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Subject  Endoscopic Anti-Reflux Procedures

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Coverage Policy

Cigna does not cover any of the following endoscopic anti-reflux procedures for gastroesophageal reflux disease (GERD) because each is considered experimental, investigational or unproven (list may not be all inclusive).

- radiofrequency energy to the gastroesophageal junction (e.g., Stretta® System)
- endoluminal gastroplasty/gastroplications (e.g., SRS™ Endoscopic Stapling System, EndoCinch™ or Bard™ Endoscopic Suturing System [BEES], Endoscopic Plication™ System, Syntheon ARD Plicator, Esophyx™ System, StomaphyX™)
- injection/implantation of biocompatible material (e.g., plexiglas or polymethylmethacrylate [PMMA], Durasphere™, Gatekeeper™ Reflux Repair System; LINX™ Reflux Management System)

General Background

Gastroesophageal reflux disease (GERD) is defined as symptoms or mucosa damage resulting from the reflux of gastric content into the esophagus. Mucosa damage can vary from none, to mild esophagitis, to more severe esophagitis, and, less commonly, Barrett’s esophagus and esophageal carcinoma. The goal of therapy is to control both the symptoms and mucosal damage.

Treatment for GERD may include lifestyle changes (e.g., elevating the head of the bed, decreasing fat intake, quitting smoking, diet), pharmacological therapy (e.g., acid suppressants) or anti-reflux surgery. The majority of GERD patients have mucosal disease, and symptoms are controlled with medical therapy. Anti-reflux surgery
may be an option for patients who have failed pharmacotherapy or for those who choose not to continue on medication therapy for the long term. An open or laparoscopic Nissen fundoplication may be considered for patients and is considered the standard surgical therapy.

**Endoscopic Therapies**

A variety of endoscopic therapies for the treatment of GERD have been developed and proposed as alternatives to pharmacological therapy or anti-reflux surgery. These techniques include the delivery of radiofrequency energy to the gastroesophageal junction, injection of bulking agents, or implantation of a bioprosthesis into the lower esophageal sphincter, implantation of titanium beads with magnetic cores and suture plication of the proximal gastric folds. These therapies are designed to alter structures at the gastroesophageal junction to prevent reflux of gastric contents (ECRI, 2012b; Richter, 2010).

Recent textbook literature reports most studies of endoscopic therapy have only limited follow-up information on a relatively small number of patients. The durability of these techniques beyond one to two years remains unclear and seems to gradually decrease over time. Most importantly, safety issues have resulted from these procedures, especially when used in the broader community of gastroenterologists. Chest pain, bleeding, esophageal perforations, mediastinitis, and at least eight deaths to date have been attributed to these endoscopic techniques (Richter, 2010). Currently, endoscopic therapies are not advocated in routine practice.

**Radiofrequency Energy:** Radiofrequency energy for the treatment of GERD requires a special single-use catheter and radiofrequency energy generator (Stretta® System, [currently manufactured by Mederi Therapeutics, Greenwich, CT]). The procedure is generally performed using standard conscious sedation but has required general anesthesia in some patients. The possible mechanisms of action that result from radiofrequency energy are scarring or neurolysis at, or near, the gastroesophageal junction. This procedure is commonly referred to as the Stretta procedure (Falk, et al., 2006a). It has been reported that this procedure is no longer commercially available (Watson, et al., 2010).

**Gastroplasty/Gastroplication:** There are two basic techniques designed to place sutures or staples at the cardia, including submucosal stitching devices and deep transmural plicating devices. Both techniques create pleats or plications of tissue just beneath the gastroesophageal junction. Sedation required for this technique varies as does procedure time. Examples of suturing/plication devices include the SRS™ Endoscopic Stapling System (MediGus Ltd.,Omer, Israel), the EndoCinch™ or Bard Endoscopic Suturing System (BESS) (Bard Endoscopic Technologies, Billerica, MA); the full-thickness NDO Surgical Endoscopic Plication™ System (NDO Surgical, Inc., Mansfield, MA); and the Syntheon ARD Plicator (Syntheon, Miami, FL).

The EsophyX™ system (EndoGastric Solutions, Inc., Redmond, WA) creates a transoral incisionless fundoplication® (TIF). The EsophyX system deploys multiple full thickness serosa-to-serosa fasteners into the gastric wall to form an interrupted suture line at the base of the gastroesophageal junction, thus recreating the gastroesophageal valve mechanically. This is sometimes referred to as the endoluminal fundoplication (ELF) technique. The predicate device to the EsophyX system is the StomaphyX™ (EndoGastric Solutions, Inc., Redmond, WA) (Demyttenaere, et al., 2010; ECRI, 2010).

**Injection/Implantation Techniques:** Bulking agents are substances injected under endoscopic guidance into the esophageal wall at the level of the esophagogastric junction to impede reflux (American Society for Gastrointestinal Endoscopy [ASGE]), 2007). In the 2006 American Gastroenterological Association (AGA) technical review on the use of endoscopic therapy for GERD, the authors reported that “there are no longer any devices that require injection of bulking agents or implantation of a bioprosthesis in the lower esophageal sphincter zone” (Falk, et al., 2006a). Implantable products/devices include:

- LINX™ Reflux Management System (Torax® Medical, Inc; St Paul, MN). The LINX Reflux Management System is an implant that consists of a small flexible band of interlinked titanium beads with magnetic cores. The magnetic attraction is proposed to help the lower esophageal sphincter (LES) resist opening to gastric pressures, preventing reflux from the stomach into the esophagus. A surgeon uses a laparoscopic incision to implant the device around the patient’s esophagus just above the stomach while the patient is under general anesthesia (ECRI, 2012a).
- expandable hydrogel prosthesis (Gatekeeper™ Reflux Repair System; Medtronic, Inc., Minneapolis, MN). It has been reported that the device was withdrawn in late 2005 before U.S. Food and Drug Administration (FDA) approval. A European sham-controlled single-blind multicenter study randomized
118 patients into Gatekeeper or sham treatment. The study was terminated early due to a lack of
efficacy (Fockens, et al., 2010).
- ethylene vinyl alcohol copolymer with tantalum dissolved in dimethyl sulfoxide (Enteryx™; Boston
  Scientific Corp, Natick, MA).
- plexiglas polymethylmethacrylate microspheres (PMMA). This agent is not commercially available in the
  United States).
- pyrolytic carbon-coated graphite beads suspended in a water-based carrier gel suitable for suspending
  the carbon-coated beads (Durasphere™, Carbon Medical Technologies, St Paul, MN). Durasphere is an
  injectable bulking agent that is being proposed in the treatment of mild-moderate GERD. A small
  nonrandomized study (n=10) was conducted by Ganz et al (2009). This study is the first report of
  Durasphere for the treatment of GERD. On the basis of the findings and limitations of this study, further
  investigation of this agent is warranted including large controlled studies with long-term outcomes.

Adverse Events
Madan et al. (2006) summarized the adverse events of endoluminal therapies for the treatment of GERD. The
FDA Manufacturer and User Facility Device Experience data base (MAUDE) was searched to examine all
voluntary adverse events reported on emerging endoluminal therapies. The adverse events were divided into
three categories: radiofrequency ablation, injection, and suture. A total of 50 adverse events were reported on
four specific therapies. Half of the complications were a result of injection-based therapy, and 44% of the
complications were found to result in radiofrequency ablation-based therapy. A total of eight deaths were
reported (i.e., five in the injection group and three in the radiofrequency ablation group). Sixty-four percent of the
adverse events resulted in hospitalizations, and 10% of the patients required surgery.

U.S. Food and Drug Administration (FDA)
Torax Medical, Inc; obtained FDA Premarket Approval (PMA) in March 2012 to market the LINX Reflux
Management System. According to documents submitted to FDA, the device “is intended for people diagnosed
with gastroesophageal reflux disease who continue to have chronic symptoms, despite the use of maximum
medical therapy for the treatment of reflux” (FDA, 2012).

The Stretta System (FDA, 2000a), EndoCinch™ or Bard Endoscopic Suturing System (FDA, 2000b), NDO
Surgical Endoscopic Plication System (FDA, 2003), Esophyx System (FDA, 2007), Esophyx2™ System (FDA,
2009), SRS™ Endoscopic Stapling System (FDA, 2012) and Stomaphyx™ (FDA, 2007) have been approved
through the 510(k) premarket notification process. The Syntheon ARD Plicator, Gatekeeper Reflux Repair
System, and PMMA are not FDA-approved devices.

The Bard® Endoscopic Suturing System FDA indications for use state, “used for endoscopic placement of
suture(s) in the soft tissue of the esophagus and stomach and for the approximation of tissue for the treatment
of symptomatic GERD” (FDA, 2000b).

The Esophyx2 System FDA indications for use state, “indicated for use in transoral tissue approximation, full
thickness plication and ligation in the GI tract and is indicated for the treatment of symptomatic chronic
gastroesophageal reflux disease in patients who require and respond to pharmacological therapy. It is also
indicated to narrow the gastroesophageal junction and reduce hiatal hernia < 2cm in size in patients with
symptomatic chronic gastroesophageal reflux disease” (FDA, 2009b).

The NDO EP NDO Surgical Endoscopic Plication System FDA indications for use state,” indicated for the
treatment of the symptoms of chronic GERD in patients who require and respond to pharmacological therapy”
(FDA, 2003).

The SRS Endoscopic Stapling System FDA indications for use state, “intended for endoscopic placement of
surgical staples in the soft tissue of the esophagus and stomach in order to create anterior partial fundoplication
for treatment of symptomatic chronic Gastro Esophageal Reflux Disease (GERD) in patients who require and
respond to pharmacological therapy” (FDA, 2012).

The Stomaphyx FDA indications for use state, “is indicated for use in endoluminal transoral tissue
approximation and ligation in the GI tract” (FDA, 2007).

Although FDA approved for GERD in April 2003, the FDA issued Advice for Patients with Enteryx for Gastroesophageal Reflux Disease, stating Boston Scientific has recalled all Enteryx Procedure Kits and Enteryx Single Pack Injectors because of reports that improper injection procedures can lead to serious patient injury or death (FDA, 2009a).

Durasphere™ received PMA-Premarket Approval in 1999. The FDA approval order statement states that, “this device is indicated for use in the treatment of adult women with stress urinary incontinence due to intrinsic sphincter deficiency” (FDA, 1999). There is no FDA indication for the treatment of GERD.

**Literature Review**

**Transoral Incisionless Fundoplication (EsophX System):** Evidence in the published, peer-reviewed scientific literature on the efficacy of transoral incisionless fundoplication (TIF) using the Esophyx system largely consists of case series. While these case series report improvements in outcomes following treatment with Esophyx, the lack of control group precludes the ability to generalize findings and draw strong conclusions regarding the impact on health outcomes. Randomized controlled trials with longer follow-up are needed to determine whether Esophyx improves outcomes compared to alternative treatment modalities.

In a multicenter prospective study, Bell et al. (2012) evaluated the safety and efficacy of TIF using the Esophyx system within different GERD subgroups (n=100) at six month follow-up. In addition, the authors attempted to identify factors associated with clinical success in patients undergoing TIF. Inclusion criteria: Age 18–75 years, GERD duration > 1 year, moderate to severe typical or atypical GERD symptoms off proton pump inhibitor (PPI)s, complete (responders) or partial (nonresponders) symptom control on PPIs. There was on comparator. Primary outcomes measured included the elimination of daily typical or atypical GERD symptoms or clinically significant improvement in global symptoms at six-month follow-up compared with baseline. The secondary effectiveness endpoints were: elimination of PPI usage; normalization or clinically significant improvement in esophageal acid exposure or number of reflux episodes measured objectively by 48-hour pH or 24-hour impedance/pH testing; healing of reflux esophagitis; and reduction of hiatal hernia. Intraoperative and postoperative serious adverse events were evaluated and patients were evaluated for common postfundoplication side effects of dysphagia, bloating, and flatulence. No adverse events were reported. Median heartburn and regurgitation scores improved significantly, from 18 (range 0-30) and 15 (range 0-30) on PPIs before TIF to 3 (range 0-25) and 0 (range 0-25), respectively; p<0.001. Median Reflux Symptom Index scores were reduced after TIF from 24 (range 14-41) to 7 (range 0-44); p<0.001. Eighty percent of patients were completely off PPIs after TIF versus 92% of patients on PPIs before TIF. Preoperative factors associated with clinical outcomes were less severe heartburn (total GERD-HRQL ≤ 30, p=0.02) and the presence of esophagitis (p<0.02). Reported limitations include the duration of follow-up and possibility of patient selection bias.

In a randomized controlled trial, Svoboda et al. (2011) evaluated the safety and efficacy of Natural Orifice Transluminal Surgery (NOTES) TIF procedures. Patients indicated for surgery of GERD were randomly assigned (ratio 2:1) to TIF n=34 and control group, where gold standard Nissen laparoscopic fundoplication (NLF) was performed (NLF group, n=18). For TIF the Plicator® method was initially used for 18 patients, but the company terminated production in 2008 without a follower. During the last two years the Esophyx® method was used for 16 patients. After the evaluation of 34 TIF patients and 18 NLF patients, similar efficacy of TIF procedures compared with NLF after three and 12 months. The hospital stay was significantly shorter (p<0.0001) in TIF group (average, 2.9±0.8 days) than in NLF group (6.4±0.7). There was one serious adverse event in the TIF group and three in the NLF group. The limitations of this study are the small sample size and lack of long-term follow-up.

Frazzoni et al. (2011) prospectively assessed reflux parameters before and after Esophyx or laparoscopic fundoplication and their relationship with symptoms in refractory GERD in 10 patients. The investigators reported that Esophyx fundoplication is significantly less effective than laparoscopic fundoplication in improving reflux parameters and accordingly, in inducing symptom remission.

In a retrospective study, Ihde et al. (2011) evaluated the safety and symptomatic outcomes of the TIF procedure with or without hiatal hernia repair (HHR) in patients with chronic GERD. Forty-eight patients underwent TIF using Esophyx in three community hospitals. Patients who presented with a hiatal hernia 3 cm or more in the
In a case series study, Velanovish et al. (2010) reports on their initial experience with the EsophyX System. Patients considered candidates for endoscopic fundoplication included those with symptomatic GERD, a small (<2 cm) hiatal hernia, objective pathologic evidence of GERD, and an absence of other esophageal motility disorders. Symptom severity was measured with the GERD-HRQL instrument (best possible score 0, worst possible score 50). The patients were followed-up for complications and symptom improvement. A total of 26 procedures were performed. The major complication rate was 11/26, including esophageal perforation, hemorrhage requiring transfusion, and permanent numbness of tongue. At a median of nine years (range 1-35 years) and were on daily double-dose of PPIs for a median of eight years (range 1-25); 97% reported ineffectiveness of symptom control on medical therapy. Of 123 patients treated successfully, 110 (89%) gave consent for follow-up and completed GERD-specific questionnaires (baseline data were based on recall). Five patients underwent laparoscopic Nissen revision and were considered lost to follow-up, rather than treatment failures. Valves in two of these five patients were reported to have been disrupted due to retching and severe cough. At a median seven-month follow-up (range 5-17), typical and atypical symptom scores were normalized in 75—80% of patients, proton pump inhibitors (PPIs) were completely discontinued by 93%, and 83% were satisfied with their current health condition. Endoscopy in 53 patients revealed Hill grade I tight valves in 89% of the cases, reduced hiatal hernia in 33/34 (97%), and healed reflux esophagitis in 25/30 (83%). Based on global analysis, 72% of the patients were in remission, 20% improved symptomatically, and only 8% had ongoing GERD. The limitation of this study is the short-term follow-up, lack of a control group and lack of pH measuring systems.

In a case series study, Hoppo et al. (2010) reported on the efficacy of transoral incisionless fundoplication (TIF) using the EsophyX system. Patients were selected for treatment if they had typical GERD symptoms, failed management with PPIs, a positive esophageal pH test with symptom correlation, and no hiatal hernia larger than 2 cm. Nineteen patients underwent the TIF. The major complication rate was 3/19, including esophageal perforation, hemorrhage requiring transfusion, and permanent numbness of tongue. At mean 10.8 months follow-up, 5/19 had completely discontinued PPIs, and 3/19 had decreased their PPI dose. However, 10/19 had been converted to laparoscopic fundoplication for recurrent reflux symptoms and an endoscopically confirmed failed valve. Nine of 17 were dissatisfied with the outcome, and eight were satisfied. Thirteen of 19 (68%) were considered to have been unsuccessful. The authors reported that at short-term follow-up, the TIF procedure is associated with an excessive early symptomatic failure rate, and a high surgical re-intervention rate. This procedure should not be performed outside of a clinical trial.

In a case series study, Bell et al. (2011) reported on the efficacy and safety of a rotational/longitudinal esophagogastric transoral incisionless fundoplication (TIF) using the EsophyX system. A total of 37 consecutive patients on antisecretory medication and with proven gastroesophageal reflux and limited hiatal hernia underwent TIF for persistent GERD symptoms. Five patients were reoperations for failed laparoscopic fundoplication. Sixty-eight percent of the patients indicated GERD-associated cough, asthma, or aspiration as a primary complaint and 32% complained of heartburn or regurgitation. Two complications occurred: one mediastinal abscess treated laparoscopically and one postoperative bleeding requiring transfusion. At six (range=3–14) months median follow-up TIF resulted in a significant improvement of both atypical and typical symptoms in 64% and 70–80% of patients, respectively, as indicated by the corresponding GERD health-related quality of life (HRQL) and reflux symptom index (RSI) score reduction by 50% or more compared to baseline on proton pump inhibitors (PPIs). No patient reported problems with dysphagia, bloating, or excess flatulence, and 82% were not taking any PPIs. Reflux characteristics were significantly improved and normalized in 61, 89, and 56% of patients in terms of acid exposure, number of refluxates, and DeMeester scores, respectively. TIF was effective in treating GERD in 75% of patients among whom 54% were in a complete “remission” and 21% were “improved.” The remaining 25% were considered failures, and five (13.5%) patients underwent revision. The reported limitations of this study are the small sample size and lack of long-term follow-up.
patients underwent an attempted endoscopic fundoplication. Two patients could not be completed because of the inability to pass the device. Of the 24 patients who underwent endoscopic fundoplication, 20 had the typical symptoms of GERD, four had symptoms of laryngopharyngeal reflux, and four had recurrent symptoms after a Nissen fundoplication. There was one major complication of a gastric mucosal tear that led to bleeding and the need for a blood transfusion. Nineteen (79%) patients reported satisfaction with their symptom relief. Of those dissatisfied, two had symptoms of laryngopharyngeal reflux, one had functional heartburn, one had associated gastroparesis, and one had failure with GERD. The median GERD-HRQL score improved from 25 (interquartile range, 19.5-28.5) to five (interquartile range, 3-9; p=0.004). The reported limitations of this study are small sample size and short-term follow-up of six to eight weeks. The authors reported that subsequent trials are needed to assess the long-term effectiveness of the technique.

In a case series study, Testoni et al. (2010) assessed the effect of transoral incisionless fundoplication (TIF) using the new (2.0) version of the EsophyX device on symptoms, PPI use, esophageal motility, and pH impedance findings in a consecutive series of patients with symptomatic GERD. The EsophyX 2.0 system deploys fasteners starting at the posterior and anterior sides of the gastroesophageal valve rather than at the middle of the valve. Eighteen patients, who had pathological GERD before the procedure, as measured by pH-impedance, were included in the outcomes analysis; two patients with normal 24-hour pH-impedance at baseline were excluded. At six months, 10 of the 18 patients (56%) had discontinued daily PPI therapy. GERD-HRQL scores improved from a mean of 45 at baseline off PPI to 16 post-treatment, a statistically significant improvement (p=0.001). However, the post-treatment value did not appear to be different from the baseline score on PPI. There were significantly fewer acid and non-acid reflexes. There was no significant difference in lower esophageal sphincter (LES) pressure or pH. Small hiatal hernias (<3cm) were eliminated in eight of 13 patients (62%) who had hernias at baseline. No serious complications arose. All patients reported transient pharyngeal irritation and moderate epigastric pain not requiring analgesics at the time of the procedure. The limitations of this study are the small sample size, uncontrolled design and the short follow-up period.

In a case series study (n=26), Demyttenaere et al. (2010) evaluated patients undergoing EsophyX fundoplication for a one-year period between September 2007 and March 2009. Patients referred for surgical management of GERD were given the option of undergoing endolumenal fundoplication. Two complications of postoperative bleed occurred, requiring transfusion. The mean follow-up period was 10 months. Although 68% of the patients were still taking antireflux medications, 21% had reduced their dose by half. Three patients had persistent symptoms requiring Nissen fundoplication, and there was one late death unrelated to the procedure. Both symptoms and health-related quality-of-life (HRQL) scores significantly improved after treatment. The authors reported that further study with pH testing and endoscopic evaluation of the neovalve are required. Increased experience will help to identify the patient population most likely to benefit from transoral incisionless fundoplication compared with other treatments. This study is limited by the lack of a control group and small sample size.

Cadiére et al. (2009) reported on two-year follow-up results from a feasibility study of the EsophyX procedure. The study included 14 of 19 patients from the original case series (Cadiére, et al., 2008a). Two patients were excluded from the original study due to gastric anomalies, two patients underwent surgical treatment or repeat endoscopic gastroplasty, and one patient was lost to follow-up. All patients had PPI-dependent GERD for more than six months. At two years, 10 patients (71%) had discontinued daily PPI therapy. GERD-Health-Related Quality of Life (HRQL) scores improved from a median of 17 at baseline on PPIs to seven post-treatment, a statistically significant improvement (p=0.004). GERD-HRQL scores <12 (indicative of heartburn elimination) were reported by 13 patients (93%). pH scores normalized in all patients, regardless of clinical response to treatment. Small hiatal hernias were eliminated in six of ten patients (60%) who had hernias at baseline. Although patients reported transient pharyngeal irritation, bloating, and mild epigastric pain at the time of the procedure, no adverse procedure-related events were reported at two-year follow-up. The authors reported that although the presented two-year results were encouraging, they had a limited value for generalization because of the small study population and the exclusion of patients who required retreatment. A multicenter study is currently underway to evaluate the long-term efficacy of TIF in eliminating symptoms and normalizing acid exposure.

In a case series study (n=20), Repici et al. (2010) evaluated the six and 12 month clinical results of endoluminal fundoplication (ELF) with EsophyX. All patients had PPI-dependent GERD for at least six months. Four patients with persistent GERD symptoms despite the use of standard PPI doses were scheduled for laparoscopic fundoplication at month six, and one patient was lost to follow-up. Seven patients (35%) had discontinued PPI
therapy at 12 months. Eleven patients (55%) had an improved GERD-HRQL >50% (median baseline GERD-HRQL = 40). There was no significant change from baseline in mean LES pressure and acid or non-acid reflux. Two additional patients (for a total of six of 20 patients, 30%) were scheduled for laparoscopic surgery after the 12-month follow-up for persistence of symptoms. Serious adverse events occurred in two patients with hematemesis on the first and eighth postoperative day. Of note, in the four patients who underwent laparoscopic fundoplication at six months, fasteners were found partially extruded as if the stomach wall had disengaged from the H suture, which was still present on the esophageal side. The authors reported that based on their experience, ELF with EsophyX should still be considered an investigational procedure with no role in routine treatment of GERD.

In a prospective study, Cadière et al. (2008b) evaluated the safety and efficacy of transoral incisionless fundoplication (TIF) using the EsophyX system in the treatment of GERD. A total of 86 patients with chronic GERD treated with PPIs were enrolled. Exclusion criteria included an irreducible hiatal hernia > 2 cm. The TIF procedure (n=84) reduced all hiatal hernias (n=49) and constructed valves measuring 4 cm (2–6 cm) and 230 degrees (160–300 degrees). At 12 months, 73% of the study participants had 50% or greater improvement in GERD health-related quality life scores. A total of 85% of the study participants discontinued daily PPI use, and 81% had complete cessation of PPIs. Less than 37% had normalization of esophageal acid exposure. EsophyX-TIF cured GERD in 56% of patients based on their symptom reduction and PPI discontinuation. Serious adverse events consisted of two esophageal perforations upon device insertion and one case of postoperative intraluminal bleeding. Other adverse events were mild and transient.

Additional clinical trials for EsophyX are limited to observational case series that do not allow for conclusions about durability and long-term effectiveness (Muls, et al., 2013; Trad, et al., 2012; Narsule, et al., 2012; Testoni, et al., 2012). A cohort study of 38 patients reported that endoluminal fundoplication improved quality of life and reduced the need for PPIs in only a subgroup of patients at three years follow-up. The amount of patients requiring additional medication and revisional surgery was high (Witteman, et al., 2012).

Radiofrequency Energy (Stretta Procedure): Improvements in symptoms, quality of life, reduction in PPI use and decreased acid exposure following treatment with radiofrequency energy have been reported in a few of the studies. None of the studies reported long-term outcomes. Adverse events including chest pain, dysphagia, and pneumonia have been reported. Larger randomized controlled trials with longer follow-up are needed to better define the risks and benefits of this procedure.

Perry et al. (2012) conducted a systematic review and meta-analysis of randomized controlled trials and cohort studies to assess the impact of endoscopic application of radiofrequency energy to the lower esophageal sphincter for the treatment of GERD. The studies included in this meta-analysis were two randomized sham-controlled trials and 18 cohort series with a mean follow-up of 15 months. Outcomes analyzed included GERD symptom assessment, quality of life, esophageal pH, and esophageal manometry. The authors reported that the meta-analysis is limited by differences in methodology and definition of criteria for some variables between studies, and absence of blindness in most of the included studies. Additionally, the heterogeneity of the study population across these reports may also influence the interpretation of the pooled results. The author’s conclusion states that “radiofrequency ablation of the LES produces significant improvement in GERD symptoms, patient satisfaction, and QOL at short and intermediate term follow-up. These findings suggest that the Stretta represents a viable treatment option for select patients with symptomatic GERD. Larger and longer-term studies are required to establish the durability of the treatment effect, and to identify the patient populations that gain the greatest benefit from this treatment.”

Arts et al. (2012) conducted a double-blind randomized cross-over study of Stretta and sham treatment. Patients underwent two upper gastrointestinal endoscopies with three months interval, during which active or sham Stretta treatment was performed in a randomized double-blind manner. In all, 22 GERD patients participated in the study; 11 in each group. Barostat distensibility test of the GEJ before and after administration of sildenafil was the main outcome measure. Initial sham treatment did not affect any of the parameters studied. Three months after initial Stretta procedure, no changes were observed in esophageal acid exposure and lower esophageal sphincter (LES) pressure. In contrast, symptom score was significantly improved and gastro-esophageal junction (GEJ) compliance was significantly decreased. Administration of sildenafil, an esophageal smooth muscle relaxant, normalized GEJ compliance again to pre-Stretta level, arguing against GEJ fibrosis as the underlying mechanism. The authors reported that Stretta improved GERD symptoms and decreased GEJ
compliance. According to the authors, the limitation of this study was reflux evaluation did not include impedance monitoring. The study was also limited by a small sample size, short term follow-up and lack of comparison to other surgical alternatives.

Aziz et al. (2010) conducted a 12-month randomized, double-blind, sham-controlled trial to assess the Stretta procedure. Thirty-six patients with antisecretory medication-dependent GERD for more than six months were randomized to receive a single-session radiofrequency (RF) procedure, a double-session RF procedure for patients who had < 75% improvement of GERD-HRQL at four 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 two 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, two of 12 patients (17%) in the single-session group, six of 12 patients (50%) in the double-session group, and zero of 12 patients in the sham group had discontinued antisecretory medication therapy. Within group comparisons showed statistically significant improvements in GERD-HRQL in all three treatment groups: In the single-session RF group, GERD-HRQL scores improved from a mean of 30 at baseline off meds to 14 post-treatment; 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. Post-treatment 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 mmHg to 16 mmHg in the single-session group, and from 12 mmHg to 20 mmHg in the double-session group; p<0.01 for both groups) but not in the sham group (14 mmHg at baseline to 16 mmHg post-treatment, p>0.05). The total time esophageal pH was less than 4.2 in a 24-hour period decreased to a statistically significant degree in the active treatment groups (from 9.4 minutes to 6.7 minutes in the single-session group (p<0.01), and from 8.8 minutes 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 post-treatment (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 one patient in the single-session group who developed pneumonia and bilateral pleural. Two patients who received double sessions of RF treatment developed prolonged gastroparesis. During 12 months of follow-up evaluation, one of these two patients showed mild improvement, whereas the other showed no improvement despite high doses of prokinetic medication. The authors reported that "worsening gastroparesis may be due to vagal injury during Stretta treatment, especially with a greater number of RF lesions."

Coron et al. (2008) conducted an unblinded randomized trial of 43 PPI-dependent GERD patients who continued the effective dose of their PPI (n=20) or received the radiofrequency Stretta procedure (n=23). At six 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. 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 epigastric discomfort or abdominal pain, odynophagia and fever. There were no adverse events in the control group. This study was interrupted prematurely because of the decision of Curon Ltd to stop the commercialization of Stretta devices. The authors report that at one year data are difficult to interpret because of the relatively small number of patients remaining in the trial.

In a prospective study, Noar et al. (2007) reported on data from a series of 109 consecutive drug-refractory GERD patients treated with the Stretta procedure who reached four-year follow-up assessment. Heartburn scores, total heartburn scores, and patient satisfaction improved (p<0.001). Medication usage decreased from 100% in patients who were on twice-daily PPI therapy at baseline to 75% of patients showing elimination of medications, or only as-needed use of antacids/over-the-counter PPIs, at 48 months (p<0.005). The authors reported no serious complications related to the procedure. The authors stated the limitations of this study are the lack of a comparative group and no long-term pH or motility studies. Similar findings were reported in a prospective study of 83 patients by Reymunde et al. (2007).

Lutfi et al. (2005) reported on data from their three-year experience with the Stretta procedure. GERD was documented by a positive 24-hour pH study. Patients were excluded from the study for the following: a hiatal hernia > 3 cm, a lower esophageal sphincter (LES) pressure < 8mm Hg, Barrett’s esophagus, active grade 3 or 4 esophagitis, American Society of Anesthesiologist 4, age < 18 years, and pregnancy. Patients were mailed
SF-12 health status questionnaires and GERD-specific quality of life questionnaires, questions about satisfaction with Stretta and medication use. Seventy-seven patients with follow-up times > six months qualified for the study. Follow-up surveys were completed by 61 patients. Sixty-one percent of the patients were satisfied with the procedure. There were no long-term procedure-related complications. Twenty-six patients were completely off PPI at follow-up. There were 39 responder patients who were taking ≤ 50% of their original dosage or were completely taken off their medications. Twenty-two patients who remained on the same preoperative dosage or reduced their original dose by 50% were considered nonresponders, including eight patients who underwent Nissen fundoplication. The overall satisfaction rate was 73%. Ninety-five percent of the responders were satisfied, while only 41% of the nonresponders were satisfied and said they would have the procedure again. Twenty-four patients who completed the questionnaires agreed to undergo the 24-hour pH study, including 18 responders and six nonresponders. There was an improvement in distal acid exposure for those patients who had the 24-hour pH study (7.8 ± 2.6% to 5.1 ± 3.3; p=0.001). The authors stated the limitations of this study are the small number of patients responding and the small number of patients who agreed to come back for the 24-hour pH study. Furthermore, the authors stated longer term studies with more complete follow-up are needed to fully assess the role of Stretta in the management of GERD.

In a randomized study, GERD patients received radiofrequency energy delivery to the gastroesophageal junction (n=35) or to a sham procedure (n=29). Principal outcomes were reflux symptoms and quality of life. Secondary outcomes were medication use and esophageal acid exposure. After six months, interested sham patients crossed over to active treatment. Results at six months indicate active treatment significantly and substantially improved patients’ heartburn symptoms and quality of life. More active (61%) versus sham (33%) patients were without daily heartburn symptoms and more had a > 50% improvement in their GERD quality of life score (61% versus 30%). Symptom improvements persisted at 12 months after treatment. At six months, there were no differences in daily medication use after a medication withdrawal protocol or in esophageal acid exposure times. There were no perforations or deaths. The authors stated, “This procedure represents a new option for selected symptomatic GERD patients who are intolerant of, or desire an alternative to, traditional medical therapies” (Corley, et al., 2003).

In a multicenter study, researchers evaluated GERD symptoms, patient satisfaction, and antisecretory drug use in 558 patients treated with the Stretta procedure. Mean follow-up was eight months. After treatment, onset of GERD relief was less than two months (68.7%) or 2–6 months (14.6%). The median drug requirement improved from PPIs twice daily to antacids as needed. The percentage of patients with satisfactory GERD control, absent or mild, improved from 26.3% at baseline, on drugs, to 77.0% after Stretta. Median baseline symptom control on drugs was 50%, compared to 90% at follow-up. Baseline patient satisfaction on drugs was 23.2%, compared to 86.5% at follow-up. Authors contend these results support the use of the Stretta procedure for patients with GERD, particularly those with inadequate control of symptoms on medical therapy (Wolfsen, et al., 2002).

A prospective study of 94 patients evaluated the Stretta procedure. At 12 months follow-up, PPI requirement fell from 88.1% to 30% of patients. Also at 12 months, GERD symptom scores, patient satisfaction score, SF-36, and esophageal acid exposure by 24-hour pH improved significantly (Triadafilopoulos, et al., 2002).

A comparative study evaluated the short-term results of the radiofrequency treatment of the gastroesophageal junction known as the Stretta procedure versus laparoscopic fundoplication (LF) in patients with GERD. Patients were offered the Stretta procedure (n=65) if they had documented GERD and did not have a hiatal hernia larger than 2 cm, LES pressure less than 8 mmHg, or Barrett's esophagus. Patients with larger hiatal hernias, LES pressure less than 8 mmHg, or Barrett's were offered LF (n=75). Preoperative esophageal acid exposure time was higher in the LF group. Preoperative LES pressure was higher in the Stretta group. There was an equal magnitude of improvement between pre- and postoperative quality of life and SF-12 scores between Stretta and LF patients. Both groups were highly satisfied with their procedure. The authors reported that patients undergoing Stretta have improved GERD symptoms and quality of life comparable to LF and believe the Stretta procedure is an effective alternative to LF in well-selected patients (Richards, et al., 2003).

There are numerous non-randomized and non-comparative studies evaluating radiofrequency energy for the treatment of GERD. The lack of a control or comparison group, small sample size and short-term follow-up limits the use of these findings with these studies (Dughera, 2011; Liu, 2011; Lutfi, 2005; Noar and Lotfi-Emran, 2007; Reymunde and Santiago, 2007; Triadafilopoulos, 2001).
Gastroplasty/Gastroplication (EndoCinch Suturing System): Comparative studies with EndoCinch have failed to show an improvement in acid exposure time when compared to sham. The studies report that there is a high rate of loss of intact sutures at follow-up. Large, well-designed, controlled trials showing long-term safety and efficacy outcomes are lacking.

In a randomized sham-controlled trial, Schwartz et al. (2007), reported on endoscopic gastroplication by the EndoCinch suturing system. A total of sixty patients with GERD were randomly assigned to three endoscopic gastroplications (n=20), a sham procedure (n=20) or observation (n=20). The primary outcome measures were PPI use and GERD symptoms. The secondary measure was 24-hour esophageal acid exposure. Follow-up assessments were performed at three, six, and 12 months. At three months, the percentage of patients who had reduced drug use by ≥ 50% was greater in the active treatment group (65%) than in the sham (25%) or observation groups (0%) (p<0.02). GERD symptoms improved more in the active group than in the sham group (p<0.01). Esophageal acid exposure was modestly decreased after active treatment (p<0.02) but was not significantly greater than after the sham procedure (p=0.61). The active treatment effects on PPI use and symptoms persisted after six and 12 months of open-label follow-up (n=41), but 29% of patients were re-treated in this period. The authors stated, "Widespread use of the endoscopic suturing device should probably be avoided until the technique is improved and efficacy on objective end points has been proved in a sham-controlled fashion" (Schwartz, et al., 2007).

Montgomery et al. (2006) reported data from 46 patients enrolled in a single-center, randomized, sham-controlled trial of EndoCinch plications. There was no difference in the use of PPIs between the sham and the EndoCinch groups at six weeks or 12 months, whereas at three months, there was a significant reduction in the use of PPIs in the treatment group compared to controls (p<0.05). Compared to baseline, there was a significant improvement in QOL as assessed by the gastrointestinal symptom rating scale (GSRS) at six weeks, as well as at three and 12 months post-procedure in both groups. At three months (but not at six weeks and 12 months), there was a significant difference in GSRS scores between the groups, favoring the treatment group versus the control group. Similarly to the sham group, the EndoCinch treatment group had no significant changes in esophageal acid exposure, as indicated by pH monitoring at three and 12 months, in any of the groups. Also noted was a marked loss of sutures, with 67% remaining at 12 months.

Chen et al. (2005) reported results of a prospective, multicenter trial with two-year follow-up of 85 patients who were treated with endoluminal gastroplication (ELGP) using the EndoCinch device for GERD. Inclusion criteria were three or more heartburn or regurgitation episodes per week, > 4.2% time in 24 hours with esophageal pH < 4, and dependency on antisecretory medications. Exclusion criteria were the presence of varices, achalasia, aperistalsis, or previous gastric resection. Patients underwent manometry, 24-hour pH monitoring, and symptom severity scoring before and after the procedure. Patient diaries were used to assess medication use and to estimate annual medication cost. The authors reported that ELGP is safe and effective for the long-term control of GERD symptoms. The procedure also appears to reduce esophageal acid exposure substantially for at least six months. Antisecretory medications were significantly decreased after ELGP, resulting in a large reduction in annual drug costs. Seven patients experienced adverse events (i.e., oozing at suture site, melena, bronchospasm, dysphagia, and hypoxemia from sedation). The authors stated patients with classic GERD symptoms who are responsive to antisecretory medications are good candidates for ELGP if an alternative to long-term medical therapy or surgery is being considered. Additional studies will be needed to evaluate whether the procedure should be routinely offered to patients who fail medical therapy or who have other unfavorable parameters.

Schiefke et al. (2005) prospectively evaluated the long-term outcome after EndoCinch. A total of 70 patients were interviewed using a standard questionnaire regarding their symptoms and medications prior to and 18 months after EndoCinch. Follow-up included endoscopy, 24-hour pH monitoring, and esophageal manometry. No major short- or long-term complications post-procedure were reported. At 18 months after procedure, 56/70 patients were considered treatment failures, as their heartburn symptoms did not improve, or PPI medication exceeded 50% of the initial dose. Endoscopy showed all sutures in situ in 12/70 patients, while no remaining sutures were detected in 18/70 patients. The authors summarized that EndoCinch was shown to be safe but not as effective as expected after 18 months of follow-up. The loss of plications was reported in the majority of patients which led to treatment failure.

A study of 87 consecutive patients compared transoral endoluminal gastroplasty (EG) by the Bard EndoCinch device and laparoscopic anti-reflux surgery (LAS) (Chadalavada, et al., 2004). Overall, 66% of patients were
satisfied with EG as compared to 93% after LAS. Postoperative PPI/motility agent use was 32% for EG and 13% for LAS. Three EG patients subsequently had LAS within six months of the procedure. These researchers believe LAS offers a greater reduction in medication use than EG, as well as more durable patient satisfaction and that the benefits of EG may include short-term symptomatic improvement while considering definitive surgical management.

An evaluation was conducted to determine any benefit of the Endocinch technique in 22 patients seen up to 12 months post-procedure (Mahmood, et al., 2003). Heartburn symptom scores and regurgitation scores were reduced. Mean (standard error of mean) pH DeMeester acid score was reduced at three months post-procedure. Percentage upright acid exposure and number of reflux episodes were also reduced significantly. Use of PPIs was reduced by 64% at 12 months post-procedure. All quality of life assessments showed significant improvement.

A multicenter trial evaluated plication in 64 patients treated with a transoral, flexible endoscopic suturing (Filipi, et al., 2001). Eleven patients required repeat procedure for suboptimal results, and ten patients withdrew. In 47 patients with complete follow-up, gastroesophageal reflux symptoms improved. Twenty-four-hour pH monitoring at three and six months indicated improvement in 24 patients studied.

**Endoscopic Plication System:** The majority of studies in the peer-reviewed literature consist of case series studies. Large, well-designed, controlled trials showing long-term safety and efficacy outcomes are lacking. The website www.clinicaltrials.gov states that several studies with the NDO Plicator have been terminated, since the sponsoring company (NDO Surgical, Inc.) has ceased business operations.

In a comparative study, Antoniou et al. (2012) evaluated the effectiveness of endoscopic plication and laparoscopic fundoplication in terms of quality of life and symptom control in comparison to another available surgical treatment. A total of 60 patients with documented GERD were randomly assigned to undergo either endoscopic plication or laparoscopic fundoplication. Quality-of-life scores and symptom grading were recorded before treatment and at three- and 12-month follow-up. Twenty-nine patients from the endoscopic group and 27 patients from the operative group were available at follow-up. Quality-of-life scores showed a substantial and similar increase for both groups after treatment. Symptoms of heartburn, regurgitation, and asthma were significantly improved in the endoscopic group, whereas laparoscopic fundoplication was more effective in controlling symptoms of heartburn and regurgitation compared to the endoscopic procedure. This study was limited by the small sample size and lack of long-term follow-up.

In a multicenter prospective, open-label, postmarket registry study, Birk et al. (2009) assessed full-thickness fundoplication using the Plicator for the treatment of GERD. The study included 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-Health Related Quality of Life (GERD HRQoL) score compared to their pre-fundoplication (off meds) score. No serious adverse events were reported. The lack of a control or comparison group limits the use of these findings.

The safety and efficacy of the Plicator procedure was studied in a prospective multicenter trial and evaluated in four subsequent reports with follow-up of 6, 12, 36 and 60 months, respectively (Pleskow et al., 2004; Pleskow et al., 2005; Pleskow et al., 2007; Pleskow et al., 2008). Sixty-four patients initially underwent plication to assess the safety and efficacy of endoscopic full-thickness plication. At six months after plication, PPI therapy had been eliminated in 74% of previously medication-dependent patients. Twenty-nine patients completed the 12-month and 36-month follow-up. All procedure-related adverse events occurred acutely, and no new events were observed during extended follow-up. At 36-months post-procedure, 57% of baseline PPI-dependent patients remained off daily PPI therapy. Treatment effect remained stable from 12–36 months, with 21/29 patients off daily PPI at 12 months compared to 17/29 patients at 36 months. Median GERD–Health Related Quality of Life (HRQL) scores remained significantly improved at 36 months versus baseline off meds scores (8 versus 19, p< 0.001). In addition, the proportion of patients achieving ≥ 50% improvement in GERD-HRQL score was consistent from 12 months (59%) to 36 months (55%). No long-term procedural adverse effects were reported. The results of the prospective, uncontrolled studies suggested that endoscopic full-thickness plication was effective, reducing symptoms and medication use associated with GERD. Treatment effect was stable for at least five years postprocedure. The authors considered the procedure safe, despite a few complications (gastric perforation, dyspnea, and mucosal abrasion in the fundus). The studies were limited by small sample size and
lack of a control group. In addition, due to termination of the initial 64-subject study and the challenge of retaining subject contact during the extended time period since initial Plicator treatment, only a subset of subjects who had originally undergone the Plicator procedure were enrolled in this 60-month follow-up study, therefore, the potential for a referral bias exists. Another limitation of this study design is its exclusion criteria. Potential GERD subjects excluded from this study are those frequently encountered in a practice setting. Their characteristics may include: presenting with a large hiatal hernia, advanced erosive esophagitis, and/or nonresponse to antisecretory therapy. A final limitation of this study is that evidence of long-term Plicator integrity was not assessed.

Studies of the Plicator procedure to date have been limited to placement of a single transmural suture to create the endoscopic gastroplication. In a prospective multicenter study, von Renteln et al. (2008) evaluated the safety and efficacy of placing multiple transmural sutures for the treatment of GERD. The study included patients with symptomatic GERD who require daily maintenance PPI therapy. Study exclusions were hiatal hernia >3 cm, grades III and IV esophagitis, Barrett’s epithelium, and esophageal dysmotility. Forty-one patients received two or more transmural sutures placed linearly in the anterior gastric cardia approximately 1 cm below the GE junction. The data demonstrated that the Plicator improved overall patient outcomes when compared with the preprocedure baseline. GERD-HRQL improved 76%, heartburn symptoms measured by VAS were improved 80%, 74% of patients experienced a positive improvement in acid exposure, and 35% of patients with mild esophagitis improved at least one grade level. The authors reported that further studies and long-term data regarding the safety and efficacy of this procedure will be necessary to define the value of the Plicator compared with already-established GERD therapies. Other limitations of this study are the small sample size and lack of a comparison with a single implant group. At 12-months, 24 of 41 patients (59%) had discontinued daily PPI therapy. Twenty-six of 41 patients (63%) had an improved GERD-HRQL >50%. GERD-HRQL scores improved from a median of 25 at baseline off PPI to eight post-treatment, a statistically significant improvement (p<0.001), and from a median of 11 at baseline on PPI to eight post-treatment, a statistically significant improvement (p=0.015). Acid exposure was not measured. All procedure-related adverse events occurred within the first post-procedure week. The authors stated that the long-term durability of the endoscopically restructured gastroesophageal junction and the long-term effects on esophagitis and pH-metry should be compared with surgical therapy. These data are necessary to define the value of the Plicator compared with established GERD therapies (von Renteln, 2009).

In a randomized, prospective multicenter trial, Rothstein et al. (2006) examined the effectiveness of endoscopic full-thickness plication for the treatment of GERD in comparison with a sham procedure. Patients with symptomatic GERD requiring maintenance PPI therapy were entered into the trial. A total of 78 patients were randomly assigned to undergo endoscopic full-thickness restructuring of the gastric cardia with transmural suture, while 81 patients underwent a sham procedure. Group assignments were revealed following the three-month evaluation. The primary end point was greater than or equal to 50% improvement in GERD-HRQL score. Secondary end points included medication use and esophageal acid exposure. By intention-to-treat analysis, at three months, the proportion of patients achieving greater than or equal to 50% improvement in GERD-HRQL score was significantly greater in the active group (56%) compared to the sham group (18.5%; p<0.001). Complete cessation of PPI therapy was higher among patients in the active group than in the sham group by intention-to-treat analysis (50% versus 24%; p=0.002). The percent reduction in median percent time pH less than four was significantly improved within the active group versus baseline (7 versus 10, 18%, p<0.001) but not in the sham group (10 versus 9, -3%, p=0.686). Between-group analysis revealed the active therapy to be superior to the sham in improving median percent time pH less than 4 (p=0.010). Twenty-four patients randomized in the study were lost to follow-up or excluded from further study because they were ruled ineligible by entry criteria. The authors stated, “Further studies, including those with longer term follow-up, will help clarify the role of this promising procedure across a broader range of patients with GERD” (Rothstein, et al., 2006).

The SRS™ Endoscopic Stapling System: There is a lack of studies in the peer-reviewed literature for the SRS Endoscopic Stapling System. Randomized controlled trials with long term follow-up are needed to determine whether the SRS Endoscopic Stapling System improves outcomes compared to alternative treatment modalities.

The LINX™ Reflux Management System: The majority of studies in the peer-reviewed literature consist of case series studies. Large, well-designed, controlled trials showing long-term safety and efficacy outcomes are lacking (Bonavina, et al., 2008; Bonavina, et al, 2010; Lipham, et al., 2012; Ganz, et al., 2013).
Ganz et al. (2013) reported the three year outcomes of a five year prospective multicenter clinical trial assessing the safety and effectiveness of a magnetic device for sphincter augmentation. This study lacks a control or comparator group. Eligible patients were age 18 to 75 years (n=100), had at least a six month history of reflux disease, and had a partial response to daily proton-pump inhibitors, with increased exposure to esophageal acid as confirmed by pH monitoring. Exclusion criteria were evidence of a large hiatal hernia, esophagitis of grade C or D according to the Los Angeles classification (in which grade A indicates one or more mucosal breaks of ≤5 mm in length, grade B one or more mucosal breaks of >5 mm, grade C mucosal breaks that extend between two or more mucosal folds but involve <75% of the circumference of the esophagus, and grade D mucosal breaks involving ≥75% of the circumference of the esophagus), a body-mass index of more than 35, Barrett's esophagus, a motility disorder, dysphagia more than three times a week, and allergy to titanium, stainless steel, nickel, or ferrous materials. The primary objective of the study was to evaluate the safety, efficacy, and direct effects of the device on exposure to esophageal acid, quality of life, and use of proton-pump inhibitors. The secondary end points, measured separately, were the number of patients with a reduction of 50% or more in the total score for quality of life, as compared with the score at baseline without proton-pump inhibitors, and a reduction of 50% or more in the dose of proton-pump inhibitors, as compared with the baseline dose. All efficacy end points were measured at one year, and the treatment was considered to be successful if the efficacy end points were reached in at least 60% of the patients. The primary outcome was achieved in 64% of patients. For the secondary outcomes, a reduction of 50% or more in the use of proton-pump inhibitors occurred in 93% of patients, and there was improvement of 50% or more in quality-of-life scores in 92%, as compared with scores for patients assessed at baseline while they were not taking proton-pump inhibitors. The most frequent adverse event was dysphagia (in 68% of patients postoperatively, in 11% at one year, and in 4% at three years). Serious adverse events occurred in six patients, and in six patients the device was removed. The authors reported that follow-up studies are needed to assess long-term safety (Ganz et al., 2013). Similar outcomes were reported in a case series study (n=100) by Bonavina et al. (2013) [article in press].

Bonavina et al. (2008) conducted a multi-center, feasibility trial to evaluate a Magnetic Sphincter Augmentation (MSA) device. Patients with typical heartburn (at least partially responding to proton-pump inhibitors [PPI]), abnormal esophageal acid exposure, and normal esophageal peristalsis were enrolled. Patients with hiatal hernia >3 cm were excluded from the study. The device was implanted laparoscopically around the distal esophagus. Over a one-year period, 38 out of 41 enrolled patients underwent this procedure in three hospitals. No operative complications were recorded. The mean follow-up was 209 days (range 12–434 days). The GERD-HRQL score decreased from 26.0 to 1.0 (p<0.005). At three months postoperatively, 89% of patients were off anti-reflux medications, and 79% of patients had a normal 24-h pH test. All patients preserved the ability to belch. Mild dysphagia occurred in 45% of patients. No migrations or erosions of the device occurred. The lack of a control or comparison group, small sample size and short-term follow-up limits the use of these findings.

Bonavina et al. (2010) conducted one and two year evaluations of a feasibility trial to assess the safety and efficacy of a laparoscopically implanted sphincter augmentation device (LINX Reflux Management System) in 44 patients for the treatment of gastroesophageal reflux disease (GERD). Complete cessation of PPI use was reported by 90% of patients at one year and by 86% of patients at two years. One device was laparoscopically explanted for persistent dysphagia without disruption of the anatomy or function of the cardia. There were no device migrations, erosions, or induced mucosal injuries. At one and two years, 77% and 90% of patients had a normal esophageal acid exposure. Additional well-designed controlled trials with a larger patient population are needed to determine the clinical relevance of these findings.

Lipham et al. (2012) conducted a follow-up to the Bonavina et al. (2010) study. A total of 44 patients who underwent a laparoscopic surgical procedure for placement of the LINX System were evaluated. Each patient’s baseline GERD status served as the control for evaluations post implant. For esophageal acid exposure, the mean total % time pH < 4 was reduced from 11.9% at baseline to 3.8% at three years, with 80% of patients achieving pH normalization. At ≥4 years, 100% of the patients had improved quality-of-life measures for GERD, and 80% had complete cessation of the use of PPIs. There were no reports of long-term device-related complications such as migration or erosion. Limitations of the study include the lack of controls and a small sample size.

The 2013 ECRI Magnetic Sphincter Augmentation (Linx Reflux Management System) forTreating Gastroesophageal Reflux Disease Emerging Technology Evidence Report summary states that “The evidence base for this technology consists of 2 prospective case series reporting on 144 patients (Ganz et al. 2013;
Lipham et al. 2012). We consider both studies to be very low quality because of deficiencies in the comparisons made, the way results were reported, patient loss to follow-up, and ad hoc analyses beyond one-year follow-up. Outcomes were reported based only on the number of patients available at last follow-up (e.g., only 116 of 144 enrolled patients appeared to be available at 3-year follow-up, although patient numbers at follow-ups for some outcomes are sometimes unclear). Both studies were manufacturer-sponsored; one was performed to provide the basis for the marketing application to the U.S. Food and Drug Administration (FDA). No well-designed, controlled studies are available comparing the device with any other GERD surgery or endoscopic treatment option. The two available studies provided pre-post-treatment data on medical therapy versus Linx for some outcomes of interest” (ECRI, 2013).

**Technology Assessments/Reviews**

In 2011, the Agency for Healthcare Research and Quality (AHRQ) updated a 2005 comparative effectiveness review (CER) that compared evidence of the different management options for adults with GERD. The report evaluated three endoscopic procedures: the EsophyX, the EndoCinch Suturing System, and Stretta. The authors reported that “As for the three available endoscopic procedures (EndoCinch, Stretta, EsophyX) for the long-term management of GERD, effectiveness remains substantially uncertain. EndoCinch (suturing) and Stretta (radiofrequency ablation) had been previously examined in the 2005 CER; EsophyX (endoscopic fundoplication) is a new introduction. 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” (Ip, et al., 2011).

Chen et al. (2009) conducted a systematic review of 33 studies examining seven endoscopic treatments for GERD. Literature databases were searched up to May 2006 without language restriction. A total of 33 studies examining seven endoscopic procedures (Stretta procedure, Bard EndoCinch, Wilson-Cook Endoscopic Suturing Device, NDO Plicator, Enteryx, Gatekeeper Reflux Repair System and Plexiglas) were included in the review. Of the three procedures that were tested against sham controls (Stretta procedure, Bard EndoCinch and Enteryx), patient outcomes in the treatment group were either as good as, or significantly better than, those of control patients in terms of heartburn symptoms, quality of life and medication usage. However, for the two procedures that were tested against laparoscopic fundoplication (Stretta) procedure and Bard EndoCinch, outcomes for patients in the endoscopic group were either as good as, or inferior to, those for the laparoscopic group. The authors concluded that, “Despite the potential benefits of these procedures, there is insufficient evidence at present to establish their safety and efficacy, particularly in the long-term.”

Fry et al. (2007) conducted a systematic review of the evidence on the effect of endoscopic therapies for GERD. Forty-three studies met their inclusion criteria including four randomized controlled trials. Many of the studies were small feasibility studies, with follow-ups of less than one year. No study comparing endoscopic techniques with other established treatment options such as PPIs existed. All endoscopic therapies were associated with a small percentage of mild to severe complications, which included perforation, abscess and death. The authors concluded that the data from most of the short-term follow-up and the few sham-controlled studies demonstrate that subgroups of patients experienced improvement or resolution of typical GERD symptoms and decreased PPI usage. The authors stated that there is limited data on safety, efficacy and durability to support the use of endoluminal therapies for GERD in routine clinical practice.

Torquati et al. (2007) conducted an evidence-based review of the literature of FDA-approved modalities of endoluminal treatment of GERD. Sixteen studies met the inclusion criteria, representing 787 patients. The studies were categorized according to the guidelines for levels of evidence and grades of recommendation supplied by the Oxford Centre for Evidence-Based Medicine. The authors concluded that, “The methodological quality of most of the included studies was average; four studies were grade 1b (individual randomized trial), 10 were grade 2b (individual cohort study), and two were grade 3b (individual case-control study). There is grade 1b and 2b evidence demonstrating the EndoCinch plication is effective in reducing GERD symptoms at short-term follow up. However, in the majority of the studies analyzed, the procedure does not significantly reduce the acid exposure in the distal esophagus. The majority of the studies with long-term outcome showed disappointing outcomes, probably due to suture loss in the majority of patients. There is grade 1b and 2b evidence demonstrating that the Stretta procedure is effective in reducing GERD symptoms at short- and mid-term follow-up. However, in the majority of the studies analyzed, the procedure did not reduce significantly the acid exposure in the distal esophagus. There is grade 1b and 2b evidence demonstrating that full-thickness plication is effective in reducing GERD symptoms, and acid exposure in the distal esophagus” (Torquati, et al., 2007).
Professional Societies/Organizations
The American College of Gastroenterology (ACG): In 2013, the ACG updated their Practice Guidelines for GERD. Under the section on surgical options for GERD the authors state, “The usage of current endoscopic therapy or transoral incisionless fundoplication cannot be recommended as an alternative to medical or traditional surgical therapy (Strong recommendation, moderate level of evidence)” (Katz, et al., 2013).

The American Society of General Surgeons (ASGS): The 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.”

The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES): In 2013, the SAGES published a Safety and Effectiveness Analysis for the LINX® Reflux Management System concluding (SAGES, 2013b):

- Implantation of the LINX device requires minimal dissection and relatively few technical steps when compared to Nissen fundoplication. This may enable the LINX surgical technique to be standardized in a manner not possible for fundoplication.
- The mechanism of action of the LINX device results in a low incidence of difficulty belching.
- The incidence of initial dysphagia following LINX implantation is high. Difficulty swallowing was more commonly reported at 12 and 24 months following LINX implantation than at baseline. Patients should be advised about the possibility that it may be more difficult to swallow following surgery, and that this symptom may persist.
- The LINX device may provide an option currently lacking in clinical practice for patients with medically refractory GERD who have not yet progressed to end-stage reflux disease with associated complications.
- Direct comparative studies between the LINX procedure and Nissen fundoplication will be needed.
- On the basis of the available evidence, the LINX device should be an option available to patients and providers for the management of medically refractory GERD.

In 2013, the SAGES published a Clinical Spotlight Review on Endolumenal Treatments for Gastroesophageal Reflux Disease (GERD). The Clinical Spotlight review is intended to indicate preferable approaches to medical problems as established by experts in the field. These recommendations are based on existing data or a consensus of expert opinion when little or no data are available. A 4-tiered system for denoting the quality of evidence (very low (+), low (+ +), moderate (+ + +), or high (+ + + +)) and a 2-tiered system for strength of recommendation (weak, or strong) were used. The devices and techniques selected for this Clinical Spotlight Review include EsophyX and Stretta (SAGES, 2013a):

- Recommendation: Long term data is not yet available for EsophyX. Further studies are required to define optimal techniques and most appropriate patient selection criteria, and to further evaluate device and technique safety. Quality of Evidence: (++). GRADE Recommendation: Weak.
- Recommendation: 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 anti-secretory pharmacologic therapy, and who have declined laparoscopic fundoplication. Quality of Evidence: (+++). GRADE Recommendation: Strong

In 2009 the SAGES published a position statement addressing endolumenal therapies for gastrointestinal diseases. The authors discuss the current gastrointestinal applications for endolumenal surgery including endolumenal therapies for GERD. The authors state that “endolumenal techniques, either existing or still in development, may well represent the procedure of choice for selected patients with GERD in the future.” The authors state that, “to facilitate progress in endolumenal therapy, several key issues still need to be addressed beyond the needed technology development. These include defining criteria for patient selection, defining the requisite skill set needed by the treating physician, defining the setting for these procedures to be performed in, and addressing reimbursement/coding issues” (SAGES, 2009). There has been no update to this statement since 2009.
The American Gastroenterological Association (AGA): The AGA Medical Position Statement on the Management of Gastroesophageal Reflux Disease states that due to insufficient information they can make no recommendation for or against the use of currently commercially available endoluminal antireflux procedures in the management of patients with an esophageal syndrome (AGA, 2008; Kahrilas, et al., 2008). There has been no update to this statement since 2008.

The AGA Institute Position Statement on the Use of Endoscopic Therapy for GERD states, “Most studies of endoscopic therapy have only limited follow-up information of a relatively small number of patients. Thus, the durability of these technologies beyond 1–2 years remains unclear. Short-term and long-term safety issues are unresolved, but serious adverse events led to the voluntary withdrawal of Enteryx by the manufacturer in September 2005 and suspension of the clinical program in late 2005. The economics of all techniques for the patient, practitioner, and society are unknown. While newer devices and improvements in endoscopic anti-reflux techniques may yield better and more durable treatment outcomes, current data suggest that there are no definite indications for endoscopic therapy for GERD at this time. Both practitioners and patients need to be aware of the limitations in the evidence that exist with these devices at present” (Falk, et al., 2006b). There has been no update to this statement since 2006.

The American Society for Gastrointestinal Endoscopy (ASGE): The ASGE Practice Guideline Role of Endoscopy in the Management of GERD states that “Most studies of endoluminal therapies for GERD have involved small numbers of PPI-dependent patients and have provided relatively limited follow-up information, so the durability of these therapies remains in question. Additionally, both short and long-term safety issues surrounding the endoluminal devices continue to be a concern, and the economics of their use are unknown. The new endoscopic antireflux techniques represent a rapidly evolving area of GI endoscopy, but additional research is needed before they can be widely recommended. Appropriate patient selection and endoscopist experience should be carefully considered before pursuing these therapies. It is important that patients and practitioners alike be aware of the limitations in the evidence that exist with these devices at the present time” (ASGE, 2007). There has been no update to this guideline since 2007.

Use Outside of the US
The LINX Reflux Management System has been commercially available in Europe since November 2008 (ECRI, 2013).

The 2013 Canadian Agency for Drugs and Technologies in Health (CADTH) Health Technology Update on The SRS Endoscopic Stapling System: A Nonsurgical Treatment for GERD states the device is licensed in Canada. In the evidence section the authors report that, “There are no published trials of SRS in peer-reviewed literature. Numerous abstracts of studies are posted on the manufacturer’s website. It should be noted that data contained in abstracts may not always accurately reflect data contained within the full article.”

The 2008 updated Asia-Pacific consensus on the management of gastroesophageal reflux disease reports under Statement 37 that endoscopic treatment of GERD should not be offered outside well-designed clinical trials. The authors report that, “we believe that until better endoscopic techniques to treat GERD are introduced, the use of any of the currently available endoscopic techniques outside well-designed clinical trials should be discouraged. Presently, the first generation of endoscopic techniques for GERD is not ready for prime time” (Fock, et al., 2008).

In 2012, the National Institute for Clinical Excellence (NICE), an organization within the United Kingdom, issued an interventional procedure guidance document titled Laparoscopic Insertion of a Magnetic Bead band for Gastroesophageal Reflux Disease. The authors concluded that the evidence on the safety and efficacy of laparoscopic insertion of a magnetic bead band for GERD is limited in quantity. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research (NICE, 2012).

In 2011, the NICE issued an interventional procedure guidance document titled Endoluminal Gastroplication for GERD. The authors report that “the evidence on endoluminal gastroplication for gastro-esophageal reflux disease (GERD) 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” (NICE, 2011).
In 2009, the NICE which provides healthcare guidance issued an interventional procedure guidance document titled Endoscopic Radiofrequency Ablation for GERD and concluded that the evidence on safety and efficacy of endoscopic radiofrequency ablation for GERD is inadequate and there are inconsistencies in the evidence on efficacy (NICE, 2009).

The 2011 Gastroenterological Society of Australia Clinical Update on Gastroesophageal Diseases in Adults reports under the section on management and endoscopic therapies that, “Experience with these techniques is relatively limited. They do not significantly reduce exposure of the distal oesophagus to acid, and many have already been removed from the market because of lack of efficacy or complications (including death). These treatments should not be used by inexperienced operators or outside a program (e.g. a clinical trial) where complications can be easily reported.”

Summary
There are several proposed modalities to treat gastroesophageal reflux disease (GERD) (i.e., medications, endoscopic therapies, surgery). For patients who have severe GERD, laparoscopic fundoplication remains the procedure of choice. Endoscopic therapy studies for the treatment of GERD have been prospective but generally not randomized or controlled. Patient selection criteria need to be optimized. Comparative studies between the different endoscopic therapies are needed. Large, well-designed, controlled trials showing long-term safety and efficacy outcomes are lacking.

The 2011 updated Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review (CER) of the different management options for adults with GERD which evaluated three endoscopic procedures: the EsophyX, the EndoCinch Suturing System, and Stretta reported that “As for the three available endoscopic procedures (EndoCinch, Stretta, EsophyX) for the long-term management of GERD, effectiveness remains substantially uncertain. EndoCinch (suturing) and Stretta (radiofrequency ablation) had been previously examined in the 2005 CER; EsophyX (endoscopic fundoplication) is a new introduction. 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” (Ip, et al., 2011).

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Experimental, investigational or unproven and not covered when used to report endoscopic anti-reflux procedures performed for the treatment or management of gastroesophageal reflux disease (GERD)/esophageal reflux:

<table>
<thead>
<tr>
<th>CPT* Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>43201</td>
<td>Esophagoscopy, rigid or flexible; with directed submucosal injection(s), any substance</td>
</tr>
<tr>
<td>43236</td>
<td>Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; with directed submucosal injection(s), any substance</td>
</tr>
<tr>
<td>43257</td>
<td>Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; with delivery of thermal energy to the muscle of lower esophageal sphincter and/or gastric cardia, for treatment of gastroesophageal reflux disease</td>
</tr>
<tr>
<td>43289</td>
<td>Unlisted laparoscopy procedure, esophagus</td>
</tr>
<tr>
<td>43499</td>
<td>Unlisted procedure, esophagus</td>
</tr>
<tr>
<td>43659</td>
<td>Unlisted laparoscopy procedure, stomach</td>
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HCPCS | Description |
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<tr>
<th>Codes</th>
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<tbody>
<tr>
<td>C9724</td>
<td>Endoscopic full-thickness placation in the gastric cardia using endoscopic</td>
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<tr>
<td></td>
<td>placation system (EPS); includes endoscopy</td>
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<tr>
<td>C9737</td>
<td>Laparoscopy, surgical, esophageal sphincter augmentation with device (eg,</td>
</tr>
<tr>
<td></td>
<td>magnetic band) (Code effective 01/01/2014)</td>
</tr>
</tbody>
</table>


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