoscopic Nissen fundoplication in PPI-resistant patients. Twenty-three of 142 patients who were assessed for persistent heartburn/regurgitation met the criteria for entering the study. Excluded were patients with Barrett's esophagus, hiatal hernia, previous anti-reflux surgery, progressive systemic sclerosis, severe cardiac/pulmonary disease, or pregnancy. Ten patients with PPI-resistant GERD chose to undergo EsophyX, and 10 chose laparoscopic fundoplication. There were no significant differences in baseline characteristics between the 2 groups. Ambulatory 24-hour impedance-pH monitoring was performed at baseline and 3 months after fundoplication. Distal and proximal refluxes were significantly reduced in the laparoscopic group (e.g., from a baseline of 73 to 25 at 3 months) but not in the endoscopic group (from 60 to 64). Esophageal acid exposure time was considered to be normal in 100% of cases after Nissen fundoplication versus 50% of cases after EsophyX. Symptoms, based on a 5-point Likert scale, remained in 0/10 laparoscopically treated patients and 6/10 patients who underwent EsophyX. Although results from this small comparative study do not support EsophyX in this select group of patients, randomized trials with a larger number of subjects and longer follow-up are needed to evaluate this procedure.

### *Prospective Studies*

In 2012, Bell and colleagues reported 6-month follow-up from a prospective multicenter registry of patients with chronic GERD who received TIF using the EsophyX<sub>2</sub> system with SerosaFuse fasteners. For the 100 consecutive patients who were treated in this community-based study, the median GERD symptom duration was 9 years (range, 1-35 years), the median duration of PPI use was 7 years (range, 1-20 years), and 92% of patients had incomplete symptom control despite maximal medical therapy. Fasteners were successfully deployed in 89% of attempted deliveries, and a mean of 20 fasteners were used for fundoplication. Hiatal hernias of 2 cm or less were completely reduced, while those greater than 2 cm were partially reduced. The primary efficacy endpoint at 6-months, the GERD-HRQL score, was normalized (score of 2 or less) in 73% of the 85 patients who had an abnormal GERD-HRQL score before the procedure. Median heartburn scores improved from 18 to 3, regurgitation scores improved from 15 to 0, and reflux symptom index score improved from 24 to 7. The percent of patients using PPIs decreased from 92% of patients before the procedure to 20% of patients after TIF, and an additional 9% of patients continued to use medications but no longer required daily PPI use. The authors noted that although the magnitude of typical symptom



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improvement was lower with TIF than is expected with traditional Nissen fundoplication, there was a very low incidence of side effects compared to traditional fundoplication.

In 2013, Muls et al. published 3-year follow-up results on 66 of 86 patients (77%) in the pivotal FDA trial who had been treated with the Esophyx device. Twelve of the 66 (18%) underwent revisional procedures (2 laparoscopic Nissen and 10 TIF revisions) and were considered treatment failures. With a modified intent-to-treat analysis ( $n = 66$ ), a clinically significant reduction in GERD-HRQL ( $\geq 50\%$  vs. pre-TIF) was observed in 65% of patients at 3 years. Of the 11 patients who underwent pH testing at the 3-year follow-up visit, 9 (82%) showed normalized pH.

### *Retrospective Series*

There are a number of retrospective case series on TIF. The largest series is by Barnes and colleagues, who reported on 124 consecutive patients with PPI-resistant GERD who underwent EsophyX fundoplication at 2 community hospitals in the U.S. All patients had chronic GERD for a median of 9 years (range, 1-35 years) and 97% reported ineffective symptom control on medical therapy. Valves in 2 of the 5 failures were reported to have been disrupted due to retching and severe cough. At a median 7-month follow-up (range, 5-17 months), typical and atypical symptom scores were normalized (no symptoms) in 75% to 80% of the remaining patients, and PPIs were discontinued by 93%. Endoscopy in 53 patients revealed Hill grade I tight valves in 89% of cases, reduced hiatal hernia in 33/34 (97%), and healed reflux esophagitis in 25/30 (83%). No patient complained of dysphagia or odynophagia. Based on global analysis, 72% of the patients were reported to be in remission, 20% improved symptomatically, and 8% had ongoing GERD.

Another moderately large series was a 2008 industry-sponsored study of the Esophyx procedure in 86 PPI-dependent GERD patients, reporting that 68% of patients discontinued PPI medication use at 12 months. Bell and Freeman reported on an industry-funded series of 37 consecutive patients with PPI-resistant GERD who underwent Esophyx fundoplication. One patient had a complication requiring removal of the fundoplication and was not included in follow-up. At a median 6-month follow-up (range, 3-14 months), no patient reported problems with dysphagia, bloating, or excess flatulence, and 82% were not taking any PPIs. Acid exposure was significantly improved and normalized in 61% of patients whose reflux characteristics on PPIs at baseline were elevated. Four patients had an increased acid exposure, 2 of whom underwent revision to laparoscopic Nissen fundoplication.

In 2010, Velanovich reported on a series of 24 U.S. patients who underwent endoscopic fundoplication with Esophyx. At an average 7-week follow-up (range, 6-8 weeks), 13 patients (54%) reported complete resolution of symptoms, and 6 patients (25%) had persistent GERD-related symptoms. In a letter to the editor in 2011, Velanovich reported that 2 of these patients subsequently had recurrence of GERD and failure of the Esophyx fundoplication; the H-fasteners had pulled through the esophagus and were attached to the gastric fundus.

### *Other Studies*

Furner et al. reported an increased risk of gastric injury with laparoscopic Nissen fundoplication after failed EsophyX fundoplication. Of 88 patients in their database who underwent EsophyX fundoplication, 11 (12.5%) subsequently underwent Nissen fundoplication for persistent ( $n = 7$ ) or recurrent symptoms ( $n = 4$ ) at a mean 8.1 months after the primary procedure. Endoscopy showed partial or total disruption of fasteners





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in 8 of the 11 patients (72.7%). Nissen fundoplication after EsophyX resulted in gastric perforation in 2 patients and conversion to laparotomy in 1 patient. Another patient developed a subphrenic abscess requiring surgical exploration. In 7 patients, the preoperative symptoms were resolved or improved after Nissen fundoplication, 3 reported symptom worsening due to new-onset daily dysphagia, and 1 had symptom worsening due to daily heartburn.

### Section Summary

The literature on the efficacy of Esophyx consists of 2 small controlled trials, registry data, and numerous case series. While these studies report improvements in outcomes following treatment with Esophyx, the lack of control group in most of the studies makes the clinical meaning of these changes unclear. Randomized controlled trials with longer follow-up are needed to determine whether Esophyx improves outcomes compared to alternative treatments.

A search of the online site [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) in October 2013 identified 2 Phase III and 2 Phase IV post-marketing studies on EsophyX sponsored by EndoGastric Solutions. Completion of one of the sham controlled Phase III trials (NCT01110811) is expected in . Completion of the other sham-controlled Phase III trial (RESPECT, NCT01136980) is expected October 2014. One of the Phase IV trials is a registry with 3-year follow-up (NCT01118585). The study has a planned enrollment of 500 patients with completion expected in 2015.

### Injection/Implantation of Prosthetics or Bulking Agents

2. Does endoscopic injection/implantation of prosthetics or bulking agents improve outcomes for patients with GERD, compared to treatment with PPIs or laparoscopic fundoplication?

### Enteryx Procedure

The available evidence for this device consists of one RCT and one prospective case series.

#### *Controlled Trials.*

In 2005, Deviere et al. reported on a single-blind RCT of 64 patients with GERD randomly assigned to either Enteryx implantation or a sham procedure. At 3 and 6 months' follow-up, patients in the Enteryx group had greater reductions in PPI use and more improvement in GERD health-related quality-of-life heartburn scores. However, the small size and short duration of the study limit interpretation of findings.

#### *Uncontrolled Case Series*

The FDA approval for the Enteryx procedure was based on a prospective case series of 85 patients who had GERD that was controlled by medical therapy including PPIs. A successful outcome was defined as elimination of PPI use or a reduction in use of PPIs by at least 50% compared to baseline usage. Therefore, the procedure was clearly designed to be an alternative to medical therapy. At 12 months, 80.3% of the study subjects met the primary outcome. While this case series reports promising results, as noted by the TEC Assessment of other transesophageal endoscopic therapies for GERD, randomized studies are required to determine treatment effectiveness. In fact, as part of the postmarketing phase of FDA regulation, the FDA required a sham-controlled study.



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In addition, the long-term efficacy of the implant is unknown. For example, more than 40% of the subjects had a greater than 25% decrease in residual implant volume at 6 and 12 months, raising concerns about the durability of the procedure. The protocol permitted reinjection of the polymer within the first 3 months of therapy; 19 of 85 patients (22%) underwent repeat injection during this period, either due to lack of effectiveness or sloughing of the implanted material. The safety and efficacy of repeat injections are unknown. Other safety concerns include the incidence of retrosternal chest pain immediately postprocedure, reported in 90% of patients. The chest pain resolved within 1 month in 90% of the patients and in all patients by 3 months. A total of 20% of patients reported dysphagia.

In September 2005, Enteryx was voluntarily removed from the market due to serious adverse effects.

### Durasphere

The available evidence for this device consists of one case series. One open-label pilot study of 10 GERD patients injected Durasphere (Carbon Medical Technologies, Saint Paul, MN), a bulking agent approved for treatment of urinary and fecal incontinence, at the gastroesophageal junction. At 12 months, 7 patients (70%) discontinued all antacid medication completely. No erosion, ulceration, or sloughing of material was noted at any injection site.

### Gatekeeper Reflux Repair System

The available evidence for this device consists of one RCT. An industry-funded sham-controlled single-blind multicenter study randomized 118 patients into Gatekeeper (n = 75) or sham (n = 43) treatment. An additional 25 patients were treated as lead-ins during the initial training of investigators and included only in the safety analysis. The patients were implanted initially with 4 Gatekeeper prostheses. At 3 months, 44% of implanted patients received retreatment with up to 4 additional prostheses due to unsatisfactory symptom control. The primary safety end point was reduction in serious device- and procedure-related adverse device effects, compared with a surgical procedure composite complication rate of 15%. Four serious adverse events were reported (2 perforations, 1 pulmonary infiltrate related to a perforation, and 1 severe chest pain). The primary efficacy end point was reduction in heartburn symptoms using the GERD-HRQL questionnaire. Planned interim analysis after 143 patients were enrolled found that heartburn symptoms and esophageal acid exposure had improved significantly in both the Gatekeeper and sham groups at 6 months, but there was no significant difference between the 2 groups. The study was terminated early due to a lack of efficacy.

### Polymethylmethacrylate Beads

The available evidence for this device consists of one case series. A 2001 publication on transesophageal submucosal implantation of PMMA beads consisted of a case series of 10 patients with GERD who were either refractory to or dependent on PPIs. While a significant decrease in symptom scores was noted at post-treatment follow-up (time not specified), the small number of patients and lack of long-term follow-up preclude scientific analysis. No additional studies have been identified evaluating this treatment option.

### **Clinical Input Received through Physician Specialty Societies and Academic Medical Centers**

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received



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does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests for clinical input on transesophageal incisionless fundoplication using Esophyx, input was received from 2 physician specialty societies and 4 academic medical centers while this policy was under review in 2011. The reviewers agreed that transesophageal incisionless fundoplication is sufficiently different from laparoscopic Nissen fundoplication to warrant evaluation as a separate procedure. The reviewers considered transesophageal incisionless fundoplication (i.e., Esophyx) to be investigational for the treatment of GERD.

### Summary

There is insufficient evidence at present to establish the safety and efficacy of these procedures, particularly in the long term. Some of the unresolved issues include questions about the safety and durability of the device/treatment and lack of consistent improvement in objective measures (esophageal acid exposure) using these devices. Also, the rate of revisional procedures on longer follow-up may be high and needs to be further defined. A number of these devices (eg, EndoCinch, NDO Plicator, Gatekeeper, Enteryx) are no longer marketed in the U.S. or actively evaluated due to lack of efficacy and/or safety issues. For procedures that are still in development, high-quality data from large RCTs are needed to compare endoscopic procedures with both sham controls and with the currently accepted treatments for GERD, namely drug therapy and laparoscopic fundoplication. Well-designed trials should use standardized outcome measures to examine whether subjective improvement, such as discontinuation of medication therapy and GERD-HRQL scores, is supported by objective improvement, such as esophageal acid exposure. Until such studies demonstrate improved net health outcomes for patients with GERD, these techniques are considered investigational.

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## Transesophageal Endoscopic Therapies for Gastroesophageal Reflux Disease

Policy # 00123

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## Transesophageal Endoscopic Therapies for Gastroesophageal Reflux Disease

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

Code Type	Code
CPT	43201, 43236, 43266 (Code 43257 was deleted due to the removal of the Stretta procedure from policy)
HCPCS	No codes
ICD-9 Diagnosis	530.11, 530.81, 530.82, 530.85
ICD-9 Procedure	44.66

### **Policy History**

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06/20/2002 Medical Policy Committee review.  
06/24/2002 Managed Care Advisory Council approval.  
04/01/2004 Medical Director review  
04/20/2004 Medical Policy Committee review. Format revision. No substance change to policy.  
04/26/2004 Managed Care Advisory Council approval  
04/05/2006 Medical Director review  
04/19/2006 Medical Policy Committee review. Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.  
04/02/2008 Medical Director review  
04/16/2008 Medical Policy Committee approval. No change to coverage eligibility.  
04/02/2009 Medical Director review  
04/15/2009 Medical Policy Committee approval. No change to coverage eligibility. Title changed to match BCBSA.  
04/08/2010 Medical Policy Committee approval  
04/21/2010 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

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04/07/2011	Medical Policy Committee review
04/13/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/12/2012	Medical Policy Committee review
04/25/2012	Medical Policy Implementation Committee approval. Added NDO Plicator and EsophyX procedures as examples of transesophageal endoscopic gastropasty. Investigational statements were combined on biocompatible polymer and PMMA beads as bulking agents.
04/04/2013	Medical Policy Committee review
04/24/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/03/2014	Medical Policy Committee review
04/23/2014	Medical Policy Implementation Committee approval. Removed the second Investigational statement regarding transesophageal radiofrequency to create thermal lesions of the gastrointestinal junction (i.e., the Stretta procedure) as a treatment of GERD.

Next Scheduled Review Date: 04/2015

\*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. Food and Drug Administration (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 technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
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  - 3. reference to federal regulations.

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