Minimally Invasive Anti-Reflux Procedures and Peroral Endoscopic Myotomy (POEM)

Overview

This Coverage Policy addresses endoscopic anti-reflux procedures for the treatment of gastroesophageal reflux disease (GERD) and Peroral Endoscopic Myotomy (POEM) for the treatment of dysphagia including esophageal achalasia.

Coverage Policy

Each of the following endoscopic anti-reflux procedures for gastroesophageal reflux disease (GERD), or any other indication, is considered experimental, investigational or unproven:

- radiowave energy to the gastroesophageal junction (e.g., Stretta® System)
- endoluminal gastropasty/gastroplications (e.g., Muse™ System, SRS™ Endoscopic Stapling System, or Bard™ Endoscopic Suturing System [BESS], Syntheon ARD Plicator, StomaphyX™)
- transoral incisionless fundoplication (TIF) (i.e. EsophyX™)
- injection/implantation of biocompatible material (e.g., plexiglas or polymethylmethacrylate [PMMA], Durasphere™)
- magnetic sphincter augmentation (e.g., LINX™ Reflux Management System)
Peroral endoscopic myotomy (POEM) is considered experimental, investigational and unproven for all indications including esophageal achalasia.

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 is considered the standard surgical therapy.

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 (Richter, 2010).

Textbooks report that most studies of endoscopic therapy have 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 death have been attributed to these endoscopic techniques (Richter, 2010). Currently, endoscopic therapies are not an established treatment option.

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]). Respiratory Technology Corporation (Restech) acquired the assets of Mederi Therapeutics in 2018 (Restech, 2018).

The Stretta system delivers radiofrequency (RF) energy to the muscle between the stomach and esophagus, which is proposed to remodel and improve the muscle tissue, resulting in improved barrier function and fewer reflux events. The procedure, known as the Stretta procedure, is generally performed using standard conscious sedation but has required general anesthesia in some patients (Falk, et al., 2006a).

U.S. Food and Drug Administration (FDA): The Stretta System is FDA approved for “general use in the electrosurgical coagulation of tissue and intended for use specifically in the treatment of GERD” (FDA, 2000a). In 2015 the FDA approved a Stretta catheter as a 510(k) Class II accessory “intended for general use in the electrosurgical coagulation of tissue and intended for use specifically in the treatment of GERD” (FDA, 2015).

Literature Review: Improvements in symptoms, quality of life, reduction in PPI use and decreased acid exposure following treatment with radiofrequency energy have been reported in some studies but outcomes are conflicting. Studies have been limited by small patient populations, short-term follow-ups, high dropout rates, loss of data and/or lack of randomization. In some studies outcomes were measured solely on patient questionnaires. 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 (Liang, et al., 2015; Hu, et al., 2015; Yan, et al., 2015; Noar, et al., 2014; Arts, et al., 2012; Richards, et al., 2003)
Fass et al. (2017) conducted a systematic review and meta-analysis to determine the efficacy of Stretta for the treatment of GERD. Inclusion criteria included: studies with at least three months follow-up; study design was a controlled trial or cohort study; and study had sufficient data for at least one of the six selected outcome variables. Primary outcomes were the relief of associated GERD symptoms. Twenty-eight studies (four randomized controlled trials, 23 cohort studies, and one registry) (n=2468) met inclusion criteria and were included in meta-analysis. Mean follow-up time ranged from 3–120 months (mean 25.4 months). Pooled results (two studies) showed that Stretta significantly improved health-related quality of life scores (p<0.001) and pooled heartburn standardized score (p<0.001). Stretta significantly reduced the incidence of erosive esophagitis by 24% (p<0.001) and esophageal acid exposure (p=0.001). Lower esophageal sphincter (LES) basal pressure was increased following Stretta by a mean of 1.73 mmHg, not significant. A total of 49% of patients required continuation of PPI following Stretta vs. 51% who did not (p<0.001). Adverse events for Stretta included small erosions and mucosal lacerations. Subcutaneous emphysema was the most frequent adverse event for LF (3%). Limitations of the studies included: heterogeneity of the studies with respect to inclusion criteria, previous surgeries, protocols for the use of antacids, monitoring of PPI use and follow-up time. Heterogeneity was highly significant (p <0.001) in all Stretta subgroups. Additional limitations of the studies include the lack of a comparator; small heterogeneous patient populations; and short-term follow-ups.

Lipka et al. (2015) conducted a systematic review and meta-analysis of randomized controlled trials (RCT) to assess the safety and efficacy of Stretta for the treatment of GERD. Four trials (n=165) met inclusion criteria. Any RCT evaluating the efficacy of Stretta compared with sham or medical treatment for GERD patients requiring PPIs was eligible for inclusion. GERD was established by the presence of erosive esophagitis on endoscopy, or abnormal ambulatory esophageal pH monitoring (defined by DeMeester score >14.7 or percentage total time pH <4 of >4.0%). Patients also were defined as having GERD by scores on health-related quality of life (HRQOL) surveys or by symptom scores, were previously on PPIs, and treated with Stretta vs. either sham or PPI therapy. Three trials compared Stretta vs sham, and one trial compared Stretta vs. PPI therapy. The primary outcomes were physiological parameters, including normalization of the percentage of a 24-hour time period spent at a pH <4 and augmentation of the lower esophageal sphincter pressure (LESP). The overall quality of evidence was “very low”. The pooled results showed no difference between Stretta and sham or management with PPI in patients with GERD for the outcomes of mean percent of time the pH was less than 4 over a 24-hour time course, LESP, ability to stop PPIs, or HRQOL.

Yan et al. (2015) conducted a non-randomized comparative study to compare outcomes of patients treated with Stretta (n=47) or laparoscopic toupet fundoplication (LTF) (n=51) for the treatment of GERD-related extra-esophageal symptoms. The patients had either failed to respond to medical treatment or opted for surgery despite effective medical management. Other inclusion criteria were: lower than normal lower esophageal sphincter (LES) pressure detected by esophageal manometry; endoscopically confirmed Los Angeles grade A or B esophagitis; non-hiatal hernia or small (<2 cm) hiatal hernia; and age >18 years. The primary outcome measures were frequency and severity of the extra-esophageal GERD symptoms, including cough, sputum, wheezing, and globus hystericus. Other outcome measures included: medication independence, satisfaction and reoperation complications. At the three year follow-up (n=90), the total of the frequency and severity scores for every symptom significantly improved within both groups from baseline (p<0.05) with no significant differences between the groups (p>0.05). There were no significant differences in symptom scores of cough, sputum, and wheezing between the two groups (p>0.05) and PPI independence following surgery (p=0.835). The score for globus hystericus was significantly improved in the Stretta group vs. the LTF group (p<0.05). Patients in the LTF group were more satisfied with their quality of life than those in the Stretta procedure group (p<0.05). In the Stretta group, one patient underwent re-operation during the first postoperative year, and six patients underwent re-operation within three postoperative years. Reported complications included: fever, pharyngeal pain, retrosternal discomfort, diarrhea, abdominal distention, and dysphagia. Most complications resolved without intervention within two weeks. Author noted limitations of the study included: small, patient population; pH and motility outcomes were not reported; and changes in respiratory drug use were not examined. Other limitations are the lack of randomization and criteria for which subjects received Stretta vs. LTF.

In an open-label, prospective trial (n=149), Noar et al. (2014) evaluated the 10-year safety, efficacy, and durability of response to radiofrequency treatment (Stretta) of the lower esophageal sphincter. The primary outcome measure was normalization of GERD-health-related quality of life (GERD-HRQL) in 70% or greater of patients at 10 years. Secondary outcomes were 50% reduction or elimination of proton pump inhibitors (PPIs)
and 60% or greater improvement in satisfaction at 10 years. Successful treatment was defined as achievement of secondary outcomes in a minimum of 50% of patients. Subjects had daily recurring symptoms of heartburn and regurgitation despite twice-daily PPI use. Exclusion criteria included: stenosis, stricture or ulceration of the pylorus, pregnancy, poor surgical risk, achalasia, previous non-Nissen fundoplication (NF) esophageal surgery, scleroderma-type collagen vascular disease, or severe uncontrolled medical illness. A total of 72% of patients achieved the primary outcome, 64% of patients experienced a 50% or greater reduction in PPI use, and 54% of patients reported a 60% or greater increase in satisfaction. Pre-existing Barrett’s metaplasia regressed in 85% of biopsied patients (28/33) and 28 had no further dysplasia. Due to dissatisfaction with first procedure results, 11 patients underwent a second Stretta procedure and one underwent a Nissen fundoplication (NF). Reported adverse events included two patients who had self-limited, minor gastric bleeding. Procedure-related side effects included: short-term chest pain, dyspepsia, increased flatulence and abdominal pain. Limitations of the study include: lack of a comparator; no long-term pH and motility data; number of patients lost to follow-up (n=68) from original study (n=217); missing data from the 149 subjects (50 patients did not complete 10-year follow-up questionnaires; 68 patients had not reached ten-year time point); and not all patients had undergone final endoscopic screening.

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, 1441 patients, with a mean follow-up of 15 months. Outcomes analyzed included GERD symptom assessment, quality of life, esophageal pH, and esophageal manometry. There were significant improvements reported in heartburn scores (n=525) (p=0.001), and quality of life as measured by GERD–health-related quality-of-life scale (p=0.001) and quality of life in reflux and dyspepsia scores (n=433) (p=0.001). Esophageal acid exposure decreased from a preprocedure Johnson-DeMeester score of 44.4 to 28.5 (n=267) (p=0.007). 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 suggested that radiofrequency ablation produces significant improvement in GERD symptoms, patient satisfaction, and QOL at short and intermediate term follow-up. However, the definition of the appropriate patient populations for Stretta therapy remains controversial. 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-HRQOL 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<0.05 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<0.05) 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."

Corley et al. (2003) conducted a randomized controlled (n=65) trial to evaluate the safety and efficacy of radiofrequency energy (Stretta) (n=35) compared to sham (n=29). 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.

Corley et al. (2003) conducted a randomized controlled (n=65) trial to evaluate the safety and efficacy of radiofrequency energy (Stretta) (n=35) compared to sham (n=29). According to the authors, this was the first comparative study done on this technology. Principal outcomes were heartburn and quality of life. Inclusion criteria (1) heartburn or acid regurgitation at least partially responsive to and requiring daily antacid medications; (2) age ≥18 years; (3) 24-hour pH study off medications showing abnormal esophageal acid exposure (>4%) or a DeMeester score of >14.7; (4) esophageal manometry showing normal esophageal peristalsis and sphincter relaxation; (5) esophagogastroduodenoscopy (EGD; on medications) showing no esophagitis worse than grade II (i.e., no substantial ulcerations), no hiatal hernia >2 cm long, and no Barrett’s esophagus; and (6) no coagulation disorders, mechanical prostheses, prominent dysphagia, or unstable disorders. At six month follow up, patients in the Stretta group reported significantly improved heartburn symptoms (p=0.05) and more than a 50% improvement in reflux disease quality of life (p=0.03). There were no significant differences in daily medication usage after a medication withdrawal protocol (p=0.67) or in esophageal acid exposure times. At the end of six month 20 sham patients crossed over to active treatment. Improvements were sustained at the 12 month follow-up. Adverse events included one esophageal ulcer bleeding, one, transient increased bloating and postprocedural retrosternal discomfort. There were no perforations. Author-noted limitations of the study included: dropout rate (n=20) and the number of sham patients who discontinued medications. The posttreatment improvement in esophageal acid exposure was shown only in subgroup analyses; random variation resulted in imbalance in number of subjects in each group. The primary evaluation of acid exposure in this study did not show an improvement over sham at six months. Another limitation is the small patient population.

A comparative study evaluated the short-term results of the radiofrequency treatment of the gastroesophageal junction with 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. Reportedly, both groups were highly satisfied with their procedure (Richards, et al., 2003).

There are non-randomized and non-comparative studies evaluating radiofrequency energy for the treatment of GERD. The lack of a control or comparison group, small to moderate sample sizes and overall short-term follow-ups limit the use of the findings of these studies (Dughera, 2011; Liu, 2011; Lutfi, 2005; Noar and Lotfi-Emran, 2007; Reymund and Santiago, 2007; Triadafilopoulos, 2002).

**Endoluminal Gastroplasty/Gastroplication**

Basic techniques were designed to place sutures or staples at the cardia, including submucosal stitching devices and deep transmural plicating devices. The technique is proposed to create pleats or plications of tissue just beneath the gastroesophageal junction. Sedation and procedure time vary. An examples of suturing/plication devices included the EndoCinch™ or Bard Endoscopic Suturing System (BESS) (Bard Endoscopic Technologies, Billerica, MA); and the Syntheon ARD Plicator (Syntheon, Miami, FL). The EndoCinch is no longer recommended for use and the manufacturer, Bard, has discontinued distribution of the System. The Endoscopic Plicator System is also no longer available (Trad, 2016; Hayes, 2015).

The EsophyX device (EndoGastric Solutions, Inc., Redmond, WA) creates a transoral incisionless fundoplication® (TIF). The 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 (GEV) 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). There are two models of EsophyX devices – EsophyX2 HD and EsophyX Z. Earlier studies used the TIF 1.0 protocol which involved gastro-gastric plications below the gastroesophageal junction and 220 degree of circumference of the re-established valve compared to the current TIF 2.0 protocol which involves esophago-gastric plications above the Z-line and 240 degree circumference.

Another device proposed for TIF is the Muse™ System formerly the SRS™ Endoscopic Stapling System (MediGus Ltd., Omer, Israel).

**U.S. Food and Drug Administration (FDA):** The EndoCinch™ or Bard Endoscopic Suturing System (FDA, 2000b), NDO Surgical Endoscopic Plication System (FDA, 2003), SRS™ Endoscopic Stapling System (FDA, 2012) and StomaphyX™ (FDA, 2007) have been approved through the 510(k) premarket notification process. The Syntheon ARD Plicator is not an FDA-approved device.

The EsophyX System (FDA, 2007), EsophyX2™ System (FDA, 2009) are also FDA 510(k) Class II approved. The EndoGastric Solutions (EGS) EsophyX™ System with SerosaFuse Fastener is "indicated for use in endoluminal, 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, 2007). The EsophyX2 HD with SerosaFuse Fasteners and Accessories WAS APPROVED IN 2014. The EndoGastric Solutions EsophyX Device models (EsophyX2 HD and EsophyX Z were 510(k) approved in 2017 for the same indications as the initial device (FDA, 2017).

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

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

Although FDA approved for GERD in April 2003, the FDA issued an 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).

Literature Review - Transoral Incisionless Fundoplication (EsophyX 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 with small patient populations (n=10–60). 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 (Bell, et al., 2014; Wilson, et al., 2014; Muls, et al., 2013; Trad, et al., 2012; Narsule, et al., 2012; Testoni, et al., 2012; Frazzoni, et al., 2011; Bell, et al., 2011; Hoppo, et al., 2010; Velanovish, et al., 2010; Testoni, et al., 2010; Demyttenaere et al., 2010; Cadire, et al., 2009; Repici, et al., 2010). Randomized controlled trials with longer follow-up are needed to determine whether EsophyX improves outcomes compared to alternative treatment modalities.

Richter et al. (2018) conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to compare the relative efficacies of transoral incisionless fundoplication (TIF) and laparoscopic Nissen fundoplication (LNF) to sham or PPI in patients with GERD. Seven studies (n=1128) met inclusion criteria. RCTs were included if GERD was established by the presence of erosive esophagitis on endoscopy and/or abnormal ambulatory esophageal pH monitoring (Demeester score > 14.7 and/or percentage total time pH < 4 of ≥ 4.0%) and quality of life surveys or by symptom scores of patients who were previously on PPIs. The primary outcome measures were decrease in proportion of a 24-hour time period spent at pH < 4 and augmentation of the lower esophageal sphincter pressure (LESP). Secondary outcomes included decreased symptom scores reported as health-related quality of life (HRQOL) and serious adverse events. Two RCTs compared TIF to proton pump inhibitors (PPI) (n=123), two compared TIF to sham (n=173) and three compared LNF to PPIs (n=875). Study durations were 6-12 months in the TIF studies and 1–5 years in the LNF vs PPI studies. The probability of best treatment was ranked using the Surface Under the Cumulative Ranking (SUCRA), a parameter to rank treatments based on their probability of ranking first, second, third, etc. The SUCRA ranges between 0% (the treatment always ranks last) to 100% (the treatment always ranks first). Analysis revealed the following:

- LNF was statistically superior to TIF in percent time pH was < 4 and had the highest probability of being the best treatment for improvement in percent time spent in pH < 4 (SUCRA, 0.99), PPI (SUCRA, 0.64), TIF (SUCRA, 0.32), and sham (SUCRA, 0.05).
- LNF was superior to TIF in increasing esophageal sphincter pressure (LESP), but the difference was not significant. LNF had the highest probability of being the best treatment for improvement in LESP (SUCRA, 0.78), followed by TIF (SUCRA, 0.72) and PPI (SUCRA, 0.01).
- TIF was superior to LNF in improved health-related quality of life (HRQOL), but the difference was not significant. TIF had the highest probability of being the best treatment for improvement in HRQOL (SUCRA, 0.96), followed by LNF (SUCRA, 0.66), sham (SUCRA, 0.35), and PPI (SUCRA, 0.042).
- LNF was superior to TIF re incidence of persistent esophagitis, but the difference was not significant. PPI had the lowest probability of being the treatment associated with persistent esophagitis (SUCRA, 0.19), followed by LNF (SUCRA, 0.38), TIF (SUCRA, 0.68), and sham
Data on harm was not consistently reported and meta-analysis could not be done. The results showed that LNF fundoplication had the highest ability to improve physiologic parameters associated with GERD, including LES pressure and decreasing the percentage of time that the pH < 4. PPIs were superior for reducing esophagitis, possibly due to dose escalation if symptoms persisted. TIF had the highest probability of symptom improvement based on HRQOL likely related to shorter follow-up time compared to LNF or PPIs. Author-noted limitations of this analysis included: lack of data on individual patients, difference in follow-up time and number of subjects (n=875 LNF; n=293, TIF); and moderate to low quality of the included studies. The authors concluded that endoscopic therapy cannot be recommended as an alternative to medical or traditional surgical treatment of GERD.

Gerson et al. (2018) conducted a systematic review and meta-analysis of randomized controlled trials that compared outcomes of the TIF 2.0 procedure with Esophyx to controls for the treatment of GERD. According to the author, the TIF 2.0 procedure is significantly different the TIF 1.0 procedure. In the TIF 2.0 procedure there is a single insertion of the device, which performs esophagogastroduodenal plications around the intra-abdominal lengthened esophagus (as opposed to gastro-gastric plications performed in ELF or TIF 1.0). The apposed fundus is wrapped around the distal esophagus, secured with fasteners placed above the Z-line (as opposed to below the Z-line), with an average of more than 20 fasteners (instead of 10 or 12). Comparators were PPI therapy or sham (with or without PPI). Patients had chronic long-term refractory GERD on optimized PPI therapy. Outcomes were esophageal pH, PPI utilization and quality of life at postoperative year three. Three studies (n=233) met inclusion criteria. One study (n=63) compared TIF2 to PPIs and two compared TIF2 to sham. At 6–12-months follow-up, a higher proportion of patients with an esophageal pH < 3 was reported in the PPI group compared to TIF patients, but the difference was not significant. For patients who crossed over to TIF At three years follow-up, patients who did not undergo the TIF continued to take higher doses of PPIs than patient who had the TIF procedure (Trad study), but the difference was not significant (p=0.1967). The group mean was 8.0 mg per day for the TIF 2.0 group and 15.8 mg for the PPI group. There was a significant difference in quality of life outcomes in the TIF patients one year after the procedure (p=0.0001), but not at year three. A significant number of PPI patients either crossed over to TIF 2.0 or did not attend a substantive number of visits beyond six months. Limitations of the analysis include the small heterogeneous patient population, short-term follow-up, patients lost to follow-up and study bias ranged from low to high.

McCarty et al. (2018) conducted a systematic review and meta-analysis of the literature to evaluate the feasibility, efficacy, and tolerability of transoral incisionless fundoplication (TIF) (Esophyx and MUSE) for the treatment of refractory GERD. Thirty-two studies (n=1475) including five randomized controlled trials, 21 prospective studies, and 6 retrospective review were included. The analysis included two MUSE studies (n=85), four TIF1 studies (n=158) and the remaining studies used TIF2. Patient populations ranged from 13–127. Inclusion criteria were studies that included human subjects treated for GERD with TIF. Patients with a body mass index (BMI) < 35 kg/m²; hiatal hernia ≤ 2 cm; grade A, B, or C esophagitis according to the Los Angeles classification; and no underlying esophageal motility disorder (e.g. achalasia, diffuse esophageal spasm) at the time of the procedure. The primary outcome measures were feasibility, efficacy, and tolerability of TIF in patients with refractory, symptomatic GERD complaints. Mean follow-up time was 15.8 months. Significant improvement was reported in the mean GERD HRQL (25 studies; n=1236) compared to baseline scores (p<0.001) and GERD-associated symptoms measured by Gastroesophageal Reflux Disease Symptom Score (GERSS) (p<0.001). Complete discontinuation of PPI therapy was achieved in a significant number of patients following TIF (p<0.001) (28 studies; n=1407). Hiatal hernia reduction or complete resolution was achieved in 91% of patients (p<0.001). Esophageal acid exposure time (i.e., percent time with pH< 4) was reported in 15 studies (n=722) and significantly improved following TIF (p<0.001). There was also a significant improvement in the number of reflux episodes in a 24-hour period (p<0.001) and DeMeester scores (p<0.001) (11 studies; n=647). A total of 7.5% patients required further endoscopic or surgical intervention (21 studies; n=1176) primarily in the first six months following surgery. Author-noted limitations of this analysis include: heterogeneity of patient populations, short-term follow-ups, and inclusion of first- and second-generation devices (Esophyx/Esophyx2), as well as heterogeneity by the use of TIF 1.0 and TIF 2.0 protocols. Randomized controlled trials with large patient populations and long-term follow-up are needed to valid the effectiveness of ESOPHX.

Trad et al. (2018) reported the five year observational outcomes (n=44) of the TEMPO multicenter, randomized controlled trial. In the original RCT (Trad, et al., 2015) TIF outcomes were compared to PPIs. At the six-month follow-up all patients crossed over to TIF. Patients were originally included who had chronic GERD with daily
Troublesome regurgitation and/or atypical symptoms refractory to PPI therapy, pathological esophageal acid exposure confirmed by 48-hour pH monitoring off PPI therapy (percentage time pH <4 greater than 5.3%), and PPI use for at least six months. Primary outcomes for this five year follow-up were elimination of daily troublesome regurgitation and atypical symptoms. Secondary outcomes were: improvement in symptom scores, PPI use, reoperations, and patient health satisfaction. Troublesome symptoms were defined as mild symptoms occurring ≥ 2 days a week, or moderate to severe symptoms more than one day a week. At the 5-year follow-up, elimination of troublesome regurgitation was achieved in 86% of patients (37/43) compared to 90% at year 3 (37/41) and 88% at year 1 follow-up (42/48). Elimination of troublesome atypical symptoms occurred in 80% of patients at year five (31/39), 88% at three years (42/48) and 82% at one year (45/55). No statistically significant differences in elimination of troublesome regurgitation or atypical symptoms were found between assessments at years one, three and five. Results were reported regardless of PPI use at the time of assessment (on or off PPI therapy). One additional patient underwent reoperation for recurrent daily troublesome GERD on PPI therapy, making a total of 3 (5%) after five years. No serious adverse events occurred. Limitations of the study include: small patient population, loss to follow-up, all patients crossed over to TIF at six months, functional tests and endoscopies were not performed at five years, and the results were reported regardless of PPI use at the time of post procedure assessment (on or off PPI therapy).

Stefanidis et al. (2017) conducted a prospective case series (n=45) to evaluate the long-term efficacy and safety of the TIF procedure in patients with a history of esophagitis or proven chronic GERD who had achieved symptom control with the administration of proton pump inhibitors (PPIs) but did not wish to continue receiving medications for life. Patients were included if they were age 18–60 years, BMI < 36 Kg/m2, had typical GERD symptoms (heartburn, regurgitation, chest pain) for more than six months for at least three times per week, and a history of esophagitis grade A and B or proven GERD by esophageal pH monitoring. Patients were excluded if they had esophagitis grade C or D or hiatal hernias > 2 cm in length. The primary outcome was GERD symptom elimination at follow up based on normalization of the GERD health related quality of life (GERD-HRQL) questionnaire. Follow-up ranged from 36–75 months (median 59 months). GERD-HRQL scores significantly improved compared to baseline (p<0.001). Heartburn was eliminated in 57.1% of patients (12/21), regurgitation was eliminated in 88.2% (15/17) and chest pain was eliminated in 83.3% (5/6) patients. Overall, 72.7% (32/44) reported elimination of their main symptom with no PPI usage. The rest of the patients reported a decreased daily dose of PPI. Adverse events included one pneumothorax and one event of hematemesis. Other events included epigastric pain and pharynx irritation. Limitations of the study include the small patient population, short-term follow-up and lack of a comparator.

Trad et al. (2017) reported on three-year follow-up data for 52 patients who underwent transoral esophagogastric fundoplication (TF) using the EsophyX device. The initial randomized controlled trial (TEMPO) (n=63) (Trad, et al., 2015) was conducted to assess the safety and efficacy of transoral esphagogastric fundoplication (TF) using the EsophyX device (n=40) vs. high dose proton pump inhibitors (PPI) (n=23). Included patients were ≥ age 18 years, had no hiatal hernia or hiatal hernia < 2 cm, had troublesome GERD symptoms while on proton pump inhibitors (PPI) for at least six month and had abnormal esophageal acid exposure (EAE). Abnormal EAE was defined as pH < 4 for more than 5.3% of total recorded time using 48-h Bravo pH testing. After the six-month evaluation period, the remaining 21 PPI patients elected to crossover to TF. Two patients were included in analysis that had undergone revisional procedures. Outcomes included: GERD symptom resolution using three GERD specific quality of life questionnaires; healing of esophagitis using endoscopy; EAE using 48-h Bravo testing; and discontinuation of PPI use. At the three-year follow-up (n=52), 90% (37/41) of patients reported elimination of troublesome regurgitation, 88% (42/48) patients reported elimination of all atypical symptoms. The mean Reflux Symptom Index score improved from 22.2 on PPIs at screening to 4.0 off of PPIs following TF (p=0.0001). The mean total time pH < 4 was improved significantly from 10.5% to 7.8% (p=0.0283). Esophagitis was healed in 86% (19/22) of patients and 71% (37/52) of patients had discontinued PPI therapy. Limitations of the study include: the small patient population; short-term follow-up; potential of bias due to the open-label crossover study design; and 11 patients lost to follow up (17%). According to the authors this 3-year report represents the longest follow-up on the TF procedure performed with the EsophyX device in the US to date.

Huang et al. (2016) conducted a systematic review and meta-analysis to evaluate the safety and efficacy of transoral incisionless fundoplication (TIF) performed with the EsophyX device for the treatment of GERD. A total of 18 studies (n=963) (five randomized controlled trials [RCTs] and 13 prospective observational studies) met inclusion criteria. The study subjects had GERD requiring PPIs and TIF with/without PPIs and primarily had
hiatal hernias less than 2–3 cm and BMI <30 or 35 kg/m². The average follow-up duration was more than three months. Outcomes included: esophageal acid exposure time (% time pH<4); 24-hour total number of refluxes; 24-hour acid reflux episodes; number of patients with complete discontinuation or reduction in proton pump inhibitors (PPIs) usage; overall response rate to TIF; and patient satisfaction. Responsiveness to TIF was defined as an improvement of at least 50% in the GERD health related quality of life (GERD-HRQL) scores or remission of heartburn and regurgitation; and/or complete cessation of PPIs use. The pooled relative risk of response rate (n=4 RCTs) to TIF versus PPIs/sham was 2.44 (95% CI 1.25–4.79; p=0.0009) in RCTs in the intention-to-treat analysis. Analysis of five RCTs showed no significant difference in percent of acid exposure (p=0.85). Subanalysis of two studies that compared TIF to sham without PPIs, showed a significant improvement following TIF in acid exposure (p=0.02). Analysis of three RCTs (n=73) evaluated the total reflux episodes before and after TIF procedure showing a significant reduction in reflux episode following TIF (p<0.0001). Two RCTs (n=71) reported no significant improvement in acid reflux episodes following TIF vs. PPIs (n=0.16). The effects of TIF decreased over time and PPIs usage led to dependence and increased dosage. Patient satisfaction from ten observational studies ranged from 45%–86% (weighted average 69.15%) at a mean six months. Severe adverse events included: seven perforations, five cases of post-TIF bleeding, and four cases of pneumothorax. One death was reported 20 months after TIF. The authors noted that there was a high degree of heterogeneity of the studies and data analysis was hampered by a lack of standardization in primary and secondary outcomes. Additional limitations of the studies included: variation in exclusion criteria and TIF technique; short-term follow-ups (range 3–36 months); and the small sample sizes used in outcome analysis.

Hunter et al. (2015) conducted a multicenter, randomized controlled trial (n=129) to determine if transoral fundoplication (TF) (EsophyX-2) (n=87) was better than PPI (n=42) for the treatment of troublesome GERD, particularly with regurgitation, in chronic PPI users. Patients were randomly assigned to groups that underwent TF and then received 6 months of placebo (n=87), or sham surgery and 6 months of once- or twice-daily omeprazole (controls, n=42). Patients were age 18–80 years, with more than a six month history of GERD symptoms and troublesome regurgitation, despite a minimum PPI dose of 40 mg per day. Treatment included TF followed by six months of placebo or sham followed by six months of PPI (omeprazole) therapy. Troublesome regurgitation was defined as mild symptoms for ≥2 days per week or moderate to severe symptoms more than one day per week, per Montreal consensus criteria. Symptom assessment was obtained by the Reflux Disease Questionnaire (RDQ), the Gastroesophageal Reflux Symptom Score, and the GERD-Health Related Quality of Life on PPI and off PPI for at least seven days. Exclusion criteria included: systemic disease not well controlled, body mass index ≥35, esophageal ulcer, stricture, Barrett’s esophagus ≥2 cm in length, hialtal hernia ≥2 cm in length, Los Angeles grade C or D esophagitis, esophageal dysmotility, previous esophageal or gastric surgery, peptic ulcer disease, gastric outlet obstruction, gastroparesis, pregnancy or plans for pregnancy in the next 12 months, immunosuppression, portal hypertension, and coagulopathy. If troublesome symptoms persisted at three months, despite twice a day medication use, the patient was declared a failure, the blind was broken and the patient was offered the opposite treatment. The primary outcome measure was the elimination of troublesome regurgitation. Secondary outcomes measures included: early failure (i.e., moderate to severe regurgitation at any time >12 weeks after surgery and after doubling medication, PPI, or placebo), control of intraesophageal acid exposure, improvement in various symptom scores (particularly heartburn), healing of esophagitis, common side effects associated with treatment (bloating and dysphagia), and significant adverse events. At six months follow-up significant improvement in troublesome regurgitation was reported in the TF group compared to PPI group (p=0.023). RDQ results were similar in both groups. In TF patients significant improvements were seen in mean reflux episodes (p<0.001), mean percent total time pH <4 (p<0.001) and mean DeMeester (p<0.001). Only the number of reflux episodes was normalized by the performance of TF. Esophagitis was healed in 10/13 FT patients vs. one sham patient. There was no significant difference between the groups in de novo esophagitis at six month. There were no significant changes in the sham group. Significantly more patients in the sham/PPI group (30/42) crossed over to TF compared to 24/87 TF patients who resumed PPI (p<0.001). Limitations of the study include: the small patient population, short-term follow-up, number lost to follow-up (19%) (11/87 in study group and 14/42 in sham group); unequal number of patients in each group; and incomplete follow-up data on 12 patients.

Hakansson et al. (2015) conducted a randomized controlled trial to compare outcomes of TIF with EsophyX (n=22) to sham procedure (n=22). The sham procedure consisted of upper GI endoscopy under general anesthesia. The primary outcome measure was the proportion of patients in clinical remission after 6-month follow-up. Inclusion criteria were: age 18–80 years, on daily PPIs for > 6 months, documented PPI-dependent,
and persistent GERD symptoms without PPI therapy (during the titration phase of the study). Subjects also showed evidence of two or more of the following for more than ten days while off PPI therapy: erosive esophagitis (Los Angeles [LA] grade A, B or C); abnormal ambulatory pH study; moderate to severe GERD symptoms, normal or near normal esophageal motility by manometry or impedance. Patients were excluded if they had a BMI > 35, Hill grade IV, hiatal hernia > 3 CM, esophagitis LA grade D, Barrett’s esophagus and other comorbidities. Patients underwent a two-month run-in period for testing the lowest possible PPI dose needed to control GERD symptoms. The primary outcome measure was time to treatment failure during the first six months after intervention. Treatment failure was defined as the need for PPI to control reflux disease. At six months follow-up, there was a significant difference in time in remission following TIF (197 days) vs. sham (107 days). Fourteen TIF patients were Hill grade I-II on endoscopic exam vs. no improvement seen in the sham group. The median GERD symptoms scores, based on the Quality of Life in Reflux and Dyspepsia (QOLRAD) estimates, improved significantly compared to baseline (p=0.0005) vs no improvement in sham group. The median GRSR score (p=0.004), median reflux dimension of Gastrointestinal Symptom Rating Scale (GSRS) score (p<0.001) were significantly improved vs. no change in the sham group. Significantly more TIF patients were off PPI therapy vs. sham (p=0.001) with a significant reduction in total acid reflux time (p=0.003). There was no significant difference in adverse events between TIF and sham. Adverse events included dysphagia, bloating, flatulence, post-operative epigastric pain, abdominal and musculoskeletal pain and vomiting and diarrhea. Limitations of the study include the small patient population and short-term follow-up.

Trad et al. (2015) conducted a multicenter randomized controlled trial to evaluate the efficacy of transoral incisionless fundoplication (TIF) using EsophyX2 (n=40) compared to proton pump inhibitors (PPIs) (n=23) for the treatment of GERD. Patients met the following criteria: age 18–80 years; GERD for > 1 year; > 6-month history of PPI use; troublesome atypical symptoms and/or regurgitation, with or without heartburn, while on daily PPI therapy; abnormal esophageal acid exposure (EAE); and Hill grade I or II. Abnormal EAE was defined as pH <4 for more than 5.3 % of total recorded time using 48-h Bravo pH testing). Patients were excluded if they had a body mass index (BMI) > 35 kg/m2; hiatal hernia > 2 cm in axial length and/or > 2 cm in greatest transverse dimensions, esophagitis grade C or D; Barrett’s esophagus > 2 cm; esophageal ulcer; fixed esophageal stricture or narrowing. Primary outcome was elimination of daily troublesome regurgitation or extraesophageal symptoms. Secondary outcomes were normalization of esophageal acid exposure (EAE), PPI usage and healing of esophagitis. Symptom assessment was conducted by using Gastroesophageal Health-Related Quality of Life (GERD-HRQL), Reflux Symptom Index (RSI), and the Reflux Disease Questionnaire (RDQ). At six-month’s follow-up, per the RDQ questionnaire 97% of TIF patients vs. 50% of PPI patients had elimination of troublesome regurgitation (p<0.001). Overall, 62% of TIF patients vs. 5% of PPI patients experienced elimination of regurgitation and extraesophageal symptoms (p<0.001). EAE was normalized in 54% of TIF patients (off PPIs) vs. 52% of PPI patients on maximum standard dose (p=0.914). Ninety percent of TIF patients were completely off PPIs, 3% were taking PPIs on demand and 8% were on daily PPIs. Endoscopic exam showed complete healing or reduction in reflux esophagitis in 90% of TIF patients compared to 38% PPI patients (p=0.018). In addition, 90% (28/31) of TIF patients (off PPIs) reported elimination of daily troublesome heartburn vs. 13% (2/16) PPI patients (p=0.003). Patient satisfaction with current health condition, as evaluated by GERD-HRQL, improved significantly in the TIF group compared to PPI group (p<0.001). No serious adverse events were reported following TIF. Limitations of the study include: heterogeneous small patient population, short-term follow-up, variety of PPIs used; and 2:1 randomization (TF:PPI). The authors noted that there could have been a potential placebo effect in the TIF group and stated that long-term follow-up was needed.

Witteeman et al. (2015) conducted a randomized controlled trial (n=60) to evaluate TIF in patients with GERD who were controlled with PPI but chose TIF over lifelong PPI therapy. Patients remained with PPI (n=20) or underwent TIF (n=40) with EsophyX. Criteria for study participation included: age 18–75 years, hiatal hernia ≤2 cm, proven reflux while off PPIs, on daily PPIs for ≥ 1 year, recurrence of GERD symptoms after cessation of PPIs, and normal or reduced lower esophageal sphincter resting pressure (5–40 mm Hg) at manometry. Patients with body mass index ≥ 35 kg/m2 and hiatal hernia > 2 cm, esophagitis grade D, Barrett’s esophagus and other comorbidities were excluded. At the six-month following-up (n=57) there was a significant improvement in quality-of-life scores in the TIF group (p<0.001) and an increase in lower esophageal sphincter resting pressure (p=0.004). There were no significant differences between the two groups in esophageal acid exposure time (p=0.228), normalization of pH, total number of reflux episodes at impedance measurements (p=0.058) or healing of esophagitis. Following TIF, cessation of PPIs occurred in 74% of patients, 17% used PPIs occasionally and 9% used PPIs daily at six months. At the end of six months the 20 PPI patients crossed over to
TIF. Twelve months (n=45) following crossover, quality of life (p<0.05), number of reflux episodes and the increase of lower esophageal sphincter pressure showed a significant improvement compared to baseline. There was no significant improvement in distal esophageal acid exposure (p=0.06). Normalization of pH was accomplished in 44% of TIF patients at six months but dropped to 29% at 12 months. The use of PPIs was discontinued by 39% of patients with 44% needing PPIs on a daily basis at 12 months. At 12-months follow-up, 5% of patients had undergone revisional surgery to control their symptoms. TIF adverse events included an incident of pneumoperitoneum, three cases of pneumonia and a readmission for severe epigastric pain. Milder adverse events (dysphagia and gas bloating) resolved within a short period of time. Limitations of the study include the small patient population; 2:1 randomization; short-term follow-up and number of patients lost to follow-up.

Wendling et al. (2013) conducted a systematic review of the impact of TIF with the EsophyX system on subjective and objective GERD indices. A total of fifteen observational, retrospective or prospective studies were included in this review from 2006 up to March 2012. No randomized controlled trials were found in the literature. Data collected included GERD-health related quality of life (HRQL) and reflux system index (RSI) scores, PPI discontinuation and patient satisfaction rates, pH study metrics, treatment failures and complications. Both GERD-HRQL scores (21.9 vs. 5.9, p<0.0001) and RSI scores (24.5 vs 5.4, p≤0.0001) were significantly reduced after TIF. Overall patient satisfaction was 72%. The overall rate of PPI discontinuation was 67% across all studies, with a mean follow-up of 8.3 months. pH metrics were not consistently normalized. The major complication rate was 3.2 % and the failure rate was 7.2% across all studies. The authors noted that additional studies of TIF, particularly in patients with moderate GERD symptoms and minimal anatomic degradation at the gastroesophageal junction, are required to identify the optimal target population for the procedure. Also, well-designed prospective clinical trials are needed to assess the effectiveness and durability of TIF compared to sham procedures and current gold standard GERD therapies prior to making any definitive recommendations for its widespread clinical use.

In a multicenter prospective, noncomparative 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. 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.
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.

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. 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

- **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).**

- **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.

**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).

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.

The Gatekeeper Reflux Repair System, and plexiglas or polymethylmethacrylate [PMMA], are not FDA-approved devices.

**Literature Review - 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. According to Hayes (2015) the EndoCinch has been discontinued.
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.

Earlier studies have primarily been in the form of case series with small patient populations and short term follow-ups with over 50% treatment failures or short-term improvement in symptoms were not maintained (Schiefke, et al., 2005; Chadalavada, et al., 2004; Mahmood, et al., 2003; Filipi, et al., 2001).

Literature Review - Endoscopic Plication™ System: Studies in the peer-reviewed literature investigating endoscopic plications systems are primarily in the form of case series. Large, well-designed, controlled trials showing long-term safety and efficacy 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).

**Literature Review - The Muse™ System (formerly the SRS™ Endoscopic Stapling System):** There is a lack of studies in the peer-reviewed literature investigating the safety and efficacy of the Muse System or SRS Endoscopic Stapling System. The studies in the peer-reviewed literature are primarily in the form of case series with small patient populations (n=14–66). Randomized controlled trials with long term follow-up are needed to determine whether the Muse System or SRS Endoscopic Stapling System improves outcomes compared to alternative treatment modalities (Kim, et al., 2016; Roy-Shapira, et al., 2015; Zacherl, et al., 2014; Danalioglu, et al., 2014).

**Literature Review - Magnetic Sphincter Augmentation Device (MSDA) (LINX™ Reflux Management System):** Overall, studies in the peer-reviewed literature are primarily in the form of case series and retrospective reviews. Large, well-designed, controlled trials showing long-term safety and efficacy are lacking (Skubleny, et al., 2016; Schwameis, et al., 2014; Bonavina, et al., 2008; Bonavina, et al, 2010; Lipham, et al., 2012; Ganz, et al., 2013). According to Sheu et al. (2015) no direct comparison study has been done comparing MSDA to laparoscopic Nissen fundoplication.

Aiolfi et al. (2018) conducted a systematic review and meta-analysis to compare outcomes of laparoscopic Nissen and Toupet fundoplication (LF) to Magnetic Sphincter Augmentation (MSA) using the LINX device. All articles comparing MSA and laparoscopic partial or total fundoplication were included in the systematic review. Six retrospective reviews and one registry study (n=1211) were included. No randomized controlled trials were found. The patient populations of the individual studies ranged from 24 to 415. A total of 686 patients (56%) received the LINX and 525 (44%) patients underwent laparoscopic total (Nissen) or partial (Toupet) fundoplication. The operative time was 42–73 min in the MSA group and 76–118 in the LF group. Overall postoperative morbidity was 0–3% in the MSA group and 0–7% in the LF group. There was no mortality. The hospital length of stay was 13–48 hours in the MSA group and 26–48 hours in the LF group. The postoperative follow-up ranged from 6–12 months. Compared to preoperative baseline, a statistically significant improvement was noted for both procedures. Reoperation was required in 13 MSA patients including 12 device removals, one for erosion and one crural release. There were 11 reoperations in the LF group. Dysphagia requiring endoscopic dilatation occurred in 9.3% of patients in the MSA group compared to 6.6% of LF patients (p=0.119), not statistically significant. The pooled odds ratio of gas/bloat symptoms, ability to vomit, and ability to belch were 0.39 (p<0.001), 10.10 (p<0.001), and 5.53 (p<0.001), respectively. The postoperative quality of life score was similar between groups (p=0.101). There were no significant differences in the pooled odds ratio of PPI suspension, endoscopic dilation, and reoperation (p=0.548, p=0.119, p=0.183, respectively). Postoperative morbidity was 0%–3% in the MSA group and 0–7% in the LF group. There was no mortality. The author’s noted
that the difference in outcomes between the two patient groups should be interpreted with caution since no comparative randomized clinical trials existed to provide strong evidence and subgroup analysis according to baseline variables was not possible because all outcomes were aggregated in the analyzed studies. This analysis is also limited by the retrospective and registry study designs, small patient populations and short-term follow-ups. Prospective randomized controlled trials with large patient populations and long-term follow-ups are needed to support the safety and efficacy of LINX.

In the 2018 update of the Hayes Technology Brief on Linx, Hayes concluded that there was an overall low-quality body of evidence that suggested that magnetic sphincter augmentation (MSA) is associated with improved quality of life and GERD symptoms. However, substantial uncertainty exists due to limited follow-up beyond one year and unclear patient selection criteria. Studies were included if they evaluated LINX for the treatment of GERD and compared LINX with alternative treatments (e.g., changes in proton pump inhibitor [PPI] use, patient reported GERD symptoms, quality of life) or harms data. Seven clinical studies (n=66 to 415 patients) met the inclusion criteria. One randomized controlled trial (RCT) that compared MSA with twice-daily PPI treatment and four poor and two very, poor quality cohort studies comparing MSA with laparoscopic fundoplication were included. Outcomes assessed generally included indicators of esophageal acid exposure before and after treatment, changes in PPI usage, patient-reported symptoms, and complications. Hayes also noted that definitive patient selection criteria have not been established for MSA with the LINX. There is a lack of data on patients with moderate-to-severe esophageal disease and moderate-to-severe obesity, a risk factor for GERD. Limitations of individual studies included small patient populations, lack of long-term data, lack of power, analysis, variable follow-up durations among patient populations, and significant differences in baseline characteristics between groups. MSA appeared to be moderately well tolerated; there were no reports of deaths, and serious adverse events were uncommon. MSA resulted in fewer patients experiencing the inability to belch or vomit. Additional prospective comparative studies with large patient populations and long-term follow-up are needed to establish the effectiveness of LINX for the treatment of GERD.

Chen et al. (2017) conducted a systematic review and meta-analysis to compare the safety and efficacy of the LINX magnetic sphincter augmentation system (MSA) to Nissen Fundoplication (NF). Four retrospective studies (n=624) met inclusion criteria. A total of 299 patients were in the MSA group and 325 in the NF group. Outcomes included differences in the use of proton-pump inhibitors, complications, and adverse events. There were no significant differences between the groups in resumption of PPIs (p=0.23), severe dysphagia for dilation (p=0.74), ability to belch (p=0.13), ability to vomit (p=0.38) and adverse events (p=0.49). A lower trend toward gas or bloating was seen in the MSA group (p=0.02). Operative time (p=0.001) and length of stay (p=0.005) were significantly shorter in the MSA group. Limitations of the studies include: the retrospective study design, small patient populations; and two trials did not match the size of hiatal hernias. Prospective studies with long-term follow-ups are needed to establish the safety and efficacy of MSA for the treatment of GERD.

Skubleny et al. (2017) conducted a systematic review and meta-analysis to compare the safety and efficacy of the LINX- magnetic sphincter augmentation system to Laparoscopic Nissen fundoplication (LNF) for the treatment of GERD. Randomized controlled trials, non-randomized comparison study and case series with greater than five patients were included. Primary outcomes included: GERD-Health-Related Quality of Life scores, DeMeester scores, operative times, ability to belch, ability to emesis, discontinuation of proton pump inhibitor (PPI), need for endoscopic dilation, procedural satisfaction, presence of gas/bloating and dysphagia. Secondary outcomes included mortality and morbidity. Two retrospective cohort comparative studies and one case series (n=688) met inclusion criteria. Mean duration of follow-up ranged from 7–16 months for LNF and 7–12 months for LINX. There was a statistically significant improvement reported with LINX in preserving the patient’s ability to belch (p=0.00001) and ability to emesis (p=0.06). However, there was no statistically significant difference between the groups in gas/bloating (p=0.06), postoperative dysphagia (p=0.43) and discontinuation of PPI use (p=0.68). Six patients required endoscopic balloon dilation following LINX vs. zero dilations post-LNF. Major morbidity for LNF included one case of intraoperative pleural injury, two cases of retroesophageal abscesses and four cases of revision due to hiatal hernia recurrence. The LINX group morbidity included one pleural injury, two episodes of intraoperative bleeding, one pneumothorax and one gastroesophageal junction obstruction. Two LINX devices were removed due to treatment failure and device erosion 20 months after surgery. Limitations of the studies included: lack of randomization; short-term follow-up; loss to follow-up (7.7%–10.6%); and heterogeneity in the size of hiatal hernia and grade of esophagitis accepted within treatment arms. The authors noted that the validity of many of the primary outcomes was decreased due to their subjective nature and lack of clear medical.
definition. Additional studies are needed to assess the long-term outcomes of LINX. The long-term implications of reversal of the LINX are unknown.

Asti et al. (2016) conducted an observational cohort study to assess and compare health-related quality of life over time in two concurrent cohorts of patients undergoing laparoscopic Toupet fundoplication (LTF) (n=103) or LINX (n=135). Inclusion criteria were age > 18 years, chronic GERD symptoms despite PPI use for at least six months, objective evidence of reflux at the pH study, and normal esophageal motility documented by manometry. The primary outcome was postoperative quality of life measured by the Gastro-Esophageal Reflux Disease-Health Related Quality of Life (GERD-HRQL) questionnaire. Secondary outcomes were PPI use, presence of gas-related symptoms or dysphagia, and reoperation-free probability. Patients in both groups were evaluated at 3–12 months, and then every 12 months with the GERD-HRQL survey plus questions about PPI use, gas-related symptoms and dysphagia. All patients had a minimum of one-year follow-up. The mean postoperative follow-up was 42 months in the LTF group and 44 months in the LINX groups. The GERD-HRQL score significantly decreased within normal values in both groups with no significant difference between the groups. There were no significant differences between the groups in PPI use (p=0.388), gas-related symptoms (p=0.532), or dysphagia (p=0.241). The duration of the surgical procedure was 87 minutes in the LTF group vs. 42 minutes in the LINX group (p<0.001). One patient in the LINX group had a respiratory arrest within the first hour postoperatively and was successfully resuscitated without consequences. Postoperative morbidity consisted of atrial fibrillation (n=1), urinary retention (n=1), and bleeding from a trocar site (n=1), all occurring in the LTF group. Author-noted limitations of the study included the fact that the GERD-HRQL is a subjective test and the LINX procedures were not standardized regarding large hernia repair (crural repair). There is also a risk of bias due to the observational design of the study. Further research is needed to investigate correlation between longitudinal quality of life data with objective long-term outcomes of these procedures.

Ganz et al. (2015) reported the five-year outcomes from a multicenter, prospective study (n=85) conducted to evaluate the safety and efficacy of LINX for the treatment of GERD. This is a follow-up to the study submitted for FDA approval. Patients were 18 to 75 years old, had GERD for at least six months, were partially responsive to daily PPIs, had not achieved adequate reflux control and had evidence of pathologic esophageal acid exposure. Patients were excluded for the following: evidence of hiatal hernia greater than 3 cm, esophagitis grade C or D according to the Los Angeles classification, body mass index >35, Barrett’s esophagus, or motility disorder. Outcomes included reflux symptoms, quality of life, and use of PPIs. Following treatment, a 50% or greater reduction in GERD-HRQL score was achieved in 83% of patients (70/84). A reduction of 50% or more in the average daily dose of PPIs occurred in 89.4% of patients (75/85) (p<0.001). Patients with moderate or severe heartburn had a decrease from 89% to 11.9%. Moderate or severe regurgitation occurred in 57% of patients at baseline and 1.2% (p<0.001). Healing of esophagitis was seen in 26 of 34 patients. All patients reported the ability to belch and vomit if needed. Symptoms of bloating/gas decreased significantly (p<0.0001). No device erosions, migrations, or malfunctions occurred. Six devices were removed at three years (7%). Reoperation rates were not available. Limitations of the study included: lack of a comparator; 15 of the original 100 patients were lost to follow-up (15%); esophageal pH testing and manometry were not performed beyond one year.

Saino et al. (2015) reported five-year data from a multicenter, prospective case series (n=33) of patients with GERD, age 18–75 years, who underwent MSAD with LINX. Patients had abnormal esophageal pH, exhibited typical GERD symptoms, and had been taking daily proton pump inhibitors (PPIs). Patients were excluded if they had a large hernia (>3 cm), Grade B or higher esophagitis, a body mass index of >35 kg/m², Barrett’s esophagus, motility disorders, gross esophageal anatomic abnormalities or a known allergy to titanium, stainless steel, nickel, or ferrous materials. Outcomes included: gastroesophageal reflux disease (GERD)-Health Related Quality of Life (HRQL) questionnaire score, esophageal pH, PPI use, and complications. Compared to baseline, there were significant improvements in mean total percentage of time with pH <4 (p<0.001) and mean total GERD-HRQL score (p<0.001) and 85% of patients achieved pH normalization or at least a 50% reduction. Complete discontinuation of PPIs was achieved by 87.8% of patients. The re-operation rate was 6.8% and due to dysphagia, continued reflux symptoms, and planned MRI imaging. There were no device erosions, malfunctions, or migrations at any point and no other long-term complications. Limitations of the study include the small patient population, lack of a comparator; loss of 12 patients from the original pilot study; failure of all sites to perform pH monitoring after the first year and no manometric evaluations were performed after the first year.
Bonavina et al. (2013) reported on 100 consecutive patients who underwent magnetic sphincter augmentation (MSA) for the treatment of GERD. Implant duration ranged from 378 days to six years (median 3 years). Patients were included if they were age 18 years and older, had GERD for at least six months, had persistent reflux symptoms despite daily proton pump inhibitors (PPIs), and pathologic reflux was confirmed by ambulatory esophageal pH monitoring. Following implant median total acid exposure time was significantly reduced from 8.0% to 3.2% (p<0.001). The median GERD Health Related Quality of Life score improved from 16 on PPIs at baseline to 24 off PPIs and significantly improved to a score of 2 (p < 0.001). A total of 85% of patients achieved freedom from daily dependence on PPIs. There were no reported events of device migrations or erosions. Three patients had the device laparoscopically removed for persistent GERD, painful swallowing (odynophagia), or dysphagia with subsequent resolution of symptoms.

**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.

**Technology Assessments/Systematic Reviews of Multiple Systems**

Coronel et al. (2018) conducted a systematic review and meta-analysis of randomized controlled trials (n=16) to evaluate the safety and efficacy of endoscopic treatment for GERD. Endoscopic therapies included: transoral incisionless fundoplication (TIF2) using EsophyX; surgical plication by NDO surgical device; Stretta radiofrequency therapy; EndoCinch endoscopic suturing system; injectable esophageal prostheses by Gatekeeper device, and biocompatible non-resorbable copolymer Enteryx device. Controls included: sham procedure, proton pump inhibitors (PPIs) or laparoscopic anti reflux surgery (LARS). Inclusion criteria were randomized controlled trials with patients over 18 years of age, undergoing endoscopic procedures for chronic GERD (symptoms ≥ 6 months in duration), and follow-ups of ≥ 3 months. Sixteen RCTs (n=1085) met inclusion criteria. The primary outcome measure was overall efficacy of endoscopic treatments versus controls. A total of 221 patients underwent TIF2, 145 surgical plications, 81 Stretta; 42 endoscopic suturing, 32 injectable esophageal prostheses and 75 biocompatible non-resorbable copolymer. Control groups (n=312) included 294 patients who underwent a sham procedure, 120 received PPIs and 63 underwent LARS. Overall, there was a statistically significant difference in treatment efficacy in favor of endoscopic treatment (p<0.00001). At three months follow-up, three trials (n=263) showed a significant difference in two endoscopic groups (p<0.00001). At six months, six trials (n=377) also showed a statistically significance difference for endoscopic subjects (p<0.00001). At 12 months follow-ups in two trials (n=67) showed no statistically significant difference (p<0.06).

Regarding efficacy of endoscopic treatments (ET) versus pharmacological (PPI) four studies (n=320) were analyzed. At six months (n=277) statistically significant difference was seen in favor of ET (Stretta, TIF2) (p<0.00001). One trial (n=43) showed no difference at the 12-month follow-up. In studies comparing ET with sham, at six months two RCTs (n=100) showed a significant difference (p<0.0001) but at 12 months there was no significant difference (1 RCT; n=24). The outcomes of normalization of esophageal acid pH (p<0.03); lower esophageal sphincter resting pressure (LESRP) (p<0.00001); mean percent of total time of esophageal pH < 4 (p<0.0001); and mean number of reflux episodes (p<0.0001) were statistically significant in favor to the ET. Overall, there was high heterogeneity between the trials in up to 12 months of follow up. The time in remission (p<0.0001), number of patients with GERD HRLQ score >50 % improvement (p<0.0001), elimination of troublesome regurgitation (p<0.0001) were statistically significant in favor of ET with very low heterogeneity between the trials at six and 12 months follow up. The mean GERD HRQL score (p<0.0001), the heartburn score (p<0.0001) and DeMeester score (p<0.0001) showed statistically significance improvement following ET up to six and 12 months but there was high heterogeneity. The SF-36 score showed improvement in favor of controls at 12 months follow up, but also with high heterogeneity between studies. When comparing endoscopic therapies only to sham, the results were similar. Most studies reported clinically significant moderate to severe post-procedure related adverse events (n=312 events) such as epigastric pain, musculoskeletal pain, dysphagia, sore throat, chest pain, nausea and vomiting, bloating and flatulence that were treated clinically, with complete resolution and no major sequelae. The event rate was 38% for ET, 24% for sham, 4% for PPI and 2% for the
LARS group. Author noted limitations included a high degree of heterogeneity in outcomes, short-term follow-ups (<6 months) and many patients were offered alternative interventions during follow-ups and the actual benefit of the endoscopic intervention was compromised. The authors noted that to date, there are no randomized studies evaluating the efficacy of endoscopic procedures with over 12 months of follow up. The role of ET for the treatment of GERD remains unclear.

Hayes (2017) conducted a comparative effectiveness Directory Report on endoscopic therapy for GERD. The report included Stretta, EsophyX and Medigus Ultrasonic Surgical Endostapler (MUSE). Fourteen comparative studies of which five were randomized and five were noncomparative studies met inclusion criteria. The report included comparative studies with follow-up ≥ 6 months and noncomparative studies with ≥ 100 patients and ≥12 months follow-up. A total of 12 Stretta studies (n= 36–217), five EsophyX studies (n=44–129) and two MUSE studies (n=27–66) were reviewed. There was insufficient evidence to support the use of MUSE for GERD patients. Although findings for Stretta and EsophyX suggested improvement in clinical and patient-reported outcomes compared to baseline for GERD patients who were unsatisfied with or uncontrolled on PPIs, the evidence was of low quality. Long-term data are lacking for these two procedures. Limitations of the studies included: lack of randomization and/or blinding, small sample size, short-term follow-up, lack of and inconsistent comparators, loss to follow-up (especially for pH measures), retrospective study designs, inconsistent use of outcome measures and potential lack of generalizability.

Chen et al. (2009) conducted a systematic review of 33 studies examining seven endoscopic treatments for GERD. 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 was insufficient evidence 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 PPI was found. 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 demonstrated that subgroups of patients experienced improvement or resolution of typical GERD symptoms and decreased PPI usage. It was also noted that there was 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 noted 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 was grade 1b and 2b evidence demonstrating the EndoCinch plication is effective in reducing GERD symptoms at short-term follow up. However, overall, the procedure did 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 was grade 1b and 2b evidence demonstrating that the Stretta procedure was effective in reducing GERD symptoms at short- and mid-term follow-up. However, in the majority of the studies, the procedure did not significantly reduce the acid exposure in the distal esophagus. There was grade 1b and 2b evidence demonstrating that full-thickness plication was effective in reducing GERD symptoms, and acid exposure in the distal esophagus (Torquati, et al., 2007).

**Peroral Endoscopic Myotomy (POEM)**
Achalasia is a rare motility disorder of the esophagus and is defined by three elements: the reduction or absence of the primary peristaltic waves in the distal two thirds of the esophagus, incomplete or no relaxation of the lower esophageal sphincter (LES) during swallowing and increased resting LES tone. There is degeneration of the esophageal muscle and the nerves that control the muscles. The cause of primary or idiopathic achalasia is unknown. Secondary achalasia is due to diseases that cause esophageal motor abnormalities (e.g., Chagas disease, esophageal cancer, Fabry disease, amyloidosis). Achalasia most commonly occurs in individuals between ages 25–60 years. Symptoms of achalasia include dysphagia, heartburn, difficulty belching, chest pain, regurgitation of undigested food and liquid, and weight loss (Spechler, 2019a; Tefas, et al., 2018; National Organization for Rare Disorders [NORD®], 2017; Hayes, 2015).

Achalasia is defined by aperistalsis and abnormal LES relaxation (integrated relaxation pressure [IRP] > 15 mmHg). The disorder is characterized manometrically by insufficient relaxation of the lower esophageal sphincter (LES) and loss of esophageal peristalsis; radiographically by aperistalsis, esophageal dilation, with minimal LES opening, “bird-beak” appearance, poor emptying of barium; and endoscopically by dilated esophagus with retained saliva, liquid, and undigested food particles in the absence of mucosal stricturing or tumor (Spechler, et al., 2019b; American College of Gastroenterology, 2013).

The three types of achalasia based on the Chicago Classification of patterns of esophageal pressurization on high-resolution manometry (HRM) (CC v3.0) include the following:

- **Type I (classic achalasia)** – Incomplete LES relaxation, aperistalsis and absence of esophageal pressurization. Swallowing results in no significant change in esophageal pressurization and has 100% failed peristalsis with a distal contractile integral (DCI, an index of the strength of distal esophageal contraction) < 100 mmHg.
- **Type II** – Incomplete LES relaxation, aperistalsis and panesophageal pressurization in at least 20% of swallows. Swallowing results in simultaneous pressurization that spans the entire length of the esophagus. Type II achalasia has 100% failed peristalsis and pan-esophageal pressurization with ≥ 20 percent of swallows.
- **Type III (spastic achalasia)** – Incomplete LES relaxation and premature contractions (distal latency [DL] < 4.5 seconds) in at least 20% of swallows. Swallowing results in abnormal, lumen-obliterating contractions or spasms. Type III achalasia has no normal peristalsis and premature (spastic) contractions with DCI >450 mmHg-sec-cm with ≥ 20 percent of swallows (Spechler, 2019a; Schlottmann, et al., 2017).

The primary treatment objective for achalasia is to relieve obstruction in the distal esophagus by decreasing the resting pressure in the lower esophageal sphincter (LES) to a level at which the sphincter no longer impedes the passage of undigested food and liquid. Established treatment options include pharmacotherapy (e.g., injection of botulinum toxin into the esophagus, use of oral nitrates) or mechanical disruption of the muscle fibers of the LES by surgical interventions (i.e., endoscopic balloon dilation, surgical Heller myotomy [LHM] with or without fundoplication) to reduce the incidence of gastroesophageal reflux disease (GERD). LHM is the treatment of choice and has an 85%–90% effect in treating the condition. When a patient has dysphagia following surgical myotomy, the first suspicion is incomplete myotomy (Spechler, 2019a; Fernandez-Ananin, et al., 2018; Tefas, et al., 2018; Hayes, 2015).

Peroral endoscopic myotomy (POEM) is a proposed, less invasive alternative to laparoscopic Heller myotomy for treatment of primary idiopathic esophageal achalasia. It is considered a natural orifice transmural endoscopic surgery (NOTES). The POEM technique involves guiding an endoscope through the esophagus, making an incision in the mucosa, creating a submucosal tunnel for access to the lower esophagus and gastroesophageal junction, and cutting the muscle fibers in the lower esophagus and proximal stomach. Internal incisions are closed with clips after myotomy is complete. The proposed advantage of POEM is that it can deliver a longer myotomy than pneumatic dilation or the Heller procedure. The length of myotomy from the esophageal to the gastric side can be adjusted on a case-by-case basis while achieving functional durability of traditional surgical myotomy. A longer myotomy may be more effective in controlling symptoms. POEM includes no antireflux procedure and can therefore result in GERD. POEM is being proposed for the treatment of other disorders, such as diffuse esophageal spasm (DES), dysphagia, Jackhammer esophagus, esophageal diverticula, or nutcracker
esophagus. POEM is also proposed for the treatment of failed surgical myotomy (Khashab, 2019; Spechler, 2019a; Inoue, et al., 2018; Hayes, 2015).

Because of its less invasive nature, POEM is proposed to reduce postoperative pain and maximize return to regular activities of daily life. Controversies regarding the use of POEM include: 1) debate over where and how to make the myotomy in order to maximize effectiveness for reducing dysphagia and minimize the potential for gastroesophageal reflux disease (GERD); 2) concerns over learning curves and the time it takes to gain proficiency with the procedure; 3) lack of comparative and long-term data to definitively support the safety and effectiveness of POEM; and 4) the use of routine postoperative computed tomography (CT) scans (Spechler, 2019a; Hayes, 2015).

Preliminary short-term studies show positive outcomes following POEM but the general consensus is that long-term data from randomized controlled trials is needed. Studies comparing POEM with laparoscopic myotomy and partial fundoplication, the gold standard, are lacking. In a review article Shaheen, et al. (2018) recommended that a cautious approach be taken when introducing this procedure into clinical practice because unrecognized complications carry significant morbidity. In a large retrospective study published by Zhang et al. (2016), delayed mucosal closure occurred in 0.8%, delayed bleeding in 0.2%, hydrothorax requiring intervention in 0.5%, and pneumothorax requiring intervention in 1.5%.

There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of POEM for the treatment of esophageal achalasia or any other indication.

**Literature Review**

Numerous systematic reviews and systematic reviews with meta-analysis have been published investigating POEM for the treatment of achalasia. Short-term significant outcomes have been reported however, there are several limitations of the studies including: small, heterogeneous patient populations; various outcomes measures; use of different POEM techniques; conflicting outcomes; lack of prospective comparative studies and randomized controlled trials; and lack of long-term data. Long-term data from prospective comparative studies are needed to establish the appropriate selection criteria for POEM candidates and the safety and efficacy of POEM for the treatment of Achalasia.

Evensen et al. (2019) conducted a systematic review to assess the outcome of POEM in treatment-naïve patients. Seven studies, of which six were retrospective reviews, met the inclusion criteria. Inclusion criteria were original articles of English language with ≥ 20 subjects of whom ≥ 90% of patients were treatment-naïve; had follow-ups ≥ 3 months; and outcome measures included symptom scores (e.g., Eckardt score [ES]) and objective tests such as high resolution manometry (HRM) or timed barium esophagogram [TBE]). Review articles, meta-analyses, pediatric data, duplicates; and articles with overlapping data were excluded. The primary outcome measures were the percentage of patients with ES ≤ 3 (i.e., clinical success) and the ES before and after POEM. Secondary outcome measures included: follow-up period; timing of clinical evaluation; percentage of patients with clinical evaluation; timing of objective tests; percentage of patients with objective tests (TBE or HRM); lower esophageal sphincter (LES) pressure (resting pressure and integrated relaxation pressure/residual pressure) before and after POEM; TBE before and after POEM; procedure-related complications; reflux symptoms after POEM; reflux esophagitis after POEM and positive 24 hour pH monitoring post-POEM. The follow-up range was 3–51 months. Short-term clinical success (ES) ranged from 91%–100% and the follow-up rate was 95%–100%. Objective tests following POEM were performed at 1–19 months, and 47%–100% of patients were evaluated by objective tests. HRM showed a significant decrease in LES-pressure after POEM. The frequency of post-POEM reflux symptoms varied from 3%–19%. Esophagitis beyond grade A according to the Los Angeles classification was demonstrated in 9% of the patients. Six studies reported procedure-related complications and reflux symptoms after POEM. Clavien Dindo (CD) classification grade 1 complications occurred in 5% of the patients. Overall, CD grade 3b was the most serious complication reported (CD Grade 1 is any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Grade 3b requires surgical, endoscopic or radiological intervention). Limitations of the studies include: retrospective study design; lack of follow-up for objective evaluations; and evaluation of post-POEM reflux only by symptom registration without applying a validated questionnaire. Due to the poor quality of available studies and retrospective study design, the safety and efficacy of POEM for treatment-naïve patients could not be established.
Lee et al. (2019) conducted a systematic review and meta-analysis to evaluate the safety and efficacy of peroral endoscopic myotomy (POEM) in children. Studies that conducted POEM in pediatric patients age < 18 years were included. Studies were excluded if they had a non-pediatric population; no clear diagnostic or clinical evaluation of achalasia (e.g., Eckardt scoring system, esophageal manometry, barium X-ray, upper endoscopy); and/or were non-human studies, case-reports, editorials, and review papers. Twelve studies (n=142) met inclusion criteria and included eight case series and four retrospective cohort studies. Three of the studies were published conference abstracts. Primary outcome measures included the Eckardt score and lower esophageal sphincter (LES) pressure before and after POEM. Secondary outcome measures were the clinical success rate and adverse events. Follow-ups ranged from 1-36 months (median 14 months). Compared to baseline, there was a significant reduction in mean Eckardt scores by 6.88 points (p<0.001) and a decrease in LES pressure by 20.73 mmHg (p<0.001). At least 93% of the patients experienced improvement or resolution of achalasia symptoms. Adverse events included mucosal injury (n=7), esophageal tear (n=1), esophageal leak (n=1), focal atelectasis (n=2), pneumoperitoneum (n=13), pneumothorax (n=4), pneumonitis/pneumonia (n=15), pleural effusion (n=9), subcutaneous or mediastinal emphysema (n=25), retroperitoneal CO2 (n=2), fever (n=1), and severe-postoperative pain (n=2). There were also cases of clinical reflux symptoms after POEM such as heartburn (n=2), regurgitation (n=11), and reflux esophagitis (n=5). Most events were minor and self-limiting. Limitations of the studies included: small patient populations; short-term follow-ups; retrospective study designs and conference abstracts; no comparators; missing data; and heterogeneity of the procedure. Randomized controlled trials comparing POEM to established treatment options are needed to establish the safety and efficacy of POEM for the treatment of achalasia in pediatric patients.

Schlottmann et al. (2018) conducted a systematic review and meta-analysis to compare the outcomes of oral endoscopic myotomy (POEM) and laparoscopic Heller myotomy (LHM) for the treatment of esophageal achalasia. Studies that investigated POEM or LHM with at least 20 patients and a follow-up greater than nine months were included. The primary outcome measures were improvement of dysphagia and posttreatment gastroesophageal reflux disease (GERD). A total of 53 studies investigating LHM (n=5834) and 21 studies on POEM (n=1958) met inclusion criteria. There were five randomized control trials investigating LHM (n=25–138). The one randomized controlled trial that included POEM was a comparison of two different surgical techniques. Mean follow-up was significantly longer for LHM studies (41.5 mos. vs. 16.2 mos.) (p<0.0001). Predicted probabilities for improvement in dysphagia at 12 months were 93.2% for POEM and 91.0% for LHM (p=0.01) and 92.7% and 90.0%, respectively, at 24 months (p=0.01). Average improvement of dysphagia was 93.2% for POEM and 87.7% after LHM. Patients undergoing POEM were more likely to develop GERD symptoms (p<0.0001), GERD evidenced by erosive esophagitis (p<0.0001) and GERD evidenced by pH monitoring (p<0.0001). The estimated odds of GERD symptoms increased by a factor of 1.16 with a 12 month increase in follow-up time. On average, length of hospital stay was 1.03 days longer after POEM (p=0.04). Since morbidity and mortality were extremely low for both procedures, statistical analysis could not performed. Although short-term symptom relief was significantly better with POEM, the authors noted that the absolute difference between the groups was only 5.5% and conclusion regarding superiority should be viewed with caution. Limitations of the studies include the retrospective study designs, lack of prospective comparative studies, and short-term follow-ups following POEM procedure.

Fernandez-Ananin et al. (2018) conducted a systematic review of the literature to evaluate the optimal treatment (i.e., repeat laparoscopic myotomy, pneumatic dilatation, POEM) when surgical myotomy fails. Failure was defined as the reappearance of symptomatology (e.g., dysphagia, chest pain, regurgitation, cough, heartburn). A total of 37 studies met inclusion criteria including: four studies (n=87) investigating pneumatic dilatation (PD), 166 patients who underwent revisional surgery (11 studies) and 36 patients treated by POEM (five studies). Studies were primarily retrospective in design. Studies with patients treated for achalasia who had failed a surgical myotomy were included. Exclusion criteria were: studies with insufficient data to verify the results of the treatment performed, as well as those that used a treatment modality different from those mentioned; case reports; systematic reviews; non-English studies, and animal studies. The primary outcome measure was synthesizing the current possibilities of treatment after laparoscopic myotomy failure in patients with achalasia and how to define its benefits and its results. The secondary outcome was to define an algorithm of action for the patients in whom evidence fails after the Heller myotomy and determine the order of their choice. PD failure (n=87) was caused by incomplete myotomy combined with fibrosis in seven patients and one case was an incomplete myotomy without fibrosis. The cause of failure was not defined in other studies. The mean time
between detection of myotomy failure and initiation of PD treatment was four months. The mean number of PDs performed to achieve the absence of symptoms was 2.5 (range: 1–3). The mean interval between dilations was 26 months (range: 0–144). The success rate with PD was 89%. Regarding LHM the cause of failure (n=93) was due to incomplete myotomy (n=64), fibrosis (n=23) or both (n=6). PD prior to re-laparoscopic Heller myotomy (LHM) was used in 64% of patients. The reported re-LHM operative time in six studies was an average of 177 minutes (range: 111–240). The conversion rate to open surgery was 6%. Hospital stays ranged from 2–8 days (mean four days). Follow-up time ranged from 6–63 months (mean 26.3 months). The success rate ranged from 69%–100%, although there was great variability in the exposure of the data. Regarding POEM the time between surgical myotomy and POEM ranged from 11–134 months (mean 98 months). PD was performed prior to POEM in 80% of patients. Operative time ranged from 62–175 minutes (mean 99 minutes). The mean hospital stay was 2.1 days. The success rate was 98.4% and the follow-up time ranged from 3–10 months (mean 7.4). The initial procedure chosen by the majority of the authors (67%) after the ineffectiveness of the surgical myotomy was PD. Fourteen re-LHM patients (14%) had mucosal perforation and one had a pneumothorax. Two studies did not address complications. Complications following POEM included: one mucosal perforation, two subcutaneous emphysema, four mediastinal emphysema, four pneumothorax and three pneumoperitoneum. The authors noted that the best treatment for failure of myotomy is prevention in the prior surgery (pre-operative functional study, extended myotomy and correct antireflux procedure). Laparoscopic re-myotomy was considered a safe technique but endoscopic surgeries can be used without significantly increasing the risk of perforation. The analysis was limited by the lack of available studies; small heterogeneous patient populations (n=2–58); heterogeneity of studies by intervention; short-term follow-ups; and lack of comparative studies.

Akintoye et al. (2016) conducted a systematic review and meta-analysis to assess the safety and efficacy of POEM for the treatment of achalasia. The primary outcome measure was the proportion of patients with an Eckardt score of ≤ 3 after the procedure. Secondary measures were the mean Eckardt score, manometry parameters, timed barium esophagogram, and weight change postoperatively. All studies reporting clinical outcomes after POEM were eligible for inclusion. Exclusion criteria included: animal studies, case reports with < 5 patients, commentaries or general reviews, conference abstracts, and overlapping publications from the same center. Thirty-six studies (n=2373) met inclusion criteria (nonrandomized prospective studies and retrospective reviews). Overall, compared to baseline there was a significant improvement in the Eckardt score, manometry and timed barium esophagogram postoperatively (p<0.05). Clinical success (Eckardt score ≤ 3) was achieved in 98% of patients. The mean Eckardt score prior to treatment was 6.9 ± 0.15 compared to 0.77 ± 0.10 at one month, 1.0 ± 0.10 at six months and 1.0 ± 0.08 at 12 months. There was a significant decrease in manometry score within six months post-POEM (p<0.05). The average heights of the barium column following a timed barium esophagogram (a simple technique for evaluating esophageal emptying in patients with achalasia) were 14 ± 2.3 and 9.7 ± 1.9 cm at one and five minutes, respectively. The column heights decreased to 4.2 ± 0.77 and 2.6 ± 0.72 cm at one and five minutes, respectively, following POEM. Average weight gain (six studies; n=488) 5.4 ± 0.73 kg after a mean follow-up of 7.4 months. Adverse events included: mucosal injury (4.8%), esophageal perforation (0.2 %), substantial bleeding requiring interventions (0.2 %), subcutaneous emphysema (7.5 %), pneumothorax (1.2 %), pneumomediastinum (1.1 %), pneumoperitoneum (6.8 %) and pleural effusion (1.2 %). After a mean follow-up of eight months the rates of symptomatic gastroesophageal reflux was 8.5%, esophagitis on EGD 13% and abnormal acid exposure following a 24-hour pH monitoring study 47%. Limitations include the heterogeneity of the study populations and POEM techniques, missing data, variable follow-ups and absence of significant heterogeneity in the primary outcomes, limiting the generalizability of the results.

Marano et al. (2016) conducted a systematic review and meta-analysis to investigate the efficacy and safety of POEM compared with laparoscopic Heller myotomy (LHM) for the treatment of achalasia. Seven retrospective reviews (n=485) including POEM (n=196) and laparoscopic Heller myotomy (LHM) (n=290) met inclusion criteria. Study populations ranged from 8 to 180 patients per study. All studies with adult patients with a diagnosis of achalasia were included. Studies that did not report the comparison between endoscopic (POEM) and surgical (LHM) treatment, animal studies, single case reports, technical reports, reviews, abstracts, and editorials were excluded. The primary outcome measure was the mean difference in reduction in the Eckardt score. Secondary outcome measures were the mean difference in procedure time, length of hospital stay, postoperative pain score and analgesic requirement, as well as complications and post-procedure symptomatic gastro-esophageal reflux (GER). Follow-ups ranged from 2–12 months. There were no significant differences in reduction in Eckardt score (p=0.217) (n=5 studies), operative time (p=0.36), and postoperative pain score (p=4.45) (n=2 studies). There was a significantly shorter hospital stay in POEM patients (p=0.049). There was a significant difference in post-
Barbieri et al. (2015) conducted a systematic review and meta-analysis (n=16 studies) to pool the results of POEM procedures, in terms of efficacy and safety, and address relevant clinical and technical issues. Studies including patients who underwent POEM for achalasia were included. Eight prospective case series (n=7–70) and eight retrospective reviews (n=4–238) met the inclusion criteria. Overlap studies and animal studies were excluded. Primary outcomes were the feasibility and clinical success of POEMs (i.e., clinically-relevant improvement of dysphagia). Number and kind of adverse events were the secondary outcomes. Follow-ups
ranged from 3–12 months (median six months). Pooled technical success rate was reported at 97% and pooled clinical success rate was 93%. A statistically significant reduction in mean dysphagia scores was reported (p<0.001). Adverse events included post-POEM esophagitis 13% (47/354) and 14% of these events required medical and/or surgical intervention. Limitations of the studies included: small patient populations, short-term follow-ups, lack of a comparator, possible selection bias, various criteria used to measure clinical degree of dysphagia and adverse events. Randomized controlled trials comparing POEM to established treatment options are needed to validate the safety and efficacy of POEM for the treatment of achalasia.

Professional Societies/Organizations

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).

In the 2013 clinical guideline for the diagnosis and management of achalasia, the American College of Gastroenterology (ACG) listed POEM as an emerging technology that should only be used in the context of clinical trials.

American Gastroenterological Association (AGA): The 2017 Clinical Practice Update by the Committee of the American Gastroenterological Association (AGA) on the use of per-oral endoscopic myotomy in achalasia proposes the following recommendations:

- “in determining the need for achalasia therapy, patient-specific parameters (Chicago Classification subtype, comorbidities, early vs late disease, primary or secondary causes) should be considered along with published efficacy data;
- given the complexity of this procedure, POEM should be performed by experienced physicians in high-volume centers because an estimated 20–40 procedures are needed to achieve competence;
- if the expertise is available, POEM should be considered as primary therapy for type III achalasia;
- if the expertise is available, POEM should be considered as treatment option comparable with laparoscopic Heller myotomy for any of the achalasia syndromes; and
- post-POEM patients should be considered high risk to develop reflux esophagitis and advised of the management considerations (potential indefinite proton pump inhibitor therapy and/or surveillance endoscopy) of this before undergoing the procedure”.

The AGA concluded that POEM appears to be safe and effective in the short-term but that long-term durability of POEM are not yet available. Existing uncontrolled reports suggested efficacy of POEM is equal to or superior to LHM but more likely to result in post-treatment reflux (Kahrilas, et al., 2017).

The AGA Medical Position Statement on the Management of Gastroesophageal Reflux Disease stated 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).

American Society for Gastrointestinal Endoscopy (ASGE): The 2015 ASGE Practice Guideline on the role of endoscopy in the management of GERD includes a discussion of endoluminal therapies including the delivery of thermal energy. ASGE stated that there are only two endoluminal GERD therapies being used in the United States: the Stretta procedure and the Transoral Incisionless Fundoplication (TIF) (EsophyX device). Following a discussion of the studies for these two procedures, ASGE stated that the endoluminal antireflux procedures represent potentially, new therapeutic indications for GI endoscopy and that appropriate patient selection and endoscopist experience and training should be “carefully considered” before pursuing these therapies. AGSA did not recommend the use of these therapies, but suggested that endoscopic antireflux therapy be considered for selected patients with uncomplicated GERD after careful discussion with the patient regarding potential adverse effects, benefits, and other available therapeutic options.

In the 2014 guideline on the role of endoscopy for the evaluation and management of dysphagia, the American Society for Gastrointestinal Endoscopy (ASGE) stated that long-term data and randomized controlled trials
comparing POEM to conventional modalities of management are necessary before the surgery can be adopted into clinical practice. Sage noted that the procedure was becoming more widely used in expert centers.

**American Society of General Surgeons (ASGS):** The ASGS issued a position statement on transoral fundoplication in 2016 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.”

In a Statement of Support, ASGS (2014) stated that based on available information and the experience of their members, the Society supports LINX for controlling GERD “when it is placed by properly trained properly trained laparoscopic surgeons with experience in foregut surgery and the management of GERD patients”.

**Society of American Gastrointestinal Endoscopic Surgeons (SAGES):** In a 2017 Technology and Value Assessment Committee (TAVAC) Safety and Effectiveness Analysis on the LINX System, SAGES concluded that LINX is a reasonable treatment option for appropriately selected patients with GERD who meet indications for antireflux surgery. The LINX System is indicated for patients diagnosed with GERD as defined by abnormal pH testing, and who continue to have chronic GERD symptoms despite medical therapy for the treatment of reflux. LINX should be performed by surgeons who are familiar with the workup and different management alternatives of GERD and LINX should not be offered in isolation. SAGES noted that 3–5 years’ experience with LINX confirms the initial safety profile that led to FDA approval and that long-term GERD control based on symptomatic outcomes, PPI utilization and pH studies have been demonstrated. Data are from case series and retrospective reviews with generally, small patient populations and short-term follow-ups.

In 2017, SAGES updated the Clinical Spotlight Review on Endoluminal 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.

- **Recommendation - EsophyX:** “Based on existing evidence, TIF [i.e., EsophyX] can be performed with an acceptable safety risk in appropriately selected patients. The procedure leads to better control of GERD symptoms compared with PPI treatment in the short term (six months), but appears to lose effectiveness during longer term follow-up and is associated with moderate patient satisfaction scores. Objective GERD measures improve similarly after TIF 2.0 compared with PPI. No comparative, controlled trials exist between TIF and surgical fundoplication, but preliminary evidence suggested that the latter can be used safely after TIF failure.” (Level of evidence ++++, strong recommendation). SAGES did not define the criteria for “appropriate selected patients”. Quality of Evidence: (++). GRADE Recommendation: Weak.

- **Recommendation - Stretta:** “Based on existing evidence, Stretta significantly improves health related quality of life scores, heartburn scores, the incidence of esophagitis, and esophageal acid exposure in patients with GERD, but does not increase lower esophageal sphincter basal pressure. In addition, it decreases the use of PPI by approximately 50%. The effectiveness of the procedure diminishes some over time, but persistent effects have been described for up to 10 years after the procedure in appropriately selected patients with GERD. Stretta is more effective than PPI, but less so than fundoplication. Stretta is safe in adults and has a short learning curve”. Level of Evidence: (+++); Strong Recommendation.

In 2009 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.

**Centers for Medicare & Medicaid Services (CMS)**

- National Coverage Determinations (NCDs): No NCD found
- Local Coverage Determinations (LCDs): Multiple LCDs found. Refer to the LCD table of contents link in the reference section.

**Use Outside of the US**

The Japan Gastroenterological Endoscopy Society (JGES) 2018 clinical practice guidelines on peroral endoscopic myotomy (POEM) included the following:

- POEM is indicated for esophageal achalasia (weak recommendation based on moderate evidence)
- POEM for straight-type esophageal achalasia is effective (weak recommendation based on moderate evidence). It was recommended that beginners start the POEM procedure with straight-type achalasia except for Chicago type III achalasia, which requires a longer myotomy and a more complicated procedure caused by severe abnormal contractions of the esophageal body and a narrow working space during the procedure
- POEM has been reported to be effective even for sigmoid type achalasia. However, the procedure should be performed by a skilled endoscopist because of the technical difficulty (weak recommendation based on weak evidence).

The guidelines note that although POEM has been reported to be effective for other esophageal motility disorders (e.g. diffuse esophageal spasm, jackhammer esophagus, etc.), there are only a few case report and further investigation is warranted (Inoue, et al., 2018).

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 National Institute for Clinical Excellence (NICE, United Kingdom), issued an interventional procedure guidance document on laparoscopic insertion of a magnetic titanium ring for the treatment of GERD. The authors concluded that there was no safety concerns but evidence is limited to short-term efficacy. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research (NICE, 2017).

In 2011, the NICE issued an interventional procedure guidance document on Endoluminal Gastroplication for GERD. The authors reported that the evidence on endoluminal gastroplication for gastro-esophageal reflux disease (GERD) raises no major safety concerns and the evidence from a number of randomized controlled trials (RCTs) shows a degree of efficacy in terms of reduced medication requirement in the short term. However, changes in other efficacy outcomes were inconsistent and there was no good evidence of sustained improvement in esophageal pH measurements.

The 2011 Gastroenterological Society of Australia Clinical Update on Gastroesophageal Diseases in Adults reports under the section on management and endoscopic therapies noted that a number of therapies have been developed for the treatment of GERD including: suturing devices, injection of inert substances, plication devices and devices that deliver radiofrequency energy to the Gastro-esophageal junction. GSA stated that experience with these techniques is relatively limited. They do not significantly reduce exposure of the distal esophagus 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 reported.

**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.

Considered Experimental/Investigational/Unproven when used to report endoscopic anti-reflux procedures performed for the treatment or management of gastroesophageal reflux disease (GERD) or any other indication:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>43192</td>
<td>Esophagoscopy, rigid, transoral; with directed submucosal injection(s), any substance</td>
</tr>
<tr>
<td>43201</td>
<td>Esophagoscopy, flexible, transoral; with directed submucosal injection(s), any substance</td>
</tr>
<tr>
<td>43210</td>
<td>Esophagogastroduodenoscopy, , flexible, transoral; with esophagogastric fundoplasty, partial or complete, includes duodenoscopy when performed</td>
</tr>
<tr>
<td>43236</td>
<td>Esophagogastroduodenoscopy, flexible, transoral; with directed submucosal injection(s), any substance</td>
</tr>
<tr>
<td>43253</td>
<td>Esophagogastroduodenoscopy, flexible, transoral; with transendoscopic ultrasound-guided transmural injection of diagnostic or therapeutic substance(s) (eg, anesthetic, neurolytic agent) or fiducial marker(s) (includes endoscopic ultrasound examination of the esophagus, stomach, and either the duodenum or a surgically altered stomach where the jejunum is examined distal to the anastomosis)</td>
</tr>
<tr>
<td>43257</td>
<td>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</td>
</tr>
<tr>
<td>43284</td>
<td>Laparoscopy, surgical, esophageal sphincter augmentation procedure, placement of sphincter augmentation device (ie, magnetic band), including cruroplasty when performed</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>
</tr>
</tbody>
</table>


References


