Kansas City

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Transesophageal Endoscopic Therapies for Gastroesophageal Reflux Disease

Policy Number: 2.01.38
Origination: 2/2001
Last Review: 2/2014
Next Review: 2/2015

Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for transesophageal endoscopic therapies for gastroesophageal reflux disease. This is considered investigational.

When Policy Topic is covered

Not Applicable

When Policy Topic is not covered

Transesophageal endoscopic gastroplasty is considered **investigational** as a treatment of gastroesophageal reflux disease (e.g., the EndoCinch™, NDO Plicator™, or EsophyX™ procedures).

Transesophageal radiofrequency to create submucosal thermal lesions of the gastroesophageal junction (i.e., the Stretta procedure) is considered **investigational** as a treatment of gastroesophageal reflux disease.

Endoscopic submucosal implantation of a prosthesis or injection of a bulking agent (e.g., biocompatible liquid polymer, polymethylmethacrylate beads, zirconium oxide spheres) is considered **investigational** as a treatment of gastroesophageal reflux disease.

Considerations

n/a

Description of Procedure or Service

Transesophageal endoscopic therapies are being developed for the treatment of gastroesophageal reflux disease (GERD). A variety of procedures are being evaluated, including transesophageal (or transoral) incisionless fundoplication (TIF), application of radiofrequency (RF) energy, and injection/implantation of prosthetic devices or bulking agents.

Background

Due in part to the high prevalence of gastroesophageal reflux disease (GERD), there has been interest in creating a minimally invasive transesophageal therapeutic alternative to open or laparoscopic fundoplication or chronic medical therapy. This type of procedure may be considered natural orifice transluminal surgery (NOTES). Three types of procedures have been investigated:

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

Currently, 3 endoscopic suturing devices have received U.S. Food and Drug Administration (FDA) 510(k) marketing clearance for use in the treatment of GERD:
    a. EndoCinch™ (CR Bard, Murray Hill, NJ) is a suture technique for partial-thickness plication, approved January 2001
    b. NDO Plicator™ (Ethicon Endo-Surgery, Chicago, IL) for full-thickness plication, approved May 2003
    c. Esophyx® (EndoGastric Solutions, Redmond, WA) for full-thickness plication, approved September 2007
2. Radiofrequency (RF) energy has been used to produce submucosal thermal lesions at the gastroesophageal junction. (This technique has also been referred to as the Stretta procedure. The CSM Stretta® System [Conway Stuart] received 510(k) marketing clearance from the FDA in 2000 for general use in the electrosurgical coagulation of tissue and is specifically intended for use in the treatment of GERD. Stretta® is currently manufactured by Mederi Therapeutics, Greenwich, CT.) Specifically, RF energy is applied through 4 electrodes inserted into the esophageal wall at multiple sites both above and below the squamocolumnar junction. The mechanism of action of the thermal lesions is not precisely known but may be related to ablation of the nerve pathways responsible for sphincter relaxation or may induce a tissue-tightening effect related to heat-induced collagen contraction.
3. 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 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®), is being evaluated. Durasphere® is a bulking agent approved for treatment of urinary and fecal incontinence (see policy number 7.01.19). 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 polymethylmethacrylate beads into the lower esophageal folds has also been investigated.

Rationale

This policy was based, in part, on a 2003 TEC Assessment of transesophageal endoscopic treatments for gastroesophageal reflux disease (GERD).(1) Since the 2003 Assessment, this policy has been updated periodically using the MEDLINE database. The most recent literature update was performed through October 16, 2013. 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.(2) The comparative

effectiveness review evaluated studies on the EndoCinch Suturing System, Stretta, Enteryx, and the NDO Plicator. A 2011 update of the AHRQ report (3) 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 Comparative Effectiveness Review (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.
- 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-HRQL [health-related quality of life] 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 3 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. (Bloating and dsyphagia are also side effects of laparoscopic fundoplication.(4) 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.).(5) The review by Chen et al. included sham-controlled and active-controlled studies for the EndoCinch™ suturing system, the Stretta® radiofrequency 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.

The review of evidence for this policy is divided into 3 separate questions, according to the 3 types of procedures included in this policy review:

1. Does transesophageal (transoral) incisionless fundoplication (TIF) improve health outcomes for patients with GERD, compared to treatment with PPIs or laparoscopic fundoplication?
2. Does radiofrequency treatment of the gastroesophageal junction (Stretta procedure) improve outcomes for patients with GERD, compared to treatment with PPIs or to laparoscopic fundoplication?
3. 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 TIF 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.(6) In 2001, Filipi et al. reported on a multicenter case series of 64 patients with symptoms of gastroesophageal reflux disease (GERD).(7) These case series were evaluated by the 2003 TEC Assessment, (1) 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, 1 nonrandomized 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. (8) 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.(9) 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 et al. reported on a nonrandomized contemporaneous comparative study of 27 patients receiving endoscopic plication with EndoCinch ™ to 24 patients having laparoscopic Nissen fundoplication. (10) 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.(11)

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.(12) 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.

Other studies. Radiofrequency (RF) 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.(13) 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 et al. reported prospectively collected data from 11 consecutive patients who underwent Nissen fundoplication after failure of EndoCinch™ gastroplication.(14) 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).(9) 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 medium 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 in October 2013 found no active trials with EndoCinch™.

Plicator™
The available evidence on Plicator™ consists of 3 RCTs 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 (15) 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 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.(16) 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.(17) 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.(18) 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-Health Related Quality of Life (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. (19) 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%. GERD-HRQL 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 in October 2013 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® TIF consists of numerous case series, 1 small randomized controlled trial, 1 small nonrandomized study with limited follow-up, and results from a multicenter registry.

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.(17) 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. (20) 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 antireflux 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 (eg, 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 Series. 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 $_2$ system with SerosaFuse fasteners.(21) 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 end point 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 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. (22) 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 (≥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.(23) 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.(24) Bell and Freeman reported on an industry-funded series of 37 consecutive patients with PPI-resistant GERD who underwent Esophyx® fundoplication.(25) 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®.(26) 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.(27)

Other studies. Furner et al. reported an increased risk of gastric injury with laparoscopic Nissen fundoplication after failed EsophyX® fundoplication. (28) 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 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 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.

Transesophageal Radiofrequency (ie, the Stretta Procedure)

1. Does radiofrequency treatment of the gastroesophageal junction (Stretta procedure) improve outcomes for patients with GERD, compared to treatment with PPIs or to laparoscopic fundoplication?

The available evidence consists of a meta-analysis and 4 RCTs, all 4 of which include a sham placebo control, along with numerous uncontrolled case series.

Systematic review and meta-analyses. Perry et al. included 20 studies (2 RCTs and 18 case series) with a total of 1,441 patients in their meta-analysis. (29) This review analyzed the within-subjects results following treatment only. The control groups of available clinical trials were not included for comparison. Analysis of the 9 studies (525 patients) that reported subjective heartburn scores showed a significant decrease from 3.55 to 1.19 at a mean of 24.1 months. Analysis of the 9 studies (433 patients) that reported GERD-HRQL showed an improvement from 26.11 to 9.25 at a mean follow-up of 19.8 months. Analysis of the 6 studies (299 patients) that reported SF-36 physical component scores showed an improvement from 36.45 to 46.12 at a mean follow-up of 9.5 months. For the 11 studies that measured esophageal pH, significant improvements were found in the Johnson-DeMeester score (from 44.37 to 28.53), the esophageal acid exposure time (from 10.29% to 6.51%), and lower esophageal sphincter pressure (from 16.54 to 20.24). This meta-analysis is limited by the inclusion of lower quality studies and by the analysis, which only examined within-subject differences and did not include between-subjects differences, as reported in the RCTs.

Controlled trials. The 2003 TEC Assessment included one randomized, sham-controlled trial.(30) This trial enrolled patients with symptoms at least partially responsive to PPIs, a pH study showing abnormal acid exposure, and the usual exclusions including severe esophagitis or significant anatomic defect. The sham procedure involved balloon inflation but no needle deployment or energy delivery. A total of 64 patients were randomized, and partial or complete 6-month follow-up data were available on 56 patients.

The results of this trial were inconsistent. Although improvement in heartburn symptoms, quality of life, and general physical quality of life was observed in the active treatment group compared to the sham group, there were no differences in medication usage and esophageal acid exposure. Thus in terms of the objective measures of GERD, the findings are equivocal. The large proportion of sham-treated patients successfully reducing medication use points to possible placebo effect of the procedure. In

addition, data are also needed from controlled comparisons with other treatment for GERD, such as Nissen fundoplication, to better characterize outcomes relative to the risks involved.

In 2010, investigators from the U.S. and Egypt reported a 12-month randomized, double-blind, sham-controlled trial to assess RF energy applied to the gastroesophageal junction (ie, the Stretta procedure).(31) Thirty-six patients with antisecretory medication-dependent GERD for more than 6 months (mean: 7 years) were randomly assigned to receive a single-session RF procedure, a double-session RF procedure for patients who had a less than 75% improvement of GERD-HRQL at 4 months, or a sham procedure. Each patient in the active treatment groups received 56 RF lesions per session. With the double-session group, the authors examined whether 112 lesions created in 2 sessions several months apart were safer than 112 lesions created during a single session, which was the initial "dose" applied during development of the procedure and resulted in esophageal perforation in a few cases. Ten of 12 patients in the double-session group (83%) underwent both sessions.

At 12 months, 2 of 12 patients (17%) in the single-session group, 6 of 12 patients (50%) in the double-session group, and 0 of 12 patients in the sham group had discontinued antisecretory medication therapy. Within group comparisons showed statistically significant improvements in GERD-HRQL in all 3 treatment groups: In the single-session RF group, GERD-HRQL scores improved from a mean of 30 at baseline *off* meds to 14 posttreatment; in the double-session RF group, GERD-HRQL scores improved from 31 to 11; and in the sham group, GERD-HRQL scores improved from 30 to 25. Posttreatment values in the active treatment groups were significantly greater than the sham group ($p<0.001$) but did not differ from each other ($p>0.05$). Lower esophageal sphincter pressure increased in the active treatment groups to a statistically significant degree (from 12 to 16 mm Hg in the single-session group and from 12 to 20 mm Hg in the double-session group; $p<0.01$ for both groups) but not in the sham group (14 mm Hg at baseline to 16 mm Hg posttreatment, $p>0.05$). The total time esophageal pH, which was less than 4.2 in a 24-hour period decreased to a statistically significant degree in the active treatment groups (from 9.4 to 6.7 minutes in the single-session group [$p<0.01$] and from 8.8 to 5.2 minutes in the double-session group [$p<0.01$]) but not in the sham group (9.9 minutes at baseline to 8.2 minutes posttreatment [$p>0.05$]). The clinical relevance of these changes is uncertain.

Transient post-procedure adverse events (retrosternal discomfort requiring oral analgesics, mild fever, nausea/vomiting, and dysphagia) were experienced by more patients in the active treatment groups than in the sham groups. Serious adverse events occurred in 1 patient in the single-session group who developed pneumonia and bilateral pleural effusion responsive to 1 week of inpatient antibiotics. Two patients who received double sessions of RF treatment developed prolonged gastroparesis. During 12 months of follow-up evaluation, 1 of these 2 patients showed mild improvement, whereas the other showed no improvement despite high doses of prokinetic medication. The authors speculate that "[w]orsening gastroparesis may be due to vagal injury during Stretta treatment, especially with a greater number of RF lesions."

Arts and colleagues reported a double-blind randomized cross-over study of Stretta and sham treatment in 22 GERD patients.(32) The initial sham treatment in 11 patients did not affect any of the outcome measures. Three months after the RF procedure, the symptom score was significantly improved (from 14.7 to 8.3), and gastro-esophageal junction compliance was significantly decreased (17.8 vs. 7.4 mL/mm Hg). The quality-of-life score for bodily pain improved from 49.5 to 24.0. No changes were observed in PPI use, esophageal acid exposure, or lower esophageal sphincter pressure after RF. The decrease in compliance of the gastro-esophageal junction was reversed by a smooth muscle relaxant, suggesting that the effect of RF on gastro-esophageal junction compliance was not due to fibrosis.

In an unblinded randomized trial, a total of 43 PPI-dependent GERD patients either continued the effective dose of their PPI or received the RF procedure (Stretta).(33) At 6 months, significantly more patients in the treatment group were able to discontinue or decrease their PPI use by at least 50% than in the control group, a difference that was not maintained at 12 months. Some authors have suggested

that PPI discontinuation rather than dose reduction is a more meaningful outcome measure. In this study, the number of patients able to discontinue PPI medication did not differ between groups. Adverse events in the treatment group were described as “transient” and included abdominal pain or epigastric discomfort, odynophagia, and fever. There were no adverse events in the control group.

Uncontrolled studies. The 2003 TEC Assessment (1) evaluated data from 3 case series of 118, 25, and 18 patients, respectively.(34-36) All 3 studies reported improvement in symptoms and symptom-related quality-of-life measures. The largest study reported 12 months’ follow-up (34); the next largest study followed up patients only to 3 months(35); and the smallest study followed up patients to 6 months.(36)

Longer term follow-up of case series have been published. Noar reported on the 4-year follow-up of 109 consecutive patients who underwent the Stretta procedure for drug-refractory GERD.(37) Ninety-six of the 109 patients had results at 4 years; of these, medication use changed from 100% receiving twice daily PPI therapy to 75% eliminating this medication or using it only on an as-needed basis. Quality-of-life scores improved. Thirteen patients required a second procedure. Reymunde and Santiago reported on the 4-year follow-up of 83 consecutive patients with refractory GERD symptoms who were treated using RF energy.(38) Daily medication use dropped from 100% to 14%. Quality-of-life scores improved. However, long-term pH monitoring was not reported in either study.

Radiofrequency for GERD-associated gastroparesis was assessed in a 1-year prospective case series of 31 patients. (39) At 6 months, 23 patients (74%) experienced normalization of gastric emptying. Among this group, GERD-HRQL and dyspepsia symptoms showed significant improvement from baseline (on medication therapy) at 12 months. Among the remaining 8 patients, only GERD-HRQL remained significantly different from baseline (on medication) at 12 months. Minor complications resolved without sequelae and included 4 cases of dyspepsia and 1 case of minor gastric bleeding. There were no serious complications. Reports with small numbers of patients describe preliminary results on use of this procedure in those who have persistent reflux symptoms following antireflux surgery.(40)

Section Summary
Four small RCTs report improvements in symptoms and quality of life following treatment with RF energy. One of the 4 trials reports a reduction in PPI use. Two of the trials also reported a decrease in acid exposure. None of these trials report outcomes past the 12-month time period. Adverse events, including nausea/vomiting, chest pain, dysphagia, and pneumonia have been reported. Larger RCTs with longer follow-up are needed to better define the risks and benefits of this procedure.

Injection/Implantation of Prosthetics or Bulking Agents

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

<u>Enteryx Procedure</u>
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.(41) 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 U.S. Food and Drug Administration (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.(42) 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.

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(43) 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.(44) 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 (PMMA) Beads

The available evidence for this device consists of one case series. A 2001 publication on transesophageal submucosal implantation of polymethylmethacrylate (PMMA) beads consisted of a case series of 10 patients with GERD who were either refractory to or dependent on PPIs.(45) 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 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 (ie, 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 randomized controlled trials are needed to compare endoscopic procedures with both sham controls and with the currently accepted treatments for gastroesophageal reflux disease (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 (Health-Related Quality of Life) 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.

Practice Guidelines and Position Statements

Updated guidelines released by the American College of Gastroenterology in 2013 state that the usage of current endoscopic therapy or transoral incisionless fundoplication cannot be recommended as an alternative to medical or traditional surgical therapy. (Conditional recommendation, moderate level of evidence).(46)

The Society of American Gastrointestinal Endoscopic Surgeons (SAGES) provided updated guidelines on endoluminal treatments for GERD in 2013.(47) SAGES gave a weak recommendation based on low-quality evidence for the EsophyX procedure, stating that long-term data is not yet available and that further studies are required to define optimal techniques and most appropriate patient selection criteria, and to further evaluate device and technique safety. SAGES gave a strong recommendation based on high-quality evidence that Stretta is considered appropriate therapy for patients being treated for GERD who are 18 years of age or older, who have had symptoms of heartburn, regurgitation, or both for 6 months or more, who have been partially or completely responsive to antisecretory pharmacologic therapy, and who have declined laparoscopic fundoplication.

The American Society of General Surgeons (ASGS) issued a position statement on transoral fundoplication in 2011 stating that “the ASGS supports the use of transoral fundoplication by trained General Surgeons for the treatment of symptomatic chronic gastroesophageal reflux disease (GERD) in patients who fail to achieve satisfactory response to a standard dose of Proton Pump Inhibitor (PPI) therapy or for those who wish to avoid the need for a lifetime of medication dependence.”(48)

The 2008 Medical Position Statement of the American Gastroenterological Association(49) makes no recommendation for or against “the use of currently commercially available endoluminal antireflux procedures in the management of patients with an esophageal syndrome” based on insufficient evidence (Grade Insufficient).

The National Institute for Health and Care Excellence (NICE) of the National Health Service of Great Britain issued updated interventional procedure guidance in 2013 on endoscopic radiofrequency treatment for GERD, concluding: “The evidence on the safety of endoscopic radiofrequency ablation for gastro-esophageal reflux disease is adequate in the short and medium term but there is uncertainty

about longer-term outcomes. With regard to efficacy, there is evidence of symptomatic relief but objective evidence on reduction of reflux is inconclusive. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research."(50) The reviewing committee noted "concern on the part of some specialists about the possibility that symptoms may improve as a result of denervation caused by the procedure; if that were the case then failure to recognize and treat reflux might lead to complications in the long term."

NICE issued guidance in 2011 on endoluminal grastroplication for GERD, concluding that "The evidence on endoluminal gastroplication for gastro-esophageal reflux disease raises no major safety concerns. Evidence from a number of randomized controlled trials (RCTs) shows a degree of efficacy in terms of reduced medication requirement in the short term, but changes in other efficacy outcomes are inconsistent and there is no good evidence of sustained improvement in esophageal pH measurements. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research."(51)

2004 Guidance from NICE on regarding bulking agents for GERD found that "Current evidence on the safety and efficacy of endoscopic injection of bulking agents for gastro-esophageal reflux disease does not appear adequate for this procedure to be used without special arrangements for consent and for audit or research."(52)

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Billing Coding/Physician Documentation Information

43200 Esophagoscopy, flexible, transoral; diagnostic, including collection of specimen(s) by brushing or washing, when performed (separate procedure) (code descriptor revised 1/1/14)

43201 Esophagoscopy, flexible, transoral; with directed submucosal injection(s), any substance (code descriptor revised 1/1/14)

43212 Esophagoscopy, flexible, transoral; with placement of endoscopic stent (includes pre- and dilation and guide wire passage, when performed) (new code 1/1/14)

43236 Esophagogastroduodenoscopy flexible, transoral; with directed submucosal injection(s), any substance (Code descriptor revised 1/1/14)

43257 Esophagogastroduodenoscopy, flexible, transoral; with delivery of thermal energy to the muscle of lower esophageal sphincter and/or gastric cardia, for treatment of gastroesophageal reflux disease (code descriptor revised 1/1/14)

43266 Esophagogastroduodenoscopy, flexible, transoral; with placement of endoscopic stent (includes pre- and post-dilation and guide wire passage, when performed.) (new code 1/1/14)

43499 Unlisted procedure, esophagus

Transesophageal endoscopic gastroplasty no longer has a specific code and would most likely be reported with code 43499 – unlisted procedure, esophagus.

There is a CPT code specific to the radiofrequency procedure:
43257: Esophagogastroduodenoscopy, flexible, transoral; with delivery of thermal energy to the muscle of lower esophageal sphincter and/or gastric cardia, for treatment of gastroesophageal reflux disease.

Endoscopic submucosal injection of a bulking agent would most likely be coded using 43201 - Esophagoscopy, flexible, transoral; with directed submucosal injection(s), any substance – or code 43236 – Esophagogastroduodenoscopy, flexible, transoral; with directed submucosal injection(s), any substance.

Endoscopic implantation of a prosthesis would most likely be coded using code 43212 – Esophagoscopy, flexible, transoral; with placement of endoscopic stent (includes pre- and postdilation and guide wire passage, when performed), code 43266 – Esophagogastroduodenoscopy, flexible, transoral; with placement of endoscopic stent (includes pre- and postdilation and guide wire passage, when performed), – or code 43499 – unlisted procedure, esophagus.

Additional Policy Key Words

- EndoCinch, Treatment for Gastroesophageal Reflux Disease
- Endoscopic Gastroplasty or Gastroplication
- Enteryx
- Gastroesophageal Reflux Disease (GERD), Transesophageal Therapies
- Gastroplasty or Gastroplication, Endoscopic
- GERD, Transesophageal Therapies
- Radiofrequency Ablation, Gastroesophageal Junction
- Stretta Procedure
- Transesophageal Therapies of GERD

Policy Implementation/Update Information

2/1/01	New policy. Added to Surgery section, considered investigational.
2/1/02	Policy statement revised to include endoscopic submucosal implantation of polymethylmethacrylate beads into the lower esophageal as investigational.
2/1/03	No policy statement changes.
2/1/04	Policy statement revised to include endoscopic submucosal implantation of a biocompatible polymer (i.e., Enteryx™) as investigational.
2/1/05	No policy statement changes.
2/1/06	No policy statement changes.
2/1/07	No policy statement changes.
2/1/08	No policy statement changes.
2/1/09	No policy statement changes.
2/1/10	No policy statement changes.
2/1/11	No policy statement changes.
2/1/12	Policy statements on biocompatible polymer and PMMA beads combined as bulking agents; remains investigational
2/1/13	No policy statement changes.
2/1/14	No policy statement changes. Added new codes revised and deleted for 2014.
