Minimally Invasive Procedures for Gastroesophageal Reflux Disease (GERD) and Achalasia (for Indiana Only)

Policy Number: CS079IN.02
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Instructions for Use

Table of Contents Page

Related Policy
- Bariatric Surgery

Application

This Medical Policy only applies to the state of Indiana.

Coverage Rationale

The Per Oral Endoscopic Myotomy (POEM) procedure is proven and medically necessary for achalasia or diffuse esophageal spasm.

The following are unproven and not medically necessary for treating gastroesophageal reflux disease (GERD) due to insufficient evidence of efficacy:
- Endoscopic therapies
- Injection or implantation techniques
- LINX Reflux Management System

Endoluminal therapy with GERDx™ is investigational, unproven, and not medically necessary for treating GERD as it has not received U.S. Food and Drug Administration (FDA) approval.

For medical necessity clinical coverage criteria, refer to the InterQual® 2021, Apr. 2021 Release, CP: Procedures, Antireflux Procedures, Endoscopic.

Click here to view the InterQual® criteria.

See the Medical Policy titled Bariatric Surgery for information regarding endoscopic therapies for the treatment of obesity.

Definitions

Achalasia: A primary esophageal motor disorder of unknown etiology characterized by degeneration of the myenteric plexus, which results in impaired relaxation of the esophagogastric junction (EGJ), along with the loss of organized peristalsis in the esophageal body (American Society of Gastrointestinal Endoscopy (ASGE)).

Diffuse Esophageal Spasm: A condition characterized by uncoordinated contractions of the esophagus that typically results in chest pain and/or dysphagia (Cameron, 2020).

Gastroesophageal Reflux Disease: A condition where the lower esophageal sphincter (LES) relaxes too often or weakens which allows stomach acid to flow backward (or reflux) into the esophagus (American College of Gastroenterology (ACG)).

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
43210	Esophagogastroduodenoscopy, flexible, transoral; with esophagogastric fundoplasty, partial or complete, includes duodenoscopy when performed
43284	Laparoscopy, surgical, esophageal sphincter augmentation procedure, placement of sphincter augmentation device (i.e., magnetic band), including cruroplasty when performed
43257	Esophagogastroduodenoscopy, flexible, transoral; with delivery of thermal energy to the muscle of lower esophageal sphincter and/or gastric cardia, for treatment of gastroesophageal reflux disease
43289	Unlisted laparoscopy procedure, esophagus
43499	Unlisted procedure, esophagus
43999	Unlisted procedure, stomach

Description of Services

Gastroesophageal reflux disease (GERD) is a condition that is characterized by either a weak or dysfunctional lower esophageal sphincter (LES) that results in partially digested food from the stomach to flow back into the esophagus, a process known as reflux. Persistent GERD may lead to esophageal damage or other serious conditions, such as severe esophagitis, strictures, Barrett's metaplasia, and adenocarcinoma of the esophagus.

Initial treatment of GERD usually involves over the counter (OTC) antacids, OTC histamine-2-receptor antagonists (H2RAs; also called H2 blockers), and proton pump inhibitors (PPI). Daily use of proton pump inhibitors (PPI) is generally effective in the treatment of the majority of patients with GERD; however, up to 40% have persisting symptoms (Weitzendorfer et al., 2018). For individuals who wish to discontinue use of these medications due to concern of long-term side effects or for individuals whose GERD is refractory to pharmacologic treatment, an open or laparoscopic Nissen fundoplication may be considered. However, some individuals may not be suitable candidates given the invasiveness and risks associated with surgery. As a result, minimally invasive procedures, including endoscopic or endoluminal therapies and laparoscopic approaches, have been proposed as alternative treatment methods to improve the function of the LES, with the objective of eliminating symptoms, healing esophagitis, preventing recurrence of symptoms or progression of disease, and reducing the need for lifelong pharmacologic therapy.

Minimally invasive approaches proposed in the treatment of GERD, include the following:

- Radiofrequency energy: The Stretta procedure administers radiofrequency (RF) energy via endoscopic needles placed in the tissues surrounding the lower esophageal sphincter. The RF energy heats this neighboring tissue, creating thermal lesions. Submucosal scarring forms as the lesions heal, causing shrinkage and tightening around the LES. The mechanism of action is believed to be related to decreased sensitivity to acid, decreased compliance of the LES or increased pressure of the LES (Stephanidis et al., 2017).
- Endoscopic plication or suturing:
  - The Bard EndoCinch and the Endoscopic Suturing Device (ESD), involves endoscopic suturing which allows for the placement of proximal to the LES. The NDO Endoscopic Plication System, also known as the NDO Plicator System, places a full-thickness transmural plication near the gastroesophageal junction under direct endoscopic visualization.
  - EsophyX is an endoluminal therapeutic option that uses a trans-oral and fastener deploying device. It is inserted orally within a thin, flexible tube and deployed inside the stomach to create a full thickness plication of the stomach fundus at the GE junction, thereby resembling an endoscopic fundoplication. The current TIF 2.0 technique (the initial TIF 1.0 technique is no longer recommended) generates a physiological valve via fasteners placed on the far posterior and anterior sides of the lesser curvature, with additional fasteners placed 1–3 cm proximal to the GE junction (Stephanidis et al., 2017).
  - GERDx™ (G-SURG) is an endoscopic full-thickness plication device that uses hydraulic elements for controlling.
  - The Medigus Ultrasonic Surgical Endostapler (MUSE™ system, Medigus) is an endoscopic stapling device for transoral partial fundoplication. According to the manufacturer's website, as the MUSE system contains the surgical stapler, microvisual, and ultrasonic capabilities, it allows a single physician to complete the procedure.
- Injection or implantation techniques include the following:
  - The Plexiglas® (polymethylmethacrylate [PMMA]) procedure involves injection of an inert polymer material into the submucosa of the proximal LES zone to provide bulking support to the sphincter and decrease transient relaxation of the lower esophageal sphincter (tLESRs).
  - Another bulking agent, pyrolytic carbon-coated beads (Durasphere®), is being evaluated for treatment of GERD.
  - The LINX™ Reflux Management System is an implant that consists of a ring that fits around the esophagus and is intended to prevent reflux of bile and acid from the stomach into the esophagus. According to the company website, the LINX system is a small flexible band of interlinked titanium beads with magnetic cores. The magnetic attraction is intended to help the (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.

Achalasia is a condition that affects the esophagus. It is a relatively rare cause of dysphagia manifested by esophageal aperistalsis and failure of relaxation of a hypertensive lower esophageal sphincter (LES) (Kohn 2019). Current treatment options include pharmacological, endoscopic and surgical.

- The Per Oral Endoscopic Myotomy (POEM) procedure is a technique that 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. POEM is an intricate endoscopic procedure that requires advanced endoscopic skills, knowledge of surgical anatomy, and expertise in submucosal endoscopy and management of adverse events (Khasab et al., 2020).

Clinical Evidence

Per Oral Endoscopic Myotomy (POEM)

In a prospective multicenter randomized open label trial, Werner et al. (2019) compared POEM to laparoscopic Heller's myotomy (LHM) plus fundoplication in 221 patients with achalasia. The patients were randomly assigned in a 1:1 ratio to undergo either POEM or LHM plus fundoplication. The POEM procedure was performed by a physician with formal POEM training including esophageal interventions such as endoscopic mucosal resection and submucosal dissection; LHM was performed according to current standards. Clinical data was collected at 3, 6, 12 and 24 months; patient assessment was performed with phone calls, mail and follow up appointments. The Eckardt symptom score was the validated questionnaire used which identified success with a score of 3 or less by the 2 year follow up appointment. Limitations included lack of obtaining appropriate consent from patients, lack of blinding, and surgeon experience was superior for HLM versus POEM. The authors concluded POEM was non-inferior to LHM in controlling symptoms of achalasia at 2 years with less adverse events; it

was noted the patients with the POEM procedure were more common to experience gastroesophageal reflux than the patients who underwent HLM.

A comparative effectiveness review by Hayes (2019), which did not include the Werner study cited above, estimate that POEM is a "potential but unproven benefit" for the treatment of esophageal achalasia. The authors of the report conclude that the available low-quality evidence suggested the POEM procedure is generally safe and may achieve at least similar results to both laparoscopic Heller myotomy (LHM) and pneumatic dilation (PD) for most efficacy outcomes. The body of evidence on POEM vs LHM was of moderate size including 16 studies, whereas evidence on POEM versus PD was presented in only 4 studies. It is suggested additional studies of fair to good quality are needed to reveal optimal treatment protocols and provide information for longer-term outcomes.

In a systematic review, which did not include the Werner study cited above, Li et al. (2019) investigated the long-term efficacy and safety of POEM with follow-up period over 2 years. Ten eligible studies met the inclusion criteria and were published between January 2015 and November 2017. A total of 372 patients successfully underwent POEM with one failure due to serious inflammation and adhesion of the esophagus. The mean follow-up period was 30 months. The mean preoperative and postoperative Eckhart scores decreased from 7.4 to 1.4, respectively. The authors found POEM to be effective and safe for the treatment of achalasia during the 2 years' long-term follow-up duration. It was concluded further multi-center studies with randomization comparing POEM with other treatment modalities are warranted for the future. Limitations of the author analysis included small sample size and bias due to majority of cases were from Asia and a single endoscopy center.

He et al. (2019) (not included in the systematic reviews cited above) collected prospective data in a case series of 115 patients to evaluate the long-term efficacy of POEM for patients with achalasia. The Eckardt scoring system was used and success was found in 91.3% of the patients. Twenty-one patients were found to have symptoms of reflux during the two-year follow-up. The authors concluded that POEM was safe and effective for treating achalasia with favorable long-term outcomes.

Crespin et al. (2017) performed a systematic review of the literature to evaluate the efficacy and safety of POEM. Of the 19 studies meeting the inclusion criteria, 10 were retrospective and 9 were prospective studies. No randomized controlled trails were identified. The Eckardt score was used for assessing the severity of achalasia and all 19 studies reported a pre- and post-POEM score; success and effectiveness was defined as a score of ≤3. In addition, the lower esophageal sphincter (LES) pressure was reported for 10 of the studies. The study had several limitations; the goal was to included studies with more than 10 cases, but a few had to be excluded. In addition, the length of myotomy was not uniformly performed and reported. And finally, sigmoid esophagus and the presence of previous treatments may make POEM more challenging and data less comparable. The authors concluded that POEM appears to be promising and an effective, safe option for achalasia. Future studies should aim research at better define complications and standard postoperative changes.

Marano et al. (2016) performed a systematic review and meta- analysis to investigate the efficacy and safety of POEM compared with LHM for the treatment of achalasia. The search produced 11 studies for eligibility. The total number of included patients was 486 (196 in POEM group and 290 in LHM group) ranging from 8 to 180 patients per study. The Eckardt score was used in five of the studies which showed non-statistically significant difference between POEM and LHM favoring POEM. The review and analysis identified some limitations including high heterogeneity rate, no randomization of patients and significant publication bias. Furthermore, all selected studies did not report follow-up results past one year. The authors concluded additional high-quality clinical trials with randomization and long-term evaluation comparing POEM with other standard procedures are needed.

Patel et al. (2016) performed a systematic review that assessed subjective and objective metrics of achalasia treatment efficacy, perioperative adverse events and the incidence of postoperative GERD in patients treated with POEM. Twenty-two studies were eligible for review; nineteen were case series and three were comparative studies. The results demonstrated consistent short-term improvement of dysphagia with Eckardt scores and LES pressure measurements. Despite the favorable outcomes for the procedure, approximately 20% of the patients had evidence of post-POEM GERD. Limitations identified included the quality of studies, lack of standardization for surgical quality and reporting of adverse events and limited data of long-term outcomes. The authors concluded POEM was safe and effective for treating achalasia showing significant improvements for the metrics identified, however randomized studies are needed.

Professional Societies

American Gastroenterological Association (AGA)

The AGA recommends POEM be considered as a primary therapy for type III achalasia. Given the complexity of the POEM procedure, the AGA also recommends the procedure be performed by experienced physicians in high-volume centers to achieve procedure competence (Kahrilas et al., 2017).

American Society for Gastrointestinal Endoscopy (ASGE)

The ASGE identifies laparoscopic Heller myotomy, pneumatic dilation, and POEM as effective therapeutic modalities for patients with achalasia. The decision made between these treatment options should depend on achalasia type, local expertise, and patient preference (Khashab et al., 2020).

Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)

In a clinical practice guideline, SAGES (Stefanidis et al. 2012) provided the following recommendation for surgical treatment of esophageal achalasia:

- Laparoscopic myotomy can be performed safely and with minimal morbidity in appropriately selected patients by appropriately trained surgeons. (Level of evidence ++++, strong recommendation)
- Laparoscopic myotomy with partial fundoplication provides superior and longer-lasting symptom relief with low morbidity for patients with achalasia compared with other treatment modalities and should be considered the procedure of choice to treat achalasia. (Level of evidence ++++, strong recommendation).

Radiofrequency Energy (Stretta System)

Currently there is insufficient evidence regarding the effectiveness of radiofrequency energy for gastroesophageal conditions and its role must be better defined in statistically robust, well-designed clinical trials with long-term results.

Viswanath et al. (2019) reported a prospective case series of 50 patients who underwent endoscopic antireflux radiofrequency treatment (Stretta) for refractory gastro-oesophageal reflux disease (GORD), Assessment involved the use of the Gastro-oesophageal Reflux Disease-Health-Related Quality of Life (GERD-HRQL) questionnaire, which evaluated symptoms and proton pump inhibitor (PPI) dependency, before and after treatment. Median follow-up post treatment was 771 days. The average GERD-HRQL score improved from 46.2/75 (±14.2) before Stretta treatment to 15.2/75 (±17.3) after Stretta treatment. The authors concluded that in select patients with GORD, Stretta improves quality of life and decreases PPI dependency, and is a viable option for patients who are unwilling or unable to undergo surgery. The also concluded that randomized controlled trials with larger patient populations are needed to further assess Stretta. Limitations of this study include lack of concurrent comparison group, its small numbers and that the pre-Stretta assessments were carried out by a variety of teams thus the potential for inconsistencies.

In a case series, Noar et al. (2017) prospectively assessed and compared patient-reported outcomes in 18 patients refractive to laparoscopic Nissen fundoplication (LNF) and 81 patients with gastrointestinal reflux disease (GERD) refractory to medical management that all underwent Stretta during 10-year follow-up. Patient-reported outcomes measured were GERD-HRQL (health-related quality of life), patient satisfaction scores, and daily medication requirements. The refractory LNF subset demonstrated median improvements in GERD-HRQL, satisfaction, and medication use at all follow-up time points ≥6 months to 10 years, which was significant from a baseline of both on- and off-medications ($p < 0.05$). Specifically, at 10 years, median GERD-HRQL decreased from 36 to 7 ($p < 0.001$), satisfaction increased from 1 to 4 ($p < 0.001$), and medication score decreased from 7 to 6 ($p = 0.040$). Nine patients decreased medication use by half at 10 years. No significant differences existed between refractory LNF and standard refractory GERD subsets at any follow-up time point ≥6 months to 10 years ($p > 0.05$) after Stretta. At 10 years, no significant differences were noted between refractory LNF and standard Stretta subsets regarding medication use ($p = 0.088$), patient satisfaction ($p = 0.573$), and GERD-HRQL ($p = 0.075$). Stretta procedures were completed without difficulty or significant intraoperative or long-term adverse events. The authors concluded that within a small cohort of refractory LNF patients, Stretta resulted in sustained improvement over 10 years with equivalent outcomes to non-LNF standard Stretta patients. Study limitations include lack of concurrent comparison group, non-randomization and small patient population.

Kalapala et al. (2017) reported short outcomes (3 months) from a prospective randomized study comparing the Stretta treatment with controls receiving proton pump inhibitors (PPIs). Patients (n=20) with symptoms of heartburn, regurgitation,

abnormal esophageal acid exposure (≥ 4%), and endoscopically confirmed esophagitis were included into the study. The primary measure was improvement in quality of life (QOL) and decrease in the frequency and severity of GERD symptoms. The mean age of the patients was 39 (± 15) years and controls were 34 (± 11) years. Three months after Stretta, 80% reported improvement in QOL compared to 40% in the control group. At the end of 3 months, significant ($p < 0.05$) improvement in GERD symptom score for heartburn, regurgitation, chest pain, and cough compared with the control group was observed. After Stretta treatment, 60% of the patients were free of PPIs whereas there was no change in the control group. Almost 80% of the patients on Stretta treatment were satisfied with the treatment compared to 30% of the patients in the control group. The study was limited by the small sample size and short follow-up, therefore, randomized controlled trials with larger patient populations and longer follow-up periods are needed to further assess Stretta.

Fass et al. (2017) conducted a systematic review and meta-analysis of randomized controlled and cohort studies to determine the efficacy of the Stretta procedure in treating patients with GERD. Twenty-eight studies (4 RCTs, 23 cohort studies, and 1 registry) representing 2468 unique Stretta patients were included in the meta-analysis. The (unweighted) mean follow-up time for the 28 studies was 25.4 [14.0, 36.7] months. The pooled results showed that the Stretta reduced (improved) the health-related quality of life score by -14.6 [-16.48, -12.73] ($P < 0.001$). Stretta also reduced (improved) the pooled heartburn standardized score by -1.53 [-1.97, -1.09] ($P < 0.001$). After Stretta treatment, only 49% of the patients using proton pump inhibitors (PPIs) at baseline required PPIs at follow-up ($P < 0.001$). The Stretta treatment reduced the incidence of erosive esophagitis by 24% ($P < 0.001$) and reduced esophageal acid exposure by a mean of -3.01 [-3.72, -2.30] ($P < 0.001$). Lower esophageal sphincter (LES) basal pressure was increased post Stretta therapy by a mean of 1.73 [-0.29, 3.74] mmHg (P = NS). The authors concluded that the Stretta procedure significantly improves subjective and objective clinical endpoints, except LES basal pressure, and therefore should be considered as a viable alternative in managing GERD. Longer-term outcomes are needed to further evaluate the Stretta procedure. (Author Dugher et al. (2014) and Noar et al. (2014) which were previously cited in this policy are included in Fass et al. (2107) meta-analysis).

Arts et al. (2012) conducted a small double-blind randomized cross-over study of Stretta and sham treatment (included in the Fass et al. (2017) systemic review above). Patients underwent two upper gastrointestinal endoscopies with 3 months interval, during which active or sham Stretta treatment was performed in a randomized double-blind manner. In all, 22 GERD patients (17 females, mean age 47±12 years) participated in the study; 11 in each group. 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 to pre-Stretta level, arguing against GEJ fibrosis as the underlying mechanism. The authors concluded 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 patient population, short follow-up, and lack of comparison to other surgical alternatives.

In an RCT, 36 patients were randomized into three groups. In group A, 12 patients underwent a single session Stretta procedure (Aziz et al., 2010, included in the Fass et al. (2017) systematic review above). In group B, 12 patients underwent a sham Stretta procedure (mirror of the active procedure in all aspects except there was no deployment of the electrodes). In group C, 12 patients underwent a single Stretta treatment followed by repeat Stretta if GERD health-related quality of life (HRQL) was not 75% improved after 4 months. At 12 months, the mean HRQL scores of patients no longer on medications, the lower esophageal sphincter (LES) basal pressure, the 24-hr pH scores, and the PPI daily dose consumption were significantly improved from baseline in both Stretta groups. The double Stretta was numerically but not significantly better than the single Stretta for mean HRQL, mean 24 h pH, mean LES pressure, and PPI use. Seven patients in the double Stretta treatment group reported normal HRQL scores at 12 months compared with 2 patients in the single-treatment group. The sham group patients had a small but statistically significant decrease in their daily PPI dosages and mean HRQL scores. The investigators concluded that the Stretta procedure significantly reduced HRQL associated with GERD, use of PPI drugs, esophageal acid exposure, LES pressure, and grade of esophagitis compared with the sham procedure. The double Stretta therapy had numerically superior outcomes for most parameters and a significantly more frequent normalization of HRQL scores compared with the single Stretta group. According to the investigators, the Stretta procedure is partially effective for the treatment of GERD symptoms. Double Stretta therapy has better efficacy than single therapy, but has greater side effects. The investigators also noted that antireflux surgery (fundoplication) has a higher success rate than that of Stretta. Furthermore, a more prolonged effect is found with antireflux surgery. The conclusions of this study are limited by small sample size and lack of comparison to other surgical alternatives.

Jeansonne et al. (2009) conducted a cohort study to compare the effectiveness of endoscopic full-thickness plication (FTP) to endoscopic radiofrequency treatments for patients with GERD. Follow-up data was obtained for 63 patients (mean follow-up was 6 months). Outcome measures included comparison of medication use, symptom scores, and pH values at baseline and follow-up. In the RF group, patients with moderate to severe heartburn decreased from 55% to 22%, and PPI use decreased from 84% to 50%. Decreases were also seen for dysphagia, voice symptoms, and cough. The pH values were unchanged. In the FTP group, patients with moderate to severe heartburn decreased from 53% to 43%, and PPI use decreased from 95% to 43%. Percentage of time that the pH was less than 4 decreased from 10.0% to 6.1%. Decreases were also seen for regurgitation, voice symptoms, and dysphagia. According to the investigators, RF and FTP both resulted in a decrease in both PPI use and in scores for voice symptoms and dysphagia. In addition, RF resulted in decreased heartburn and cough, while FTP resulted in the most dramatic reduction in regurgitation. The investigators concluded that both procedures are effective, providing symptomatic relief and reduction in PPI use. For patients whose chief complaint is regurgitation, FTP may be the preferred procedure. Study limitations included lack of randomization, small sample size, and short follow-up.

In another small RCT, Coron et al. (2008, included in the Fass et al. (2017) systematic review above) compared radiofrequency and a PPI in PPI-dependent patients. Patients were randomly allocated to either RF or PPI regimen alone. The primary endpoint, evaluated at 6-months, was defined as the possibility for the patient to stop or to decrease PPI use to <50% of the effective dose required at baseline. In the radiofrequency group, 18/20 patients stopped (n=3) or decreased (n=15) PPI use compared to eight of 16 in the PPI group. None of the control patients could stop PPI. HR-QOL scores were not significantly different between groups. No significant change in oesophageal acid exposure (OAE) was noted between baseline and 6-months after radiofrequency treatment. The investigators concluded that in a majority of patients, PPI therapy cannot be completely stopped. Furthermore, the efficacy of RF does not seem to be related to a decrease in OAE. Limitation of these finding were small sample size, large loss to follow up and lack of group difference at the 12-month follow-up point for the main outcomes.

Numerous other non-randomized and non-comparative cohort studies evaluated radiofrequency energy for the treatment of GERD (Dughera et al., 2011; Liu et al., 2011; White et al., 2009; Dundon et al., 2008; Noar and Lotfi-Emran et al., 2007; Reymunde and Santiago, 2007; Lutfi et al., 2005). The body of evidence is of low quality due to overall weaknesses in study design, including lack of comparison groups, lack of randomization, short follow-up periods, and small patient populations.

Torquati et al. (2007) conducted an evidence-based systematic review of the literature of FDA-approved modalities of endoluminal treatment of GERD. Study authors concluded that the methodological quality of most of the included studies was average. The authors stated that there is grade 1b (individual randomized trial) and 2b (individual cohort study) evidence demonstrating that the Stretta procedure is effective in reducing GERD symptoms at short- and mid-term follow-up. However, in the majority of the studies analyzed, the procedure did not significantly reduce acid exposure in the distal esophagus.

The National Institute for Health and Care Excellence (NICE) guideline on endoscopic radiofrequency ablation for GERD considers the evidence on this procedure to be adequate in the short and medium term but there is uncertainty about longer-term outcomes. Regarding efficacy, there is evidence of symptomatic relief but objective evidence on reduction of reflux is inconclusive (NICE, 2013).

Endoscopic Plication or Suturing

There is a lack of evidence to support the use of endoscopic plication or suturing for GERD; additional studies are needed to support the safety and efficacy of these techniques with long-term effectiveness.

EndoCinch

Schwartz et al. (2007) conducted a single-center, double-blind, randomized, sham-controlled trial of endoscopic gastroplication by the Endocinch suturing system in 60 patients. Patients with GERD were randomly assigned to three endoscopic gastroplications (n=20), a sham procedure (n=20) or observation (n=20). The research nurse and patients in the active and sham groups were blinded to the procedure assignment. After 3 months, open-label active treatment was offered to all patients. At 3 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%). The active treatment effects on PPI use, symptoms and quality of life persisted after 6 and 12 months of open-label follow-up (n=41), but 29% of patients were retreated in this period. The investigators concluded that endoscopic gastroplication, using the Endocinch device, reduced acid-inhibitory drug use, improved GERD symptoms, and improved the quality of life at 3 months compared with a sham procedure with durable effects

up to 12 months. However, the reduction in oesophageal acid exposure was not significantly different between treatment and sham groups.

Torquati et al. (2007) conducted a systematic review of endoluminal therapies for GERD, including EndoCinch. The authors identified evidence demonstrating that EndoCinch plication is effective in reducing GERD symptoms in the short term. However, they noted that the procedure does not significantly reduce the acid exposure in the distal esophagus.

In a randomized-placebo controlled study by Montgomery et al. (2006), 46 patients with GERD requiring regular use of PPIs were enrolled to evaluate the effects of the EndoCinch plication technique. Patients were randomized to the EndoCinch plication technique or a sham procedure. Reflux-specific symptoms and use of PPIs (total intake, as well as number of patients not taking PPIs) significantly improved in the treatment group compared with the sham control group at 3 months of follow-up. Gastro-esophageal endoscopy showed that 71% and 67% of sutures remained at 3 and 12 months, respectively. The authors concluded that although some short-term positive effects were achieved, there were no significant differences between the treatment and control groups after 12 months. Additionally, the lack of reduction of esophageal acid exposure suggests that the EndoCinch plication technique is not recommended for use in clinical practice. Researchers suggest that the lack of long-term effects is primarily due to detachment of the sutures in about 30% of patients.

In an RCT, endoluminal gastroplasty (EndoCinch) was compared with polymer injection (Enteryx). The study included 51 patients dependent on PPI therapy. Twenty-six patients were assigned to EndoCinch treatment, 23 patients received Enteryx implantation, and 2 patients dropped out before applying endoscopic therapy. At 6 months, PPI therapy could be stopped, or dosage was reduced by ≥ 50% in 20 of 26 EndoCinch-treated patients and in 20 of 23 patients treated by Enteryx. The authors concluded that EndoCinch and Enteryx seem to be equally successful in the treatment of GERD by significantly reducing the PPI dosages, and also improving symptoms of patients (Domagk et al., 2006). Conclusions regarding long-term health outcomes could not be made based on the short-term follow-up duration of this study.

Other clinical trials for EndoCinch are limited to observational case series that do not allow for conclusions about durability and long-term effectiveness (Paulssen and Lindsetmo, 2008; Ozawa et al., 2009).

Endoscopic Plicator or Suturing

De Moura et al. (2018) evaluated long-term results of 47 patients non-responsive to PPIs who underwent endoluminal plication (n=26) or polymer injection (n=21) for the treatment of GERD as part of a case series. The number of patients with no response to endoscopic treatment with reintroduction of PPIs increased in time for both techniques. There was symptomatic improvement up to 12 months, with progressive loss of this trending up to 60 months for both procedures. Health-related quality of life score (GERD-HRQL) demonstrated total response in both procedures at 1, 3, 6 and 12 months. The 60-month analysis showed an increased number of patients with no response in both groups. The quality of life assessment (SF-36) showed benefit in polymer injection up to 3 months and showed a higher rate of complications. There were no deaths. There was healing of esophagitis at 3 months in 45% of patients in polymer injection and 40% in endoluminal plication. There was no improvement in manometric or pH findings. The authors concluded that endoscopic therapies were ineffective in controlling GERD in the long term. Limitations included lack of control group or placebo and lack of uniform objective data analysis.

In a randomized, single-blind, prospective, multicenter trial by Rothstein et al. (2006), 159 patients were selected to either undergo endoscopic full-thickness restructuring of the gastric cardia with transmural suture (n=78) or a sham procedure (n=81) to determine the effectiveness of endoscopic full-thickness plication for the treatment of GERD. Group assignments were revealed following the 3-month evaluation. By intention-to-treat analysis, at 3 months, the proportion of patients achieving ≥50% improvement in GERD-HRQL score was significantly greater in the active group compared with the sham group. Complete cessation of PPI therapy was higher among patients in the active group than in the sham group. However, the median percent time that pH < 4 was not significantly improved between the active and sham group. Between-group analysis revealed the active therapy was superior to sham treatment in improving the median percent time that the pH value was < 4. The authors concluded that endoscopic full-thickness plication was effective in reducing GERD symptoms and PPI use compared with a sham procedure. Additional studies are needed to evaluate the durability of endoscopic full-thickness plication for the treatment of GERD, as this study is limited by a relatively short follow-up.

In an RCT, Antoniou et al. (2012) evaluated the effectiveness of endoscopic plication and laparoscopic fundoplication in terms of QOL and symptom control. A total of 60 patients with documented GERD were randomly assigned to undergo either endoscopic plication or laparoscopic fundoplication. QOL scores and symptom grading were recorded before treatment and at

3- and 12-months of follow-up. Twenty-nine patients from the endoscopic group and 27 patients from the operative group were available at follow-up. QOL 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. The authors concluded that endoscopic plication and laparoscopic fundoplication resulted in significant symptom improvement with similar QOL scores in a selected patient population with GERD, whereas operative treatment was more effective in the relief of heartburn and regurgitation at the expense of higher short-term dysphagia rates. Small sample size and lack of long-term follow-up limit the validity of these conclusions.

GERDx™

Weitzendorfer et al. (2018) assessed the clinical safety and efficiency of the GERDx™ device by evaluating clinical parameters, reflux symptom scores, and quality of life (QoL) in a case series. Patients (n=40) with at least one typical reflux symptom despite treatment with a PPI for > 6 months, pathologic esophageal acid exposure, hiatal hernia of size < 2 cm, and endoscopic Hill grade II-III were included. Evaluation of Gastrointestinal Quality of Life Index (GIQLI), symptom scores, esophageal manometry, and impedance-pH-monitoring were performed at baseline and at 3 months after surgery. Four out of forty patients experienced postoperative complications requiring intervention. Seven of forty patients were subjected to laparoscopic fundoplication 3 months after endoscopic plication due to persistent symptoms and were lost to further follow-up. Thirty out of forty patients were available at 3-month follow-up. There was an improvement of the GIQLI score, from a mean of 92.45 ± 18.47 to 112.03 ± 13.11 ($p < 0.001$). The general reflux-specific score increased from a mean of 49.84 ± 24.83 to 23.93 ± 15.63 ($p < 0.001$), and the DeMeester score from a mean of 46.48 ± 30.83 to 20.03 ± 23.62 ($p < 0.001$). There was no significant change in manometric data after intervention. Three of thirty patients continued daily antireflux medication. The authors concluded that endoscopic plication with the GERDx™ device reduced distal acid exposure of the esophagus, reflux-related symptoms, and improved GIQLI scores with minimal side effects in a selected cohort of patients and may be a safe alternative in the treatment of GERD. Randomized clinical trials with larger patient populations and longer follow-up periods are needed to further assess GERDx.

MUSE™

Kim et al. (2016) reported in a case series long-term outcome from the Zacherl et al. (2015) MUSE study using the Medigus Ultrasonic Surgical Endostapler (MUSE™). Efficacy and safety data for 37 patients were analyzed at baseline, 6 months, and 4 years post-procedure. In one center (IU), efficacy and safety data were evaluated at baseline, 6 months post-procedure, and then annually up to 4 years. No new complications have been reported in our long-term analysis. The proportions of patients who remained off daily PPI were 83.8% (31/37) at 6 months and 69.4% (25/36) at 4 years post-procedure. GERD-Health Related Quality of Life (HRQL) scores (off PPI) were significantly decreased from baseline to 6 months and 4 years post-procedure. The daily dosage of GERD medications, measured as omeprazole equivalents (mean ± SD, mg), decreased from 66.1 ± 33.2 at baseline to 10.8 ± 15.9 at 6 months and 12.8 ± 19.4 at 4 years post-procedure ($P < 0.01$). The authors conclude that the MUSE™ stapling device appears to be safe and effective in improving symptom scores as well as reducing PPI use in patients with GERD and that the results appeared to be equal to or better than those of the other devices for endoluminal GERD therapy. Future studies with larger patient series, sham control group, and greater number of staples are awaited to further evaluate MUSE. Findings are limited by lack of comparison group.

Zacherl et al. (2015) reported 6-month outcomes from a multi-center prospective case series using the MUSE™ for the treatment of GERD (N=69; 3 lost to follow-up). Six months after the procedure, the GERD-HRQL score improved by >50% off PPI in 73% (48/66) of patients (95% CI 60–83%). Forty-two patients (64.6%) were no longer using daily PPI medication. Of the 23 patients who continued to take PPI following the procedure, 13 (56.5%) reported a ≥50% reduction in dose. The mean percent of total time with esophageal pH <4.0 decreased from baseline to 6 months ($P < 0.001$). Common adverse events were peri-operative chest discomfort and sore throat. Two severe adverse events requiring intervention occurred in the first 24 subjects, no further esophageal injury or leaks were reported in the remaining 48 enrolled subjects. Early experience with the device necessitated procedure and device changes to improve safety, with improved results in the later portion of the study. Continued assessment of durability and safety are ongoing in a three-year follow-up study of this patient group. Findings are limited by lack of comparison group.

Other clinical trials regarding endoscopic plicator or suturing are limited to observational case series that do not allow for conclusions about durability and long-term effectiveness (Birk et al., 2009; von Renteln et al., 2009).

EsophyX™ System (Transoral Incisionless Fundoplication [TIF])

A custom product brief from ERCI (updated 2020) focused on the safety and efficacy of EsophyX™ and how it compared with those of laparoscopic Nissen fundoplication or other GERD treatments. One low quality systematic review identified EsophyX™ as safe and improved the quality of life in most patients, however no additional studies were found that directly compared EsophyX™ to laparoscopic Nissen fundoplication.

Janu et al. (2019) examined the safety and efficacy of the EsophyX TIF (transoral incisionless fundoplication) device in a case series of patients with hiatal hernias between 2 and 5 cm. Data was collected from 99 patients aged 18 to 75 years with moderate to severe GERD symptoms for greater than one year, more than six months of daily proton pump inhibitors (PPI) and a hiatal hernia. Three validated questionnaires ((GERD-HRQL (Health-Related Quality of Life), RSI (Reflux Symptom Index), and GERSS (Gastroesophageal Reflux Symptom Score)) were administered before the procedure and again at six- and twelve-months post-procedure. Scores of ≤2 for each question were indicative of successfully treated symptoms. Symptoms were considered significantly improved if the total GERDHRQL, GERSS, and RSI scores were reduced by ≥50% at the follow-up assessments. The questionnaire response rate was 73% at 6 months, 67% at 12 months, and 48% for both. The authors found that the results at twelve months indicated all scores moved in a positive direction; they concluded the HH repair and TIF provided significant control from heartburn with no long-term dysphagia or bloating. Limitations of the study included lack of a comparison group, relatively short-term follow-up, lack of objective outcomes data such as pH testing, and incomplete data.

Trad et al. (2018) reported 5-year outcomes from the previously described TEMPO clinical trial (TIF 2.0). A total of 63 patients with chronic GERD refractory to PPI therapy, absent or ≤2 cm hiatal hernia, and abnormal esophageal acid exposure were randomized to the TIF group or PPI group. Following the 6-month evaluation, all patients in the PPI group elected for crossover to TIF. Of 63 patients, 60 were available at 1 year, 52 at 3 years, and 44 at 5 years for evaluation. Troublesome regurgitation was eliminated in 88% of patients at 1 year, 90% at 3 years, and 86% at 5 years. Resolution of troublesome atypical symptoms was achieved in 82% of patients at 1 year, 88% at 3 years, and 80% at 5 years. No serious adverse events occurred. There were 3 reoperations by the end of the 5-year follow-up. At the 5-year follow-up, 34% of patients were on daily PPI therapy as compared with 100% of patients at screening. The total GERD Health-related quality-of-life score improved by decreasing from 22.2 to 6.8 at 5 years ($P < .001$). The authors concluded that in this patient population, the TIF 2.0 procedure provided safe and sustained long-term elimination of troublesome GERD symptoms. Study limitations include small patient population, loss to follow-up, and lack of comparison group after the six-month cross-over.

Richter et al. (2018) conducted a systematic review and meta-analysis of randomized controlled trials to indirectly compare TIF and laparoscopic Nissen fundoplication (LNF) using a network meta-analysis technique. Included were 7 trials comprising 1128 patients, none of which including a direct comparison between the two methods. The authors found LNF to have the greatest ability to improve physiologic parameters of GERD, including increased LES pressure and decreased percent time pH <4. Although TIF produced the largest increase in health-related quality of life, this could be due to the shorter follow-up time of patients treated with TIF vs LNF or PPIs. TIF is a minimally invasive endoscopic procedure, yet based on evaluation of benefits vs risks, the authors do not recommend it as a long-term alternative to PPI or LNF treatment of GERD. Limitations identified were lack of individual patient data, differences in follow-up time and number of participants across LNF and TIF studies and studies were of moderate to very low in quality. Additionally, this analysis is limited by the inherent indirectness of network meta-analyses.

Ebright et al. (2017) reported follow-up data on endoscopic fundoplication performed on 80 patients using a case series design. Although symptoms and satisfaction improved significantly over a mean follow-up period of 24 months, approximately 30% of patients continued to take PPIs. Future studies are needed to focus on longer-term durability and comparisons with laparoscopic techniques.

Stefanidis et al. (2017a) evaluated the long-term benefit of TIF using the EsophyX device (n=45) for the management of GERD responsive to medical therapy in a case series. After a median follow up period of 59 months (36-75) the median GERD-HRQL scores improved significantly from 27 (2-45) at baseline to 4 (0-26) ($P < 0.001$) in the 44 patients completing the study. Heartburn was eliminated in 12 out of the 21 patients included (57.1%), regurgitation was eliminated in 15 out of the 17 patients included (88.2%) and finally chest pain was eliminated in 5 patients out of the six patients included (83.3%). Overall, 32 patients out of the 44 patients (72.7%) that completed the study follow up reported elimination of their main symptom, without the need for PPI administration. Furthermore, six more patients (13.6%), five with heartburn, and one with regurgitation reported half PPI dose taken for <50% of the preceding follow up period (occasional PPI usage), while six more patients (four with heartburn, one with regurgitation, and one with chest pain) reported full or half PPI dose taken for more than 50% of the preceding follow up

period (daily PPI usage). Randomized clinical trials are needed to validate these results in comparison with other treatments for GERD.

Trad et al. (2017) reported 3-year outcomes from the TEMPO trial (TIF 2.0). A total of 63 patients with chronic GERD refractory to PPI therapy, absent or ≤2 cm hiatal hernia, and abnormal esophageal acid exposure were randomized to the TIF group or PPI group. Following the 6-month evaluation, all patients in the PPI group elected for crossover to TIF. At 3-year follow-up, elimination of troublesome regurgitation and all atypical symptoms was reported by 90% (37/41) and 88% (42/48) of patients, respectively. The mean Reflux Symptom Index score improved from 22.2 (9.2) on PPIs at screening to 4 (7.1) off PPIs 3 years post-TF, p < 0.0001. The mean total % time pH <4 improved from 10.5 (3.5) to 7.8 (5.7), p = 0.0283. Esophagitis was healed in 86% (19/22) of patients. At the end of study, 71% (37/52) of patients had discontinued PPI therapy. All outcome measures remained stable between 1-, 2-, and 3-year follow-ups. Study limitations include small patient population and lack of comparison group after the six-month cross-over.

Huang et al. (2017) performed a systematic review with meta-analysis of studies evaluating the role of TIF in GERD. Only randomized controlled trials evaluating the efficacy of TIF, and prospective observational studies reporting outcomes after TIF were included. The authors identified that the total number of refluxes was reduced after TIF compared with the PPIs/sham group. The esophageal acid exposure time and acid reflux episodes after TIF were not significantly improved. PPI usage increased with time and most of the patients resumed PPIs treatment at reduced dosage during the long-term follow-up. The total satisfaction rate after TIF was about 69.15 % in 6 months. The incidence of severe adverse events consisting of gastrointestinal perforation and bleeding was 2.4 %. The authors concluded that TIF has comparable short-term patient satisfaction as an alternative intervention to GERD-related symptoms. Long-term results showed decreased efficacy with time and patients often resumed PPIs at reduced doses.

In a double-blind sham-controlled study in patients with moderate to severe GERD who were chronic PPI users, Håkansson et al. (2015) evaluated the TIF2 procedure (using the EsophyX device) versus sham (upper GI endoscopy). Patients (n=44) were randomized into the two groups. The primary effectiveness endpoint was the proportion of patients in clinical remission after 6-month follow-up. Secondary outcomes were: PPI consumption, esophageal acid exposure, reduction in Quality of Life in Reflux and Dyspepsia and Gastrointestinal Symptom Rating Scale scores and healing of reflux esophagitis. The time (average days) in remission offered by the TIF2 procedure (197) was significantly longer compared to those submitted to the sham intervention (107), P < 0.001. After 6 months 13/22 (59%) of the chronic GERD patients remained in clinical remission after the active intervention. Likewise, the secondary outcome measures were all in favor of the TIF2 procedure. No safety issues were raised. Although the authors concluded that the TIF2 procedure is effective in chronic PPI-dependent GERD patients, the study was limited by small patient population and short follow-up period.

Rinsma et al. (2015) conducted a randomized controlled trial to evaluate the effect of endoscopic fundoplication and PPI therapy on baseline impedance and heartburn severity in GERD patients. Forty-seven GERD patients randomized to endoscopic fundoplication (n=32) or PPI therapy (n=15), and 29 healthy controls were included. Before randomization and 6 months after treatment, baseline impedance was obtained during 24-h pH-impedance monitoring. Heartburn severity was evaluated using the GERD-HRQL questionnaire. Before treatment, baseline impedance in GERD patients was lower than in healthy controls (p < 0.001). Antireflux therapy increased baseline impedance (from 1498 [IQR 951-2472] to 2393 [IQR 1353-3027] Ω, p = 0.001), however it only led to a partial recovery when compared to healthy controls (2393 [IQR 1353-3027] vs 2983 [2335-3810] Ω, p < 0.01). The effect of both treatment options was not significantly different (p = 0.13) despite the increased number of non-acid reflux events in the PPI group. No correlation was found between baseline impedance and GERD symptoms before or after treatment.

Testoni et al. (2015) evaluated a case series of 50 patients with GERD who underwent TIF 2.0. All underwent GERD-HRQL and GERD-QUAL questionnaires, upper GI endoscopy, esophageal manometry, and 24-h pH-impedance before and 6, 12, and 24 months after TIF, and subsequent yearly clinical re-evaluation. Patients were followed for up to six years (mean 52.7 ± 19.7 months). In all, 83.7, 79.6, 87.8, and 84.4% of patients stopped or halved the PPI therapy 6, 12, 24, and 36 months after TIF. Three-year figure remained stable up to 6 years. Symptom scores off PPI were significantly lower at 6, 12, 24, and 36 months. At 6 months, Hill's grade I of the newly created valve persisted in all pre-procedure Hill's grade I patients, in 66.7% of grade II and 58.3% of grade III. This figure remained substantially unchanged at 12 and 24 months. Impedance monitoring indicated significantly fewer total and acid refluxes after treatment (p = 0.01). Factors predicting good outcomes were pre-procedure Hill's grade I-II, no hiatal hernia or hernia ≤2 cm (p = 0.03), absence of ineffective esophageal motility (p < 0.0001), and number of

fasteners deployed (p = 0.01). The study is limited by lack of comparison group undergoing a different approach to GERD treatment.

In a prospective, sham-controlled trial, Hunter et al. (2015) aimed to determine if TIF reduced troublesome regurgitation to a greater extent than PPIs in patients with GERD. Patients with GERD, taking daily PPIs, and hiatal hernias ≤2 cm 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 blinded to therapy during follow-up period and reassessed at 2, 12, and 26 weeks. At 6 months, patients underwent 48-hour esophageal pH monitoring and esophagogastroduodenoscopy. By intention-to-treat analysis, TF eliminated troublesome regurgitation in a larger proportion of patients (67%) than PPIs (45%) (P=.023). A larger proportion of controls had no response at 3 months (36%) than subjects that received TF (11%; P=.004). Control of esophageal pH improved after TF (mean 9.3% before and 6.3% after; P < .001), but not after sham surgery (mean 8.6% before and 8.9% after). Subjects from both groups who completed the protocol had similar reductions in GERD symptom scores. Severe complications were rare (3 subjects receiving TF and 1 receiving the sham surgery). Based on evaluation 6 months after the procedure, the authors concluded that TF was an effective treatment for patients with GERD symptoms, particularly in those with persistent regurgitation despite PPI therapy. Short follow-up period and relatively small sample size were limitations of this study.

Witteman et al. (2015) conducted a randomized controlled trial of TIF vs. PPIs for the treatment of GERD in 60 patients who opted for endoscopic option versus lifelong dependence on PPIs. A total of 60 patients (TIF n=40, PPI n=20, mean body mass index 26 kg/m (2), 37 male) were included. At 6 months, GERD symptoms were more improved in the TIF group compared with the PPI group (P<0.001), with a similar improvement of distal esophageal acid exposure (P=0.228) compared with baseline. The pH normalization for TIF group and PPI group was 50% and 63%, respectively. All patients allocated for PPI treatment opted for crossover. At 12 months, quality of life remained improved after TIF compared with baseline (P<0.05), but no improvement in esophageal acid exposure compared with baseline was found (P=0.171) and normalization of pH was accomplished in only 29% in conjunction with deteriorated valve appearances at endoscopy and resumption of PPIs in 61%. Although TIF resulted in an improved GERD-related quality of life and produced a short-term improvement of the antireflux barrier in a selected group of GERD patients, no long-term objective reflux control was achieved.

In a retrospective case series, Trad et al. (2012) evaluated the safety, symptom resolution, patient satisfaction, and medication use 1-2 years after TIF in patients with GERD and/or laryngopharyngeal reflux (LPR) symptoms. Thirty-four patients with a confirmed diagnosis of GERD symptoms that were inadequately controlled by antisecretory medications, and who were either dissatisfied with their current therapy or not willing to continue taking medication, underwent TIF using EsophyX. Follow-up assessments were completed in 28 patients. At a median 14-months follow-up, 82% (23/28) of patients were off daily PPIs (64% completely off PPIs), and 68% (19/28) were satisfied with their current health condition compared to 4% before TIF. Median GERD Health-Related Quality of Life scores were significantly reduced to 4 (0-25) from 26 (0-45) before TIF (P < 0.001). Heartburn was eliminated in 65% (17/26) and improved by >50% in 86% (24/28) of patients. Regurgitation was eliminated in 80% (16/20) of patients. Atypical LPR symptoms such as hoarseness, coughing, and throat clearing were eliminated in 63% (17/27) of patients as measured by Reflux Symptom Index scores. Small patient population, retrospective analysis, and non-randomization are study limitations.

Bell and Freeman (2011) retrospectively evaluated the efficacy and safety of a rotational/longitudinal esophagogastric transoral incisionless fundoplication (TIF) in a case series of 37 patients on antisecretory medication, and with proven gastroesophageal reflux and limited hiatal hernia. Five patients were re-operations for failed laparoscopic fundoplication. The authors concluded that rotational/longitudinal esophagogastric fundoplication using the EsophyX device significantly improved symptomatic and objective outcomes in over 70% of patients at median 6-month follow-up. According to the authors, limitations of this study include its retrospective study design an incomplete data set for all patients, and the short 6-month duration of follow-up. Furthermore, the lack of comparison group limits the conclusions that can be drawn from this study.

In a retrospective case series, Barnes et al. (2011) evaluated clinical outcomes in 110 consecutive GERD patients who underwent TIF. At a median 7-month follow-up, typical and atypical symptom scores were normalized in 75% to 80% of patients and PPIs were completely discontinued by 93% of patients. According to the authors, these results supported the safety and efficacy of TIF. However, the retrospective study design, the lack of a control group, and the short term follow up limits the validity of these study results.

Other clinical trials for EsophyX are limited to observational case series that do not allow for conclusions about durability and long-term effectiveness (Narsule et al., 2012; Testoni et al., 2012; Frazzoni et al., 2011; Hoppo et al., 2010; Repici et al., 2010; Demyttenaere et al., 2010; Testoni et al., 2010).

Polymer Injection and Implantation Techniques

Plexiglas and Durasphere

The available evidence for plexiglas and Durasphere techniques for gastroesophageal conditions is insufficient to consider the procedure proven to be effective and safe; additional randomized studies are warranted.

In a small case series, Ganz et al. (2009) assessed the long-term safety and effectiveness of Durasphere (Carbon Medical Technologies), an injectable bulking agent, in the treatment of mild to moderate GERD. Nine patients completed the 12-month trial. There were no adverse events. The procedure was well tolerated with minimal patient discomfort and no dysphagia. At 12 months, 70% of patients discontinued all antacid medication completely and 90% of patients reduced PPI use by greater than 50%. There were no reports of esophagitis (at 12 months), erosion, ulceration, or sloughing of material at any injection site. The Durasphere material did not appear to migrate. The authors concluded that Durasphere appears to be a promising new injectable bulking agent for the treatment of mild to moderate GERD, with demonstrable efficacy and no significant adverse events in a small cohort of patients. Study limitations include lack of control group and small number of subjects.

Chen et al. (2009) conducted a systematic review that included 33 studies examining 7 endoscopic procedures (Stretta procedure, Bard EndoCinch, Wilson-Cook Endoscopic Suturing Device, NDO Plicator, Enteryx, Gatekeeper Reflux Repair System and Plexiglas) Of the three procedures that were compared with 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, QOL, and medication usage. However, for the two procedures that were compared with the laparoscopic fundoplication (Stretta) procedure and the Bard EndoCinch device, outcomes for patients in the endoscopic group were conflicting. Some patients in the endoscopic group experienced comparable outcomes as patients undergoing the laparoscopic approach, while others experienced inferior outcomes. The authors concluded that there is insufficient evidence to determine the safety and efficacy of endoscopic procedures for GERD, particularly over the long term (Chen et al., 2009).

LINX Reflux Management System

There is insufficient evidence to conclude LINX is effective and safe on the long-term for GERD treatment; additional research involving larger, randomized control trials with long-term outcomes is needed to establish its safety and efficacy, in the context of other mechanical approaches to GERD treatment that have shown benefits on the short-term but not on the long-term.

An ECRI (2020) custom product brief on the LINX® Reflux Management System for treating GERD identified a review of evidence from 2017 through 2020 that included two systematic reviews, one randomized control trial, one retrospective pre-post study and two economic studies. It was concluded longer follow-up and comparisons of LINX with other GERD devices would be useful and there are currently 3 ongoing trials that may partially address these evidence gaps.

Based on a review of the evidence from Hayes (2020) for the Magnetic Sphincter Augmentation (LINX Reflux Management System) for treatment of GERD, it was concluded that while the body of evidence was low, MSA appears to be safe and effective with GERD improvement. The authors concluded that this device may be a good choice for patients that do not want to undergo a more invasive surgery. However, it was identified that there was a lack of long-term efficacy and safety assessments performed.

Schizas et al. (2020) conducted a systematic review to investigate the safety and efficacy of the LINX® Reflux Management System. After screening 614 articles, a total of 35 studies fit the criteria and were analyzed. According to the authors, although laparoscopic fundoplication (LF) and magnetic sphincter augmentation (MSA) both appear to be safe and effective procedures, MSA appears to have a few distinct advantages such as a less technical procedure, less bloating and superiority in the ability to vomit/belch, easily reversible and if it fails, LF is still a viable option after device removal. The authors' findings suggested that MSA with the Linx device is a safe procedure and has the potential to bridge the treatment gap between maxed out medical treatment and laparoscopic fundoplication. The authors also concluded that further studies with longer follow-up are needed.

A prospective, multicenter, randomized control trial was conducted by Bell et al. (2019, included in the ECRI report) comparing magnetic sphincter augmentation (MSA) (n-50) to double-dose proton-pump inhibitor (PPI) therapy (omeprazole, 20 mg, twice a day) (n-102). The goal of the study was to compare the effect of the two treatments for elimination of moderate to severe regurgitation. As reported on a foregut symptom questionnaire, at six months, 89% of patients treated with MSA reported relief of regurgitation, with 81% reporting ≥50% improvement in GERD-health-related quality of life scores. Ten percent of the PPI group reported relief of regurgitation with eight percent of the PPI group reporting ≥50% improvement in GERD-health-related quality of life scores. However, twenty-eight percent of MSA patients reported transient dysphagia, with 4% reporting ongoing dysphagia. The authors concluded that patients who continue to experience moderate to severe regurgitation despite PPI treatment should be considered for MSA. Randomized controlled trials with larger patient populations and long term follow up are needed to further assess the long-term safety and efficacy of MSA.

Louie et al. (2018, included in the Schizas et al. (2020) systematic review above) reported one-year results from a mandated post-approval multicenter, prospective case series of 200 patients with pathologic acid reflux confirmed by esophageal pH testing, who underwent magnetic sphincter augmentation (MSA). Predefined clinical outcomes were assessed at the annual visit including a validated, disease-specific questionnaire, esophagogastroduodenoscopy (EGD) and esophageal pH monitoring, and use of proton pump inhibitors. At 1 year, the mean total acid exposure time decreased from 10.0% at baseline to 3.6%, and 74.4% of patients had normal esophageal acid exposure time (% time pH<4 ≤5.3%). GERD Health-Related Quality of Life scores improved from a median score of 26.0 at baseline to 4.0 at 1 year, with 84% of patients meeting the predefined success criteria of at least a 50% reduction in total GERD Health-Related Quality of Life score compared with baseline. The device removal rate at 1 year was 2.5%. There was a report of one erosion, and no serious adverse events were reported. Although the authors conclude that safety and effectiveness of MSA has been demonstrated outside of an investigational setting, study limitations include lack of contemporaneous comparison group receiving a different GERD treatment and relatively short follow-up period.

In a retrospective observational study, Warren et al. (2018, included in the Schizas et al. (2020) systematic review above) analyzed factors influencing the outcome of MSA for chronic GERD using data from a pivotal trial (N=99) and the authors prospectively maintained esophageal database (N=71). A priori outcomes were defined as excellent (GERD-HRQL <5, no PPI, no esophagitis), good (GERD-HRQL 6-15, no PPI, grade A esophagitis), fair (GERD-HRQL 16 to 25, PPI use, grade B esophagitis), and poor (GERD-HRQL >25, PPI use, grade C/D esophagitis). Univariable and multivariable logistic regression analyses were performed to determine predictors of achieving an excellent/good outcome. A total of 170 patients underwent MSA with a median age of 53 years, [43-60] and a median BMI of 27 (IQR = 24-30). At baseline, 93.5% of patients experienced typical symptoms and 69% atypical symptoms. At univariable analysis, excellent/good outcomes were negatively impacted by BMI, preoperative LES residual pressure, Hill grade, and hiatal hernia. At multivariable analysis, BMI >35 (OR = 0.05, 0.003-0.78, p = 0.03), structurally defective LES (OR = 0.37, 0.13-0.99, p = 0.05), and preoperative LES residual pressure (OR = 0.89, 0.80-0.98, p = 0.02) were independent negative predictors of excellent/good outcome. The authors' conclusion is that MSA results in excellent/good outcomes in most patients but a higher BMI, structurally defective sphincter, and elevated LES residual pressure may prevent this goal. The authors' conclusion is that a higher BMI, structurally defective sphincter, and elevated LES residual pressure may prevent optimal treatment with MSA. The findings however do not provide evidence for the safety and efficacy of MSA compared to other therapeutic approaches.

Aiolfi et al. (2018, included in the Schizas et al. (2020) systematic review above) conducted a systematic review and meta-analysis of early results of MSA versus fundoplication for the treatment of GERD. Seven observational cohort studies, published between 2014 and 2017, matched the inclusion criteria. Overall, 1211 patients, 686 MSA and 525 LF, were included. Postoperative morbidity ranged from 0 to 3% in the MSA group and from 0 to 7% in the LF group, and there was no mortality. Dysphagia requiring endoscopic dilatation occurred in 9.3% and 6.6% of patients respectively (OR = 1.56, 95% CI = 0.61-3.95, p = 0.119). The pooled OR of gas/bloat symptoms, ability to vomit, and ability to belch were 0.39 (95% CI 0.25-0.61; p < 0.001), 10.10 (95% CI 5.33-19.15; p < 0.001), and 5.53 (95% CI 3.73-8.19; p < 0.001), respectively. The postoperative GERD-HRQL was similar (p = 0.101). The pooled OR of PPI suspension, endoscopic dilation, and reoperation were similar in the two patients' groups (p = 0.548, p = 0.119, p = 0.183, respectively). The authors concluded that both anti-reflux procedures are safe and effective up to 1-year follow-up. PPI suspension rate, dysphagia requiring endoscopic dilatation, and disease-related quality of life are similar in the two patient groups. MSA is associated with less gas/bloat symptoms and increased ability to vomit and belch. The findings are limited by inclusion of observational studies only and relatively short follow-up periods.

Alicuben et al. (2018, included in the Schizas et al. (2020) systematic review above) reported on the worldwide experience with erosion of the MSA device in a large case series. In total, 9453 devices were placed and there were 29 reported cases of

erosions. The median time to presentation of an erosion was 26 months with most occurring between 1 and 4 years after placement. The risk of erosion was 0.3% at 4 years after device implantation. Most patients experienced new-onset dysphagia prompting evaluation. Devices were successfully removed in all patients most commonly via an endoscopic removal of the eroded portion followed by a delayed laparoscopic removal of the remaining beads. At a median follow-up of 58 days post-removal, there were no complications and 24 patients have returned to baseline. Four patients reported ongoing mild dysphagia. The authors concluded that erosion of the LINX device is an important but rare complication to recognize that has been managed via minimally invasive approaches without long-term consequences. Continued monitoring and reporting of MSA erosion will provide longer-term experience.

In a systematic review and meta-analysis of the LINX® magnetic esophageal sphincter augmentation versus Nissen fundoplication for gastroesophageal reflux disease, Skubleny et al. (2017) included randomized controlled trials, non-randomized comparison study and case series with greater than 5 patients. Five hundred and forty-seven titles were identified through primary search, and 197 titles or abstracts were screened after removing duplicates. Meta-analysis was performed on postoperative quality of life outcomes, procedural efficacy and patient procedural satisfaction. Three primary studies identified a total of 688 patients, of whom 273 and 415 underwent Nissen fundoplication and MSA, respectively. MSA was statistically superior to LNF in preserving patient's ability to belch (95.2 vs 65.9%,
$p < 0.00001$) and ability to emesis (93.5 vs 49.5%, $p < 0.0001$). There was no statistically significant difference between MSA and LNF in gas/bloating (26.7 vs 53.4%, $p = 0.06$), postoperative dysphagia (33.9 vs 47.1%, $p = 0.43$) and proton pump inhibitor (PPI) elimination (81.4 vs 81.5%, $p = 0.68$). The authors' conclusion is that magnetic sphincter augmentation appears to be an effective treatment for GERD with short-term outcomes comparable to the more technically challenging and time-consuming Nissen fundoplication. The authors also concluded that long-term comparative outcome data past 1 year is needed in order to further understand the efficacy of magnetic sphincter augmentation.

Warren et al. (2017) conducted a retrospective case series to evaluate the manometric changes, function, and impact of magnetic sphincter augmentation (MSA) on the lower esophageal sphincter (LES). Inclusion criteria (n=121) consisted of a confirmed diagnosis of gastroesophageal reflux disease by an abnormal esophageal pH study (body mass index <35 kg/m, hiatal hernia <3 cm, and absence of endoscopic Barrett disease). Manometric changes, pH testing, and proton pump inhibitor use were assessed preoperatively and 6 and 12 months after MSA. MSA was associated with an overall increase in the median LES resting pressure (18 pre-MSA vs 23 mm Hg post-MSA; $P = 0.0003$), residual pressure (4 vs 9 mm Hg; $P < 0.0001$), and distal esophageal contraction amplitude (80 vs 90 mm Hg; $P = 0.02$). The percent peristalsis remained unaltered (94% vs 87%; $P = 0.71$). Overall, patients with a manometrically defective LES were restored 67% of the time to a normal sphincter with MSA. Those with a structurally defective or severely defective LES improved to a normal LES in 77% and 56% of patients, respectively. Only 18% of patients with a normal preoperative manometric LES deteriorated to a lower category. The authors concluded that a manometrically defective LES can be restored to normal sphincter, whereas a normal LES remains stable. The study is limited by lack of comparison group receiving other treatment for GERD.

Warren et al. (2016, included in the Hayes report) conducted a multi-institutional, retrospective cohort study of patients with GERD undergoing either magnetic sphincter augmentation (MSA) or Nissen fundoplication (NF). Comparisons were made at 1 year for the overall group and for a propensity-matched group. A total of 415 patients (201 MSA and 214 NF) underwent surgery. At a minimum of 1-year follow-up, 354 patients (169 MSA and 185 NF) had significant improvement in GERD-HRQL scores (pre to post: 21-3 and 19-4). MSA patients had greater ability to belch (96 vs. 69%) and vomit (95 vs. 43%) with less gas bloat (47 vs. 59%). Propensity-matched cases showed similar GERD-HRQL scores and the differences in ability to belch or vomit, and gas bloat persisted in favor of MSA. Mild dysphagia was higher for MSA (44 vs. 32%). Resumption of daily PPIs was higher for MSA (24 vs. 12, $p=0.02$) with similar patient-reported satisfaction rates. The authors concluded that in appropriate candidates, MSA is a valid alternative surgical treatment for GERD management, as MSA for uncomplicated GERD achieves similar improvements in quality of life and symptomatic relief, with fewer side effects. However, the authors found that MSA had lower PPI elimination rates when compared to propensity-matched NF cases. The study is limited by lack of randomization and relatively short follow-up.

Ganz et al. (2016, included in the Schizas et al. (2020) systematic review above) reported in a case series the 5-year follow-up evaluation of patients who received a magnetic sphincter augmentation (MSA) device for GERD. The original prospective study at 14 centers in the United States and the Netherlands was conducted on 100 adults with GERD for 6 months or more, who were partially responsive to daily proton pump inhibitors (PPIs) and had evidence of pathologic esophageal acid exposure. At baseline, the median GERD-HRQL scores were 27 in patients not taking PPIs and 11 in patients on PPIs; 5 years after device placement this score decreased to 4. All patients used PPIs at baseline; this value decreased to 15.3% at 5 years. Moderate or

severe regurgitation occurred in 57% of subjects at baseline, but only 1.2% at 5 years. All patients reported the ability to belch and vomit if needed. Bothersome dysphagia was present in 5% at baseline and in 6% at 5 years. Bothersome gas-bloat was present in 52% at baseline and decreased to 8.3% at 5 years. The authors concluded that MSA provides significant and sustained control of reflux, with minimal side effects or complications, which in their opinion validates the long-term safety and efficacy of MSA for patients with GERD. The study is however limited by lack of comparison group.

In an observational cohort study, Asti et al. (2016, included in the Schizas et al. (2020) systematic review above) compared the quality of life in patients undergoing laparoscopic Toupet fundoplication (LTF) versus LINX. Consecutive patients undergoing LTF or LINX over the same time period were compared by using the propensity score full matching method and generalized estimating equation. Of 238 eligible patients, 103 underwent an LTF and 135 a LINX procedure. All patients had a minimum 1-year follow-up. Over time, patients in both groups had similar GERDHRQL scores (odds ratio [OR] 1.04, confidence interval [CI] 0.89–1.27; P=0.578), PPI use (OR 1.18, CI 0.81–1.70; P=0.388), gas related symptoms (OR 0.69, CI 0.21–2.28; P=0.542), dysphagia (OR 0.62, CI 0.26–1.30; P=0.241), and reoperation-free probability (stratified log-rank test=0.556). In 2 concurrent cohorts of patients with early stage GERD undergoing LTF or LINX and matched by propensity score analysis, health related quality of life significantly improved and GERD-HRQL scores had a similar decreasing trend over time up to 7 years of follow-up. Based on these findings, the authors concluded that LTF and LINX provide similar disease-specific quality of life over time in patients with early stage GERD. The study is limited by lack of randomization and relatively short follow-up.

Saino, et al. (2015) completed the 5-year follow-up from a prospective, multicenter case series which evaluated the safety and efficacy of the MSAD. Prior to MSAD placement, patients (n=44) had abnormal esophageal acid and symptoms poorly controlled by proton pump inhibitors (PPIs). 33 patients completed the 5-year follow-up. Mean total percentage of time with pH <4 was 11.9% at baseline and 4.6% at 5 years (P < .001), with 85% of patients achieving pH normalization or at least a 50% reduction. Mean total GERD-HRQL score improved significantly from 25.7 to 2.9 (P < .001) when comparing baseline and 5 years, and 93.9% of patients had at least a 50% reduction in total score compared with baseline. Complete discontinuation of PPIs was achieved by 87.8% of patients. No complications occurred in the long term, including no device erosions or migrations at any point. Based on long-term reduction in esophageal acid, symptom improvement, and no late complications, the authors concluded that this study shows the relative safety and efficacy of magnetic sphincter augmentation for GERD. The study was limited by small patient population and no comparison group.

In a retrospective case series, Desart et al. (2015, included in the Schizas et al. (2020) systematic review above) evaluated whether the LINX® magnetic sphincter augmentation system is a safe and effective option for patients with new gastroesophageal reflux disease following laparoscopic sleeve gastrectomy. At 2-4 weeks after the LINX procedure, all patients (n=7) were noted to have self-reported greatly improved gastroesophageal reflux symptoms: statistically significant improved severity and frequency of their reflux, regurgitation, epigastric pain, sensation of fullness, dysphagia, and cough symptoms in their postoperative GERD symptoms compared with their preoperative evaluation. The authors concluded that the LINX® device is a safe and effective option in patients with de novo refractory gastroesophageal reflux disease after a laparoscopic sleeve gastrectomy despite appropriate weight loss. The study is limited by lack of comparison group, small sample size and short follow-up period. In addition, there was lack of information about use of PPIs prior to or after the procedure.

Reynolds et al. (2015, included in the Schizas et al. (2020) systematic review above) conducted a retrospective analysis of 1-year outcomes of patients undergoing magnetic sphincter augmentation (MSA) with the LINX device and laparoscopic Nissen fundoplication (LF) from June 2010 to June 2013. Patients were matched using propensity scores incorporating multiple preoperative variables. Outcomes were measured by GERD Health Related Quality of Life scores, proton-pump inhibitor use, satisfaction, and complications. One hundred and seventy-nine patients met inclusion criteria, 62 MSA and 117 LNF. At 1 year after surgery, both groups had similar GERD Health Related Quality of Life scores (4.2 MSA and 4.3 LNF; p=0.897) and proton-pump inhibitor use (17% of MSA and 8.5% of LNF; p=0.355). Analogous GERD patients had similar control of reflux symptoms after both MSA and LNF. The inabilities to belch and vomit were significantly fewer with MSA, along with a significantly lower incidence of severe gas-bloat symptoms. These results support the use of MSA as first-line therapy in patients with mild to moderate GERD.

Reigler et al. (2015, included in the Hayes report) evaluated using a retrospective cohort study design the evidence for magnetic sphincter augmentation device (MSAD) and laparoscopic fundoplication (LF) in clinical practice. Two hundred forty-nine patients (202 MSAD patients and 47 LF patients) had completed one-year follow-up. The LF group was older and had a greater frequency of large hiatal hernias and Barrett's esophagus than the MSAD group (P < 0.001). The median GERD-health related quality of life score improved from 20.0 to 3.0 after MSAD and 23.0 to 3.5 after LF. Moderate or severe regurgitation

improved from 58.2 to 3.1% after MSAD and 60.0 to 13.0% after LF (P=0.014). Discontinuation of PPIs was achieved by 81.8% of patients after MSAD and 63.0% after LF (P=0.009). Excessive gas and abdominal bloating were reported by 10.0% of patients after MSAD and 31.9% following LF (P ≤ 0.001). Following MSAD, 91.3% of patients were able to vomit if needed, compared with 44.4% of those undergoing LF (P < 0.001). Reoperation rate was 4.0% following MSAD and 6.4% following LF. The authors conveyed that antireflux surgery should be individualized to the characteristics of each patient, taking into consideration anatomy and propensity and tolerance of side effects. They concluded that both MSAD and LF showed significant improvements in reflux control, with similar safety and reoperation rates. In their opinion, in the treatment continuum of antireflux surgery, MSAD should be considered as a first-line surgical option in appropriately selected patients without Barrett's esophagus or a large hiatal hernia in order to avoid unnecessary dissection and preserve the patient's native gastric anatomy. The study is however limited by lack of randomization.

Ganz et al. (2013) conducted a case series (n=100; 52% men; median age, 53 years, range 18-75) of patients with a history of GERD for at least 6 months and who had experienced a partial response to PPI treatment. The primary outcomes were normalization of esophageal acid exposure or a ≥50% reduction in acid exposure at 1 year of follow-up. Secondary outcomes were 50% reduction in the QOL score compared with the score without PPIs at baseline. The esophageal sphincter device was implanted using standard laparoscopy by surgeons with experience with fundoplication. Normalization of or at least a 50% reduction in esophageal acid exposure was achieved in 64% of all patients (64/100). Secondary outcomes of a 50% reduction in the QOL score compared with the score without PPI at baseline was achieved in 92% of all patients (92/100). Post-hoc analysis demonstrated a reduction of ≥50% in the average daily dose of PPI was observed in 93% of all patients (93/100). Six patients experienced serious adverse effects, 4 of whom required removal of the device. In 3 patients, the device was removed at various time points following implantation because of persistent dysphagia. The most frequently reported adverse effect was dysphagia occurring in 68% of all patients. At 1 year, 11% of patients reported persistent and ongoing dysphagia. The preliminary and positive results of this study are limited by the low-quality design, which includes lack of comparison group, and relatively short follow-up.

Lipham et al. (2015) conducted a case series of antireflux surgery with a Magnetic Sphincter Augmentation Device (MSAD). The aim of the study was to examine the safety profile of the MSAD in the first 1000 implanted patients. The author compiled data from multiple sources starting in July 1, 2013. The analysis included intra/perioperative complications, hospital readmissions, procedure-related interventions, reoperations, and device malfunctions leading to injury or inability to complete the procedure. The authors report that approximately 1000 patients worldwide have been implanted with the MSAD, at 82 institutions with median implant duration of 274 days. They concluded that the safety analysis of the first 1000 patients treated with MSAD for gastroesophageal reflux disease confirms the safety of this device and the implantation technique. The preliminary and positive results of this study are hampered by lack of an adequate comparator group.

Bonavina et al. (2010, included in the Schizas et al. (2020) systematic review above) conducted a case series with 1- and 2-year evaluations of a feasibility trial to assess the safety and efficacy of a laparoscopically implanted sphincter augmentation device (LINX Reflux Management System) in 44 patients with GERD. Complete cessation of PPI use was reported by 90% of patients at 1 year and by 86% of patients at 2 years. One device was laparoscopically explanted for persistent dysphagia without disruption of the anatomy or function of the cardia. There were no device migrations, erosions, or induced mucosal injuries. At 1 and 2 years, 77% and 90% of patients, respectively, had a normal esophageal acid exposure. According to the authors, the new laparoscopically implanted sphincter augmentation device eliminates GERD symptoms without creating undue side effects and is effective at 1 and 2 years of follow-up. The study is limited by lack of comparison group.

As a follow-up to the Bonavina et al. (2010) study, Lipham et al. (2012) evaluated 44 patients who underwent a laparoscopic surgical procedure for placement of the LINX System using a case series design. Each patient's baseline GERD status served as the control for post implant evaluations. For esophageal acid exposure, the mean total % time pH < 4 was reduced from 11.9% at baseline to 3.8% at 3 years, with 80% of patients achieving pH normalization. At ≥4 years, 100% of the patients had improved QOL measures for GERD, and 80% had complete cessation of the use of PPIs. There have been no reports of long-term device-related complications such as migration or erosion. The authors concluded that sphincter augmentation with the LINX Reflux Management System provided long-term clinical benefits with no safety issues. According to the authors, patients with inadequate symptom control with acid suppression therapy may benefit from treatment with sphincter augmentation. Limitations of the study include the lack of controls and a small sample size.

Bonavina et al. (2008, included in the Schizas et al. (2020) systematic review above) conducted a multi-center case series to evaluate safety and efficacy of a magnetic sphincter augmentation (MSA) device. Over a 1-year period, 38 out of 41 enrolled

patients underwent implantation of this device. The mean follow-up was 209 days. At 3 months post-operatively, 89% of patients were no longer taking anti-reflux medications and 79% of patients had a normal 24-hr pH test. Mild dysphagia occurred in 45% of patients. No migrations or erosions of the device occurred. The authors concluded that laparoscopic implant of the MSA device is safe and well tolerated and thatit requires minimal surgical dissection and a short learning curve compared to the conventional Nissen fundoplication. The small study population and lack of comparison group limits the validity of the conclusion of this study.

Smith et al. (2017) reported that out of a total of 3283 procedures reviewed for MSAD, device removal occurred in 2.7% of cases. The most common causes of removal were dysphagia, continued reflux, and device erosion into the esophagus. Salvador et al. (2017), Parmar et al. (2017), and Lipham, et al. (2015), report similar findings.

The National Institute for Health and Care Excellence (NICE) encourages further research into laparoscopic insertion of a magnetic titanium ring for GERD, including long-term outcome data and comparative trials with other anti-reflux surgery. Their recommendations do not identify any major safety concerns with this procedure (NICE, 2017).

Professional Societies

American Gastroenterological Association (AGA)

In a position statement published in 2008, the AGA assigned a grade of “Insufficient” regarding the use of current and commercially available endoluminal antireflux procedures for the management of patients with an esophageal syndrome. The AGA provides no recommendation since there is insufficient evidence to recommend for or against its use (Kahrilas et al., 2008).

American Society for Gastrointestinal Endoscopy (ASGE)

In a 2015 clinical guideline on the role of endoscopy in the management of GERD, ASGE suggests 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.

American College of Gastroenterology (ACG)

In 2013, the ACG published practice guidelines regarding the diagnosis and management of GERD. They state that the “usage of current endoscopic therapy or transoral incisionless fundoplication cannot be recommended as an alternative to medical or traditional surgical therapy.” This recommendation is considered conditional, based on a moderate level of evidence (Katz et al., 2013).

American Society of General Surgeons (ASGS)

In 2014, the ASGS published a position statement regarding its support for the LINX procedure. ASGS states that total management of GERD will likely rely upon a combination of medical and surgical care in the current and near future. ASGS recommends that when considering a surgical procedure, the procedure will need to provide safe control of GERD with minimal side effects. The ASGS states, “Based on currently available information and the experience of their members with the procedure, they support the LINX procedure as a mechanism for controlling GERD when it is placed by properly trained laparoscopic surgeons with experience in foregut surgery and the management of GERD patients.”

In April 2011, the ASGS published a position statement regarding the use of TIF stating that it supports the use of TIF in patients with symptomatic chronic GERD who are not responsive to a standard dose of PPI therapy (ASGS, 2011). The ASGS also supports its use for patients who wish to avoid lifetime drug therapy for this condition. The ASGS also supports the adoption of the procedure by trained general surgeons as a less invasive alternative to more conventional surgical techniques, stating that the preferred surgical technique should be based on the discretion and judgment of the surgeon and the patient’s clinical circumstances.

In a statement regarding coverage for TIF, ASGS states that there is a sufficient body of peer reviewed literature that establishes transoral fundoplication as reasonable and medically necessary for a subset of patients who are candidates for surgical fundoplication; specifically, patients who either cannot obtain satisfactory relief from standard PPI therapy or who wish to avoid a lifetime of dependence on such medications, and present with a 2 centimeter or smaller hiatal hernia (ASGS, 2011).

Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)

In an updated review of endoluminal treatments for the treatment of GERD, SAGES (Stefanidis et al., 2017b) provided the following recommendations:

- Based on existing evidence, TIF 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 (6 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 suggests that the latter can be used safely after TIF failure. (Level of evidence +++, strong recommendation)
- Based on existing evidence, Stretta significantly improves health related quality of life score, 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 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)

The SAGES Technology and Value Assessment Committee (TVAC) updated its safety and effectiveness analysis of the LINX Reflux Management System.

- Review of published studies suggests that magnetic sphincter augmentation is safe with no reported deaths and a 0.1% rate of intra/perioperative complications.
- Long-term efficacy of LINX appears good for typical GERD symptoms with reduced acid exposure, improved GERD symptoms, and freedom from PPI in 85-88% at 3-5 years.
- Dysphagia resolves in most patients and the incidence is roughly 10% at 1 year and 4% at 3 years. The need for endoscopic dilation ranges from 6-12% and the primary reason for explantation appears to be persistent dysphagia with a rate in larger series from 3-6%.
- Erosion appear to be rare, with one case reported in the 1st 1,000 patients, one additional published case report, a large series reporting 2 erosions, and several additional reports in the FDA MAUDE dataset (true number unknown, as multiple entries in this dataset may be made for each patient). Based on very limited literature, erosion can be successfully treated with explantation (Telem et al., 2017).

U.S. Food and Drug Administration (FDA)

The Medigus Ultrasound Surgical Endostapler (MUSE™ System) received 510K approval on January 15, 2015 for the endoscopic placement of surgical staples in the soft tissue of the esophagus and stomach in order to create anterior partial fundoplication for treatment of symptomatic chronic GERD in patients who require and respond to pharmacological therapy. See the following website for additional information: https://www.accessdata.fda.gov/cdrh_docs/pdf14/k143634.pdf. (Accessed July 21, 2020)

These products are Class II devices (moderate risk) deemed substantially equivalent to other endoscopic devices utilizing other procedures.

Enteryx™, a biocompatible liquid polymer, received FDA approval in 2003 through the premarket approval (PMA) process for the treatment of symptomatic GERD. However, on September 22, 2005, Boston Scientific Corporation issued a recall of Enteryx due to the device polymerizing shortly after injection into a spongy material that cannot be removed. Serious adverse events involved unrecognized transmural injections of Enteryx into structures surrounding the esophagus, potentially resulting in serious injury or death. See the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRes/res.cfm?id=42034. (Accessed July 21, 2020)

Torax Medical obtained FDA premarket approval (PMA) in March 2012 for the LINX Reflux Management System. Additional approvals for PMA supplements can be found on the FDA website. See the following website for more information using PMA number P100049: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm. (Accessed July 21, 2020)

Durasphere is approved by the U.S. Food and Drug Administration (FDA) as an injectable bulking agent for gastro-urology use in the treatment of adult women with stress urinary incontinence due to intrinsic sphincter deficiency. Use of this product for

esophageal reflux would be considered off-label use. See the following website for more information, using PMA number P980053: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm. (Accessed July 21, 2020)
This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Several endoscopic antireflux (endoluminal) devices have received approval by the FDA for treatment of gastroesophageal reflux disease (GERD).

The Stretta System (Mederi Therapeutics) was approved in April 2000 for radiofrequency thermal ablation treatment of GERD. Additional information is available at: http://www.accessdata.fda.gov/cdrh_docs/pdf10/k103017.pdf. (Accessed July 21, 2020)

The Bard EndoCinch Endoscopic Suturing System (Bard Endoscopic Technologies, Billerica, MA, a subsidiary of C.R. Bard Inc), was approved in January 2001 for endoscopic suturing in the treatment of GERD. Subsequent FDA approval was received in September 2007 for an updated version. Additional information is available at: http://www.accessdata.fda.gov/cdrh_docs/pdf7/k071651.pdf. (Accessed July 21, 2020)

The NDO Surgical Endoscopic Plication System was approved in September 2007 for endoscopic suturing in the treatment of GERD in patients who require and respond to pharmacological therapy. Additional information is available at: http://www.accessdata.fda.gov/cdrh_docs/pdf7/k071651.pdf. (Accessed July 21, 2020)

The current generation of EsophyX, EsophyX2, was cleared for marketing as substantially equivalent to the original EsophyX system with minor changes in November 2009 under the FDA510(k) process. The original system was cleared for marketing in September 2007 as substantially equivalent to the predicate devices NDO Surgical Endoscopic Plication System, Bard EndoCinch, and EGS StomaphyX Endoluminal Fasteners and Delivery System. According to the approval summary letter, EsophyX2 is indicated for:

- Use in transoral tissue approximation
- Full-thickness plication and ligation in the GI tract
- The treatment of symptomatic chronic gastroesophageal reflux disease in patients who require and respond to pharmacologic therapy
- Narrowing of the gastroesophageal junction
- Reduction of hiatal hernia <2 cm in patients with symptomatic chronic gastroesophageal reflux disease

See the following websites for more information:

- http://www.accessdata.fda.gov/cdrh_docs/pdf7/K071651.pdf
- http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?db=PMN&id=k092400

(Accessed July 21, 2020)

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These products are Class II devices (moderate risk) deemed substantially equivalent to other endoscopic devices utilizing other procedures.

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Torax Medical obtained FDA premarket approval (PMA) in March 2012 for the LINX Reflux Management System. Additional approvals for PMA supplements can be found on the FDA website. See the following website for more information using PMA number P100049: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm. (Accessed July 21, 2020)

Durasphere is approved by the U.S. Food and Drug Administration (FDA) as an injectable bulking agent for gastro-urology use in the treatment of adult women with stress urinary incontinence due to intrinsic sphincter deficiency. Use of this product for esophageal reflux would be considered off-label use. See the following website for more information, using PMA number P980053: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm. (Accessed July 21, 2020)

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Policy History/Revision Information

Date	Summary of Changes
07/01/2021	Coverage Rationale • Replaced reference to "InterQual® 2020" with "InterQual® 2021" Supporting Information • Archived previous policy version CS079IN.01

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

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