# Minimally Invasive Procedures for the Treatment of Upper Gastrointestinal Diseases

**Policy Number**: 2026T0322LL
**Effective Date**: February 1, 2026

Instructions for Use

**Table of Contents** **Page**



**Related Commercial/Individual Exchange Policies**

- Bariatric Surgery
- Botulinum Toxins A and B (for Commercial Only)
- Botulinum Toxins A and B (for Individual Exchange Only)

**Community Plan Policy**

- Minimally Invasive Procedures for the Treatment of Upper Gastrointestinal Diseases

**Medicare Advantage Policy**

- Gastroesophageal and Gastrointestinal (GI) Services and Procedures

## Application

### UnitedHealthcare Commercial

This Medical Policy applies to UnitedHealthcare Commercial benefit plans.

### UnitedHealthcare Individual Exchange

This Medical Policy applies to Individual Exchange benefit plans.

## Coverage Rationale

**Gastric electrical stimulation (GES) therapy is proven and medically necessary for treating refractory Gastroparesis that has failed other therapies, or chronic intractable (drug-refractory) nausea and vomiting secondary to Gastroparesis of diabetic or idiopathic etiology.**

Refer to the U.S. Food and Drug Administration (FDA) section for information regarding FDA labeling and Humanitarian Device Exemption (HDE) for GES.

**Surgical pyloroplasty (open or laparoscopic) is proven and medically necessary for treating refractory Gastroparesis that has failed other therapies, or chronic-intractable (drug-refractory) nausea and vomiting secondary to Gastroparesis of diabetic or idiopathic etiology.**

**The per oral endoscopic myotomy (POEM) procedure is proven and medically necessary for treating individuals with Achalasia or Diffuse Esophageal Spasm.**

**Per oral endoscopic myotomy (POEM) is unproven and not medically necessary for all other indications (e.g., Zenker's diverticula) due to insufficient evidence of efficacy.**

**Gastric per oral endoscopic myotomy (G-POEM) is unproven and not medically necessary for the treatment of Gastroparesis.**

**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.**
Refer to the Medical Policy titled Bariatric Surgery for information regarding endoscopic therapies for the treatment of obesity.

## Medical Records Documentation Used for Reviews

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. Medical records documentation may be required to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the service requested; refer to the guidelines titled Medical Records Documentation Used for Reviews.

## 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**: Rare esophageal motility disorder characterized by simultaneous, uncoordinated, or rapidly propagated contractions that are of normal amplitude and accompanied by dysphagia (National Library of Medicine).

**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)].

**Gastroparesis**: A digestive disorder in which the motility of the stomach is either abnormal or absent; it is also known as delayed gastric emptying (Camilleri, 2013, updated 2022).

## 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 |
| 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 |
| 43284 | Laparoscopy, surgical, esophageal sphincter augmentation procedure, placement of sphincter augmentation device (i.e., magnetic band), including cruroplasty when performed |
| 43289 | Unlisted laparoscopy procedure, esophagus |
| 43497 | Lower esophageal myotomy, transoral (i.e., peroral endoscopic myotomy [POEM]) |
| 43499 | Unlisted procedure, esophagus |
| 43647 | Laparoscopy, surgical; implantation or replacement of gastric neurostimulator electrodes, antrum |
| 43648 | Laparoscopy, surgical; revision or removal of gastric neurostimulator electrodes, antrum |
| 43659 | Unlisted laparoscopy procedure, stomach |
| 43881 | Implantation or replacement of gastric neurostimulator electrodes, antrum, open |

| CPT Code | Description |
|---|---|
| 43882 | Revision or removal of gastric neurostimulator electrodes, antrum, open |
| 43999 | Unlisted procedure, stomach |
| 64590 | Insertion or replacement of peripheral, sacral, or gastric neurostimulator pulse generator or receiver, requiring pocket creation and connection between electrode array and pulse generator or receiver |
| 64595 | Revision or removal of peripheral, sacral, or gastric neurostimulator pulse generator or receiver, with detachable connection to electrode array |



# 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.

Individuals with Gastroparesis may experience symptoms of frequent nausea and vomiting, early satiety, bloating, postprandial fullness, and epigastric pain and burning. Although Gastroparesis can occur with no obvious cause, patients with diabetes frequently develop this condition. If Gastroparesis causes nausea and persistent vomiting, it can lead to frequent hospitalization for hypoglycemia, hyperglycemia, acidosis, dehydration, pseudo-obstruction, electrolyte dyscrasias, or other complications. The diagnosis of Gastroparesis requires objective evidence of clearly delayed gastric emptying in symptomatic patients. Scintigraphy is the reference standard for measurement of gastric emptying (Keller et al., 2018).

Gastric electrical stimulation (GES) involves implanting a device which sends electrical pulses to the stomach muscles to enhance gastric motility, which accelerates stomach emptying and alleviates the frequency and intensity of related symptoms (Hayes 2018).

Pyloroplasty is a surgical procedure used to address conditions that obstruct the stomach's outlet. It involves enlarging the pylorus-the muscular opening at the lower end of the stomach—to allow food to pass more easily into the small intestine (duodenum). This procedure can be performed either through traditional open surgery or minimally invasively using a laparoscope.

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).

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.

Diffuse Esophageal Spasm (also known as distal esophageal spasm) is a condition that leads to premature and rapidly produced contractions in the distal esophagus. Most patients present with difficulty swallowing and often have a sensation of foods stuck in their esophagus. Distal esophageal spasm is distinguished from other esophageal motility disorders that are associated with dysphagia by esophageal manometry testing.

Minimally invasive procedures, including endoscopic or endoluminal therapies and laparoscopic approaches, have been proposed as 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.

- Endoscopic plication or suturing:
  - 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.
  - GERDx™ (G-SURG) is an endoscopic full-thickness plication device that uses hydraulic elements for controlling the LES.
  - 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.
  - 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 (Hayes 2023).
- 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.

# Clinical Evidence

## Gastric Electrical Stimulation (GES) Therapy

Cassidy et al. (2024) conducted a retrospective, single-center case series of patients who were treated for medically refractory gastroparesis (MRG) with GES to evaluate the safety and efficacy of GES. The study included 157 patients (median age 45.3 years, 61.8% female) who underwent placement of GES and who completed Gastroparesis Cardinal Symptom Index (GCSI) surveys preoperatively and at subsequent follow-up visits with data extracted from a prospective, internal review board (IRB) approved database. The patients included 57 (36.3%) with diabetic gastroparesis, 93 (59.2%) with idiopathic gastroparesis, and 7 (4.5%) with postsurgical gastroparesis. At one year follow-up, 141 patients (89.8%) completed the GCSI survey, while 110 patients (70.1%) completed the GCSI survey at five-year follow-up. The authors reported that symptom severity in all nine gastroparesis symptoms evaluated by the GCSI, as well as the total GCSI score, was reduced significantly at one-year post-implantation, and that the improvements were sustained through the five-year follow-up. Patient satisfaction with improvement in their gastroparesis symptoms was reported by the authors to be high with 87.1% "satisfied" or "very satisfied" at one year and 79.7% at five years. When the authors evaluated the efficacy of GES in patients based on the cause of gastroparesis, they reported that they observed no difference between patients with idiopathic gastroparesis and those with diabetic gastroparesis. The authors also reported that the use of prokinetic and antiemetic medications was reduced during the follow-up period with reduction in prokinetic medications from 1.9 agents preoperatively to 0.3 at one year and 0.4 at five years, and with reduction in antiemetics from 2.1 agents preoperatively to 0.6 at one year and 0.7 at five years. Hospitalizations due to gastroparesis symptoms were also reported to be reduced with 91 hospitalizations reported preoperatively to 18 in the first year and 16 in the fifth year. GES devices were reported to be explanted in five patients (one for infection and four for lack of sufficient improvement), while 12 patients required generator exchanges, and seven patients required reoperation for mechanical issues (four for lead erosion and fracture, and three for displaced device leads) over the five-year study period. The authors concluded that GES was associated with sustained symptomatic relief, reduced reliance on medications on medications, and reduced gastroparesis related hospitalizations. Limitations of the study include the retrospective design, the lack of a comparison group, the inability to capture potential hospitalizations at other facilities, and the single-center design.

Samaan et al. (2022) conducted a single-center, retrospective study of 181 consecutive patients who underwent GES or primary gastrectomy (PG) for MRG between January 2003 to December 2017 to compare the therapeutic efficacy of GES versus PG for MRG. The authors collected data through chart review and a follow-up telephone survey. There were 130 patients (68.5% female, median age 42 years) who underwent GES and 51 (74.5% female, median age 44 years) who

underwent PG as their primary intervention. Of the 130 patients that underwent GES placement, 44 (33.8%) underwent GES removal and subsequent secondary gastrectomy (SG) for clinically significant persistence of gastroparesis symptoms. The authors reported that patients who underwent GES were more likely to have diabetic and idiopathic gastroparesis (GES 95% versus PG 39%) while the patients who underwent PG were more likely to have post-surgical gastroparesis (GES 5% versus PG 43%) and that postoperatively, primary PG patients had a higher rate of major inpatient morbidity events (GES 5% versus PG 18%) and longer lengths of stay (GES three days versus PG nine days). Although previous foregut surgery was more common in patients with PG (66.7% versus GES 43.1%) The authors noted that, over an average of 37.3 month (range 0.3-176.8) follow-up period, there were no differences between the GES patient population and the PG patient population in the rates of major morbidity, readmissions or mortality and that multivariable regression analysis showed that patients who underwent GES as their primary intervention were less likely to report improvement in symptoms on follow-up when compared to patients with PG. The authors also reported that patients who converted to PG from GES were more likely to have post-surgical gastroparesis as the primary etiology. Limitations of the study include the retrospective, observational, single-center design, the potential for recall bias related to the use of the postoperative telephone survey, the heterogeneity of the types of gastropareses and with the various gastrectomy types that were performed, and the potential for selection bias as the cohort consisted of patients who were willing to comply with the survey and follow-up requirement of the study. The authors concluded that patients who underwent GES as a first-line surgical treatment of MRG had worse outcomes than those who underwent PG. They also concluded that post-surgical etiology was associated with an increased likelihood of GES failure and that for patients who experienced GES failure, upfront gastrectomy may be a superior alternative to GES. The authors recommended further studies to determine patient selection criteria for operative treatment of MRG.

In a systematic review of the therapeutic role of gastric pacemakers in adults with gastroparesis, Rajamanuri et al. (2021) reviewed 12 studies that included data on adults with MRG that required GES therapy and found that the studies showed varying effects of GES on gastroparesis symptoms like nausea, vomiting, and abdominal bloating. They also concluded that there was significant weight gain noted based on the evidence in the studies they reviewed and that, while most of the studies suggested a significant improvement in the quality of life and the Gastroparesis Cardinal Symptom Index (GCSI) scores, the evidence supporting no difference in the quality of life seemed stronger, as shown by the meta-analysis and randomized controlled trials vs. open-label trials that showed positive results for quality of life with gastric pacing. The authors also found other beneficial effects of GES including reductions in inflammatory indicators, improved metabolic hormone levels and improved mucosal electrogram frequencies over baseline that were sustained for over six months. The authors noted that their review was limited due to the inclusion of open-labeled studies. They recommended additional RCTs to analyze the impact of gastric pacemakers in the improvement of symptoms in patients with gastroparesis, studies that evaluate the efficacy for the different causes of gastroparesis, such as diabetes, idiopathic and post-surgical, and future studies that include the pediatric population. (Ducrotte et al. 2020, Chu et al. 2012 and Shada et al. 2018, which were previously cited in this policy, are included in this systematic review)

Hayes (2018, updated 2022) published a Health Technology Assessment (HTA) on the safety and efficacy of GES for gastroparesis following their review of 12 studies, including three RCTs, six pretreatment/ posttreatment studies, one non-randomized comparative study, one comparative cohort study and one compilation of case series. The Hayes HTA stated that the effectiveness of GES for treating chronic gastroparesis remains uncertain, as findings have not provided consistent evidence. They noted that the available randomized studies provide little confirmation of the apparent benefit that was seen in unblinded studies. The report noted that GES appears safe in most patients but that serious complications can occur, including the movement of the stimulator and/or the electrical leads following implantation. They noted that the device removal rates in the studies they reviewed were between 7% to 12%. The overall quality of the evidence for GES for the treatment of gastroparesis was low due to the individual study limitations and inconsistency in the findings. The HTA concluded that additional randomized and placebo-controlled studies are needed to determine whether GES is a reliable therapy for gastroparesis and whether the benefits of GES treatment outweigh the potential risks.

Levinthal and Bielefeldt (2017) conducted a systematic review and meta-analysis to determine if GES is effective in reducing symptoms in patients with gastroparesis. Five studies randomly allocated patients to periods with or without GES. Total symptom severity (TSS) scores did not differ between these periods [0.17 (95% confidence interval: -0.06 to 0.4); $p = 0.15$]. However, sixteen open label studies of GES showed a significant TSS decrease [2.68 (2.04-3.32); $q = 39.0$; $p < 0.001$]. Other treatment modalities similarly improved TSS by 1.97 [(1.5-2.44) for medical therapy (MED), by 1.52 (0.9-2.15) for placebo arms (PLA), and by 2.32 (1.56-3.06) for botulinum toxin (BTx)]. There were significant differences in baseline TSS ratings among these studies [GES: 6.28 (6.28-7.42); MED: 4.76 (4.09-5.42); PLA: 4.59 (3.77-5.42); BTx: 6.02 (5.3-6.74); $q = 35.1$; $p < 0.001$]. Meta-regression analysis showed these baseline differences to significantly impact TSS ratings during treatment ($q = 71.8$; $p < 0.001$). Independent of the treatment modality, baseline symptom severity impacts treatment results in gastroparesis. Considering the skewed population with refractory symptoms, regression to the mean likely contributes to the substantial discrepancies between the reported results of

controlled and open label GES studies. (Chu et al. 2012, which was previously cited in this policy is included in this systematic review)

Heckert et al. (2016) assessed the effectiveness of GES with Enterra® for treatment for refractory symptoms of gastroparesis, the improvement in specific symptoms of gastroparesis, and clinical factors impacting on outcome in a cohort of 151 patients with refractory gastroparesis at a single center. Patients with gastroparesis [n = 151; (120 females) with refractory gastroparesis (72 diabetic, 73 idiopathic, six other) underwent GES with Enterra® (Medtronic)]. Patients filled out a symptom severity questionnaire (PAGI-SYM) prior to insertion. At each follow-up visit, the patient filled out PAGI-SYM and assessed their therapeutic response using the Clinical Patient Grading Assessment Scale (CPGAS). The investigators concluded that GES improved symptoms in 75% of patients with 43% being at least moderately improved. Response in patients with diabetes was better than in patients without diabetes. Nausea, loss of appetite, and early satiety responded the best. The unknown length of study follow-up did not allow for assessment of intermediate and long-term outcomes. Furthermore, lack of comparison group limits the conclusions that can be derived from this case series.

## *Clinical Practice Guidelines*

### American College of Gastroenterology (ACG)

The ACG published a clinical guideline for the management of gastroparesis that states that GES may be considered for control of gastroparesis symptoms as a humanitarian use device (HUD), as defined by the Food and Drug Administration (FDA) for medically refractory diabetic gastroparesis or idiopathic gastroparesis. This conditional recommendation was based on a low-quality body of evidence (Camilleri, 2013, updated 2022).

### American Gastroenterological Association (AGA)

The AGA published a clinical practice update on the management of MRG based on a review of existing literature combined with expert opinion to provide practical advice. Based on this review, the AGA stated that clinicians can consider gastric electrical stimulation for patients with gastroparesis and refractory/intractable nausea and vomiting who have failed standard therapy and are not on opioids. This guidance was based on their review of six published studies that they stated showed that GES improved refractory nausea and vomiting in some patients with gastroparesis and may improve glycemic control, nutritional status, and quality of life, while reducing hospitalizations and medication use. They noted that this document was not based on a systematic review, so no formal rating of the quality of evidence or strength of recommendation was made (Lacy, 2022).

In a white paper on current approaches for the treatment of gastroparesis, the AGA (Pasricha et al., 2017n) includes GES therapy (recommendation: conditional; level of evidence: moderate).

### National Institute for Health and Care Excellence (NICE)

The National Institute for Health and Care Excellence (NICE) (2014) interventional procedure guidance on GES for gastroparesis notes that GES is an option for treating chronic, intractable nausea and vomiting secondary to gastroparesis, observing that further publications providing data about the effects of the procedure on symptoms in the long term and on device durability would be useful.

## Surgical Pyloroplasty

Fonseca et al. (2021) conducted a systematic literature review examining current therapeutic approaches for gastroparesis, including dietary, medical, and surgical management strategies. The review encompassed 68 full-text articles published between 1980 and 2018, involving a total of 4,878 individuals. Among these, 435 individuals underwent surgical pyloroplasty—either as a standalone procedure (n = 81), in combination with fundoplication (n = 227), or alongside GES (n = 127). Included in the population were 142 individuals with idiopathic gastroparesis, 89 with diabetic gastroparesis, and 28 with postsurgical gastroparesis. The authors reported success rates varied by intervention: pyloroplasty alone achieved a 61% success rate, pyloroplasty with fundoplication reached 86%, and pyloroplasty combined with GES showed a 74.8% success rate. Improvements in gastric emptying time were observed in 75% of patients who underwent pyloroplasty alone, 85% in those who had pyloroplasty with fundoplication, and 75% in patients treated with GES. The authors concluded that pyloroplasty can effectively normalize gastric emptying and alleviate symptoms in individuals with idiopathic and diabetic gastroparesis. Furthermore, when combined with gastric neurostimulation, additional reductions in nausea, vomiting, bloating, and abdominal pain may be achieved.

Zoll et al. (2018) conducted a systematic literature review to evaluate the outcomes of three surgical treatments for refractory gastroparesis: GES, pyloric interventions (PI), and gastrectomy (GTx). The review included 38 studies, with a total of 441 patients undergoing GES, 141 receiving PI, and 263 treated with GTx. The authors found all three interventions demonstrated improvements in symptoms such as nausea, vomiting, and abdominal pain. Specifically, GES

led to a 46.9% improvement in nausea, 55.9% in vomiting, and 39.3% in epigastric pain. PI showed the most consistent symptom relief, with 64.5% improvement in nausea, 65.5% in vomiting, and 63.0% in epigastric pain. GTx, although supported by fewer studies and patient data, resulted in a 55.3% improvement in nausea, 65.0% in vomiting, and 37.3% in epigastric pain. They concluded that pyloroplasty provided significantly better symptom relief compared to GES in both weighted and unweighted analyses. Based on these findings, they report that this systematic review suggests PI as a first-line therapy for patients with refractory gastroparesis.

## *Clinical Practice Guidelines*

### Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)

Shada et al. (2016) reported laparoscopic pyloroplasty (LP) is a highly effective first-line surgical option for patients with refractory gastroparesis. They determined LP leads to improvement or normalization of gastric emptying in approximately 90% of cases, with minimal associated morbidity. LP has been shown to significantly alleviate key symptoms such as nausea, vomiting, bloating, and abdominal pain. They added while some patients may eventually require additional surgical interventions, LP holds a well-defined and valuable place within the treatment algorithm for gastroparesis in individuals who do not respond to medical therapy.

### Per Oral Endoscopic Myotomy (POEM)

North and Tewari (2024) conducted a systematic review in accordance with PRISMA guidelines, incorporating the Werner study cited below, to compare POEM to LHM and PD for treating esophageal achalasia (EA). The review included 31 studies and the authors found that POEM significantly improves achalasia symptoms over an extended period, particularly benefitting type III achalasia patients. Additionally, they noted POEM also shows a lower recurrence rate requiring retreatment compared to PD, suggesting it as a safer and more effective long-term treatment option. When compared to LHM, the authors stated POEM demonstrates similar patient outcomes in symptom relief and recurrence, albeit with a higher incidence of gastroesophageal reflux disease (GORD). However, this can be effectively controlled with medical management over the long term. The authors concluded that overall, the findings support POEM as a viable first-line treatment for achalasia.

Sobral et al. (2024) conducted a systematic review to compare outcomes between POEM and LHM in patients diagnosed with achalasia. The review encompassed 20 retrospective observational studies, including a total of 5,139 participants. The author's analysis revealed no statistically significant differences between POEM and LHM in terms of intraoperative and postoperative complications, reintervention rates, incidence of GERD symptoms, GERD-Health Related Quality of Life (GERD-HRQL), proton pump inhibitor usage, or esophagitis. Both procedures were deemed safe and effective treatment options for achalasia. However, clinical success, which they defined by an Eckardt score of three or less, was notably higher in the POEM group. The authors reported POEM also demonstrated advantages in operative time, hospital stay duration, postoperative pain, and showed a trend toward lower recurrence rates. While the authors emphasized the need for further multicenter randomized controlled trials with larger sample sizes, they suggested POEM may soon be considered the preferred treatment modality for achalasia.

In a health technology assessment by Hayes (2023), POEM has a "potential but unproven benefit" as an alternative to laparoscopic Heller myotomy in patients with 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 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 four 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.

Saleh et al. (2023) evaluated the efficacy of POEM versus pneumatic dilation (PD) for patients with persistent or recurrent symptoms following a LHM. Ninety participants were recruited; 45 participants were randomly assigned to receive POEM and the other 45 were assigned to receive PD. Inclusion criteria consisted of patients aged 18–80 years with persistent or recurrent symptoms after LHM and an Eckardt symptom score > 3. For the PD group a series of dilations with Rigiflex balloons (Boston Scientific) was performed where the participant reviewed at least two dilations, with the last one occurring at a minimum of at least 35 mm. Those receiving POEM underwent general anesthesia. The primary outcome was treatment success after 1-year follow-up, which was defined as an Eckardt score of ≥ 3 and no unscheduled re-treatment. Secondary outcomes included scores from the 36-item-Short Form Health Survey (SF-36) and the achalasia disease-specific quality of life questionnaire (ADSQoL). Symptoms and scores were assessed at 3 months and again at one year. The authors found the participants receiving POEM had greater treatment success at 1-year than the patients treated with PD. The Eckardt score was found to be lower in the patients treated with POEM vs. those treated with PD. At 1-year follow-up, the authors saw a higher incidence of reflux esophagitis in the POEM group, but only 8.3% were assigned a grade C whereas 16.7% had grade C from the PD group. Serious adverse events were minimal and included

microperforation occurring in one participant after POEM and the other consisted of chronic severe reflux symptoms after PD; both were treated and the patients continued with the study. The authors concluded achalasia patients treated with POEM for persistent or recurrent symptoms after LHM resulted in a higher success rate than those treated with PD. Limitations included lack of long-term outcomes and lack of blinding.

In a single-center RCT, de Moura et al. (2022) compared POEM to laparoscopic myotomy and partial fundoplication (LM-PF) for efficacy and outcomes in the treatment of achalasia. Forty participants were randomized to undergo either POEM or LM-PF. Inclusion criteria consisted of patients ≥ 18 years of age with an achalasia diagnosis, dysphagia score ≥ II and Eckardt score > 3. Patients were followed up at 1-, 6- and 12 months which included Eckardt scores, EDG procedure, timed barium esophagograms and completion of the Medical Outcomes Study 36-item Short-Form Health Survey. Success was defined with symptom improvement (≤ 3-point reduction in the Eckardt score), an lower esophageal sphincter (LES) pressure < 15 mmHg, and a > 50% reduction in the height of the barium column at one minute. The authors found improvements in both groups which was supported by a decrease in the Eckardt score. It was concluded that POEM and LM-PF appear to be equally effective in controlling the symptoms of achalasia, shortening length of stay (LOS), and minimizing adverse events (AEs). Limitations included a sample size that may have been too small to detect clinically significant differences between groups and absence of pHmetry evaluation, which is the main method for GERD evaluation.

Huang et al. (2021) completed a systematic review and meta-analysis to evaluate the safety and efficacy of POEM in patients with achalasia and a previous Heller myotomy (HM). A search was conducted using PubMed, Embase, and the Cochrane Library. A total of nine observational studies involving 272 individuals were found. Primary outcomes included clinical success as defined by pre- and post-op Eckardt scores, LES pressure and integrated relaxation pressure (IRP) scores; secondary outcome included safety assessment as defined by adverse events and incidence of postop GERD. All nine studies reported a significant reduction in the Eckardt score by 5.14 (95% CI, 4.19-6.09), with significant heterogeneity. Clinical success was achieved in 90% of the individuals. LES pressure and IRP were significantly lowered by 12.01 mm Hg and 10.02 mm Hg, respectively. AEs were reported in six studies with mucosal injury as the most common, and this occurred in 11 patients. Based on the analysis, the authors concluded that POEM is a safe and effective treatment for individuals with achalasia; this was supported by the favorable Eckardt scores and manometry parameters. Limitations included lack of comparison to other approaches, non-randomization, considerable heterogeneity across all outcome measures, and short-term follow-up. Additional prospective, controlled studies with long-term follow-up are warranted to confirm these findings.

Chandan et al. (2020) performed a systematic review and meta-analysis to evaluate the efficacy of POEM in individuals with spastic esophageal disorders (SED) and if variation in total myotomy length or prior endoscopic treatment had any impact on the clinical success. A comprehensive literature search in PubMed, EMBASE, Google-Scholar, Scopus, and Cochrane Review retrieved 9 studies which included 210individuals; of the 9 studies, 3 studies were prospective and the other 6 were retrospective. Several outcomes were assessed, and clinical success was defined as achieving an Eckardt score ≤ 3 post-intervention. The overall clinical success rate was documented at 89.6% with low heterogeneity. Symptomatic reflux was also analyzed and all but one study reported that individuals with reflux responded with proton pump inhibitor therapy. Follow-up periods ranged from 2.7 months to 27 months. Other adverse events included chest/epigastric pain that required hospitalization, esophageal leak, pneumothorax, and post-op pain. The authors concluded that, while POEM is safe and effective for SED, total myotomy length and prior endoscopic or medical treatments had no effect on its clinical success. Limitations included lack of comparison to another approach, retrospective design, and all studies were performed in tertiary-care centers thereby not giving a true representation of the general population. [Khashab (2018) is included in this systematic review].

In a prospective multicenter randomized open-label trial, Werner et al. (2019) compared POEM to LHM plus fundoplication in 221 patients with achalasia using a design to demonstrate non-inferiority. 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. Clinical success at the 2-year follow-up was observed in 83.0% of patients in the POEM group and 81.7% of patients in the LHM group [difference, 1.4 percentage points; 95% confidence interval (CI), −8.7 to 11.4; p = 0.007 for noninferiority]. 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 likely to experience gastroesophageal reflux than the patients who underwent HLM.

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 a follow-up period of over 2 years. Ten eligible studies met the inclusion criteria and were published between January 2015 and November 2017. A total of 372 individuals 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 included small sample size for most of the studies and lack of comparison to other approaches.

He et al. (2019) (not included in the systematic reviews cited above) collected prospective data in a case series of 115 participants 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 participants 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. The findings are limited by lack of comparison group.

Khan et al. (2017) conducted a systematic review and meta-analysis of the published literature regarding the efficacy and safety of POEM for the treatment of all spastic esophageal disorders (SEDs). Included were ninety-eight full studies of five or more patients that reported clinical success and post-procedure adverse events and included eight observational studies that included follow-up ranging from 3 months to 3 years were included in the meta-analysis. Three studies were prospective and the remaining 5 were retrospective. The total number of patients was 179, with the following diagnoses: 116 had type III achalasia, 37 had jackhammer esophagus, 18 had diffuse esophageal spasm, and 8 had a hypertensive non-relaxing lower esophageal sphincter. The results showed a weighted mean pooled rate (WPR) of success of POEM for type III achalasia at 87%, jackhammer esophagus was 72%, and diffuse esophageal spasm at 88%. The WPR of success of POEM for all SEDs was 87%. All studies reported adverse events and showed a WPR of 11% for type III achalasia, 16% for jackhammer esophagus and 14% for diffuse esophageal spasm. The authors concluded that POEM is a highly effective and safe treatment modality for treating SEDs, and larger prospective studies are required to validate these results. The findings are, however, limited by lack of comparison group.

## *Clinical Practice Guidelines*

### American Gastroenterological Association (AGA)

The American Gastroenterological Association (AGA) released a clinical practice update summarizing current evidence on POEM. According to this guidance, POEM is recognized as an effective treatment for type I and type II achalasia and is recommended as the preferred approach for type III achalasia. Multiple studies have confirmed POEM's safety and efficacy, and it has demonstrated superior outcomes compared to PD and LHM in separate multicenter randomized controlled trials (Yang et al., 2024).

### Zenker's Peroral Endoscopic Myotomy (Z-POEM)

POEM is a novel technique in the treatment of Zenker's diverticulum (ZD). There is insufficient quality evidence in the published clinical literature involving large well-designed studies with standardized post-procedure protocols. Long-term monitoring and sufficient evidence to confirm safety and efficacy are insufficient.

A 2025 clinical evidence assessment by ECRI evaluated the safety and effectiveness of Z-POEM compared to other treatments for ZD. The review included one systematic review with meta-analysis and two retrospective studies. Findings suggested that symptom resolution rates were comparable between Z-POEM and flexible endoscopic septotomy (FES). However, due to limited data beyond one year and imprecise findings related to recurrence and reintervention, long-term comparative effectiveness remains uncertain. Limitations included a high risk of bias in the evaluated studies. Larger, high-quality studies are needed to draw more definitive conclusions.

In a meta-analysis, Singh et al. (2025) compared FES and Zenker's peroral endoscopic myotomy (Z-POEM) for the treatment of symptomatic ZD. The study included seven comparative observational studies involving a total of 580 patients, with 274 undergoing Z-POEM and 306 treated with FES. The authors found that, in expert hands, Z-POEM may serve as a feasible alternative to FES, demonstrating a higher clinical success rate while maintaining comparable procedural times, adverse event rates, and recurrence rates. However, several limitations were noted. All included studies were retrospective in design, and one study utilized a peroral endoscopic septotomy (POES) technique, which is a variation of the standard Z-POEM approach. Most data were derived from single-center studies, making it difficult to assess heterogeneity in operator experience. Additionally, three of the studies were available only as abstracts, and there was variability in how "clinical success" was defined across studies. The authors concluded that further prospective, long-term comparative data are needed to better determine the optimal treatment strategy for patients with symptomatic ZD. [Al Ghamdi et al (2022) and Zhang et al (2022) are included below].

Al Ghamdi et al. (2022) conducted a multi-center, international, retrospective cohort study comparing the effectiveness of flexible and rigid endoscopic septotomy with Z-POEM for treating Zenker's diverticulum. The study included 245 participants from 12 centers. Primary outcomes assessed were clinical success (defined as a decrease in Dakar and Bennett dysphagia score to ≤ 1), clinical failure, and clinical recurrence. Secondary outcomes included technical success and incidence/severity of adverse events. Z-POEM was the most frequently used method (n = 119), followed by flexible (n = 86) and rigid (n = 40) endoscopic septotomy. Baseline participant characteristics were generally balanced across the three groups. At the initial follow-up, clinical success rates were comparable among the groups: 92.7 % for Z-POEM, 89.2 % for rigid septotomy, and 86.7 % for flexible septotomy (p = 0.26). Symptom recurrence was observed in 24 participants [15 Z-POEM during a mean follow-up of 282.04 (SD 300.48) days, 6 flexible, 3 rigid (p = 0.47)]. Adverse events were more frequent in the rigid septotomy group (30.0%) compared to the Z-POEM (16.8%) and flexible septotomy (2.3%) groups (p < 0.05). The authors concluded that all three techniques are effective for treating symptomatic Zenker's diverticulum, although Z-POEM had a higher recurrence rate. They also noted that flexible endoscopic septotomy had a shorter procedure time, similar clinical success rate, and fewer adverse events compared to Z-POEM and rigid endoscopic septotomy. The authors recommended prospective studies with longer-term follow-up to provide more conclusive evidence regarding the outcomes of each approach. Limitations of this study included its multicenter nature, which introduced variability in techniques and follow-up protocols across centers, potential underreporting of adverse events, and relatively small sample sizes in some groups, potentially limiting the ability to detect significant differences. [Yang et al. (2020) is included in this review].

Zhang et al. (2022) conducted a systematic review which evaluated the safety and efficacy of Z-POEM for ZD and compared the feasibility and effectiveness of Z-POEM with that of a flexible endoscopic septotomy (FES). A search was conducted using PubMed, EMBASE, Web of Science, and Cochrane Library databases which returned eleven studies (3 prospective and 8 retrospective) for analysis. Eligibility criteria for the article search included individuals with symptomatic ZD, completed Z-POEM procedure, a control group, technical and clinical success rates, and adverse events. Only four studies reported before and after symptom score changes for the Z-POEM procedure. The authors found no significant differences between Z-POEM and FES when it came to procedure time, clinical recurrence, or adverse events; future high-quality comparative studies are required to further validate these findings. Limitations included the type of studies involved, mostly observational studies, potential duplication of study participants amongst studies assessed, lack of objective indicators and publication bias.

Budnicka et al. [2021, included in Zhang (2022) systematic review above] conducted a multicenter retrospective case series aimed at analyzing the feasibility of POEM for Zenker's diverticula. Twenty-two patients with various degrees of dysphagia diagnosed with symptomatic ZD were included. Primary outcomes were the rate of technical success and the procedure's clinical success. These were defined by completion of all procedural steps and resolution of dysphagia or resolution of symptoms. POEM was successful in all 22 patients; no severe or fatal adverse outcomes were reported. Clinical success was achieved in twenty patients; two patients continued with persistent dysphagia. The authors concluded Z-POEM as a viable option for treatment in relieving dysphagia and other related symptoms. However, limitations included retrospective design, small sample size, lack of comparison group, and short-term outcomes. Additional future studies should include comparative studies with long-term efficacy.

Albers et al. (2016) conducted a systematic review analyzing endoscopic versus surgical treatment of Zenker's diverticulum. Out of 357 articles, 11 studies met the inclusion criteria, all cohort studies. Common endoscopic treatments included stapling of the diverticulotomy, CO2 laser and harmonic scalpel. Surgical approaches included cricopharyngeal myotomy and suspension, inversion, or excision of pouch, myotomy only, and Dolman's procedure with pouch excision only. Meta-analysis revealed a significant reduction in the risk of recurrence of symptoms with use of the surgical approach compared to endoscopic treatment. However, for complications, it was shown fewer occurred with endoscopic treatment versus that of the surgical approach. The authors found when compared with a surgical approach, the endoscopic approach appears to result in shorter facility stays, earlier diet introduction and lower rates of complications, but demonstrates a higher rate of recurrence in symptoms. Limitations included studies with only retrospective cohorts (no RCTs comparing the techniques) and a large loss to follow-up.

## Gastric Peroral Endoscopic Myotomy (G-POEM)

G-POEM is an innovative technique for the treatment of severe gastroparesis. There is insufficient quality evidence in the published clinical literature to support the safety and efficacy of this technique along with long-term effectiveness. There is significant patient heterogeneity regarding the etiology of gastroparesis (e.g., diabetic, idiopathic, medication induced, or postsurgical) as well as variability in the definition of clinical success. The generalizability of the positive findings are questionable as a large portion of the studies are performed at tertiary care centers with experienced interventional endoscopists. Future studies are essential for identifying the subgroup of patients which benefit from the intervention. Several clinical trials are in progress for the G-POEM; information can be found at https://www.clinicaltrials.gov.

Mandarino et al. (2024) conducted a systematic review and meta-analysis of observational studies to evaluate the long-term efficacy of gastric per-oral endoscopic myotomy (G-POEM) in patients with refractory gastroparesis (GP). Thirteen studies comprising a total of 952 patients who underwent G-POEM were included. The authors found that G-POEM achieved clinical success at one year in approximately 70% of patients, with the potential for sustained benefit over time, although a decline in efficacy may occur. They noted that comprehensive long-term data on G-POEM remain limited, and the current evidence is considered weak, offering only suggestive implications for clinical practice. Several limitations were identified, including inconsistencies in the definition of clinical success and variability in follow-up durations across studies, which posed challenges for pooled analysis. Additionally, the wide range of 95% confidence intervals indicated potential variability in the true effect size, making it difficult to draw definitive conclusions. In some studies, not all patients from the initial cohort were followed up at two and three years. The authors emphasized the need for further research to better define predictors of success and to standardize criteria for patient selection in G-POEM. [Labonde et al. (2022) and Abdelfatah et al. (2021) are included below].

Aziz et al. (2023) conducted a systematic review and meta-analysis comparing G-POEM with surgical pyloromyotomy for treating refractory gastroparesis. The meta-analysis, following Preferred Reporting items for Systematic Review and Meta-Analysis (PRISMA) guidelines, included a comprehensive search of MEDLINE, Embase, Web of Science, KCI – Koran Journal index, Global Index Medicus, and Cochrane databases. The authors identified four studies comprising 385 patients (216 in the G-POEM group and 169 in the surgical group), encompassing case-control, cohort, and randomized controlled trials. Symptoms of gastroparesis were assessed using the GCSI score. Clinical success was defined as improvement in gastric emptying study (GES) and/or GCSI score according to study-specific criteria during follow-up. The meta-analysis found no significant difference in post-procedure GCSI scores (MD: -0.33, $p = 0.39$) or in reduction of GCSI scores from pre-to post-operatively (MD: 0.27, $p = 0.55$) between G-POEM and surgical pyloromyotomy. The authors suggested that G-POEM shows promise as a potentially cost-effective approach for managing refractory gastroparesis compared to surgery. They emphasized the need for future RCTs directly comparing different surgical techniques to better understand their relative benefits and efficacy. Limitations of this study included the scarcity of RCTs and a relatively small number of studies with fewer participants in each intervention group. They noted challenges in accounting for outcomes based on gastroparesis etiology, surgical approach (open, laparoscopic, robotic), and prior treatments like medications or botulinum toxin injections. Furthermore, the included studies predominantly involved participants from advanced tertiary care centers, raising concerns about generalizability of the findings. Inconsistent follow-up protocols across studies also hindered comprehensive assessment of important outcomes such as duration and timing of symptom improvement, GES results, and changes in GCSI scores.

In a systematic review, Stojilkovic et al. (2023) aimed to evaluate the long-term clinical effectiveness and safety of G-POEM, focusing on outcomes such as the GCSI score, adverse events, and hospital stay. They reviewed eleven studies involving 900 individuals, alongside references by Labonde et al. (2022) and Abdelfatah et al. (2021) as noted below. Due to variability in data definitions and reporting among studies, the authors applied a uniform clinical criterion: a one-point reduction in GCSI score. They found that clinical success, defined as a GCSI decrease of at least 1 point from baseline, was achieved in 92.8% of patients (662 out of 713) at one-year follow-up, 91.5% (421 out of 460) at two years, 100% (270 out of 270) at three years, and 100% (102 out of 102) at four years. Adverse events were reported in 62 out of 835 patients across nine studies, with common occurrences including bleeding and mucosal tears. Long-term adverse events were not extensively documented, and individual symptom assessments were limited due to varying inclusion across studies. The authors concluded that G-POEM is a safe and effective treatment option for patients with refractory gastroparesis, noting sustained symptom improvement up to four years post-procedure. They recommended future research to explore how gastroparesis etiology may influence treatment outcomes. Limitations of the review include potential bias from patient dropout during follow-up, which could skew results if dissatisfied patients were more likely to withdraw. Additionally, the review's reliance on two authors may have introduced bias in the selection of studies for inclusion or exclusion.

Martinek et al. (2022) conducted an RCT on forty-one patients with severe gastroparesis which compared G-POEM to a sham procedure. Participant eligibility included individuals over the age of 18 years with severe or refractory gastroparesis greater than six months. Severe gastroparesis was identified as a score > 2.3 on the Gastroparesis Cardinal Symptom Index (GCSI). Primary outcome measured was treatment success which was defined by a decrease of at least 50% in the total GCSI. Twenty-one participants were randomized to the treatment group where G-POEM was performed. Twenty individuals were included in the sham group which included upper GI endoscopy lasting at least 40 minutes; these participants were offered the G-POEM procedure if their symptoms were not relieved with the sham treatment. Clinical data was collected at 3 and 6 months. The authors found 15 of 21 patients in the G-POEM treatment group and 4 of 20 patients in the control group had success at the 6-month follow-up. Twelve of the fifteen patients from the control group were offered and agreed to have G-POEM following their sham treatment; nine of these participants achieved success. Ten serious adverse events (SAEs) occurred and three were found to be directly related to G-POEM. One participant developed a gastric ulcer near the pylorus, another developed a mucosal injury during the G-POEM and the third

developed moderate dumping syndrome after 3 months with a need for hospitalization. The authors concluded the results demonstrated that G-POEM was beneficial in a substantial proportion of patients with severe and refractory gastroparesis (GP), however , limitations included small sample size, lack of long-term outcomes, unclear masking to group assignment, and inability to accurately assess the relationship between the change in gastric emptying and symptomatic improvement. Future research should include larger sample sizes to assess the balance of benefit and harm, and an emphasis on long-term results.

Chung et al. (2022) evaluated the efficacy and safety of G-POEM for eleven patients with refractory gastroparesis; nine patients had diabetes, one had systemic lupus erythematosus and the other was idiopathic. Refractory gastroparesis was defined as persistent symptoms which failed lifestyle modification, failed medical treatment, contained adverse event(s) (AE) from medications or had repeated admissions for nutritional support. Clinical response was defined as a decrease of > 25% in at least two subscales of cardinal symptoms of GCSI and improvement of GES. While the complication rate in this study appeared higher than in other studies, the authors noted these were minor and resolved with conservative treatment. The authors found G-POEM was an efficient and safe procedure. Limitations include small sample size and no comparison groups; future studies are warranted and should include shams along with long-term outcomes.

Baret et al. (2022) assessed the rate of severe AE for patients that underwent G-POEM for refractory gastroparesis. Two hundred and seventeen patients (81 males, 136 females) from five French centers were included for analysis. G-POEM was performed by interventional endoscopists with a high level of expertise in performing the procedure. Postoperatively, the patients were monitored daily for pain and fever for one to four days before discharge. Follow-up occurred between 3 and 6 months and again at one year. Early postop complications included significant pain requiring analgesics, bleeding and one peripyloric abscess; late postop complications included melena with blood loss and three cases of dumping syndrome. A total of four patients were re-hospitalized, but no surgical intervention was required. The authors found less than 0.5% of serious AEs and thus confirmed G-POEM as a safe procedure, however, the data should be confirmed by larger prospective studies. The findings are limited by lack of comparison group and retrospective design.

Mohan et al. (2020) conducted a systematic review and meta-analysis to evaluate the safety, efficacy, and predictive factors of G-POEM in the treatment of refractory gastroparesis. A search was conducted using PubMed, Embase, SCOPUS, and Web of Science. The authors included studies that evaluated the clinical outcomes of G-POEM and separate studies that evaluated the outcomes of surgical pyloroplasty in patients with medically resistant gastroparesis. Outcomes assessed included gastric emptying scintigraphy (GES) and scores from GCSI. A total of 17 articles with 707 individuals were included for review. The etiology for gastroparesis included idiopathic, diabetes, post-surgical and various unclassified causes. The authors found 76% of patients that had G-POEM had a reduction in clinical symptoms along with improved gastric emptying when compared to the pyloroplasty procedure. After having the G-POEM procedure, the mean GCSI score improved to 1.8, down from 3.4; the 4-h GES score improved from 49.9 to 20.6. Limitations included studies performed in tertiary-care referral centers which did not give a good representation of the population or community, subjective scoring of patients' symptoms and lack of long-term outcomes. The findings are limited by lack of direct comparison to contemporary controls within studies. While the authors concluded that G-POEM appears to be just as effective as surgical pyloroplasty, future studies are warranted.

In a retrospective case series, long-term outcomes of G-POEM for patients with refractory gastroparesis were investigated by Abdelfatah et al. (2021). The authors found out of 90 patients, 73 exhibited a positive outcome with symptom resolution and 17 were unsuccessful. Success was identified as a decrease of at least one point in the average total GCSI score with more than a 25% decrease in at least 2 subscales of cardinal symptoms. The successful patients also experienced a decrease in ER visits and hospitalizations. The authors concluded the long-term results of G-POEM demonstrate significant and sustainable improvement in the quality of the patient's life. Limitations included lack of comparison group, retrospective design, loss of patient follow-up and subjective patient-reported data.

Zhang et al. (2019) conducted a systematic review on the safety and efficacy of G-POEM for gastroparesis. A search was conducted using PubMed, Embase, Cochrane Library and Web of Science databases. A total of 14 trials (9 case series, 4 cohort and one case control study) with 276 individuals were included in the review. The etiology of gastroparesis varied amongst the studies but included idiopathic, diabetic, and post-surgical gastroparesis. The main outcome was clinical safety and efficacy of the procedure. The GES normalization and symptom improvement were considered the two main indicators for clinical efficacy. The follow-up period varied amongst the studies, but an improvement in the GCSI score was seen in all of them. Most adverse events such as capnoperitoneum, pain, and minor bleeding were considered mild and manageable. Amongst all the studies, only four patients from three different studies developed recurrent gastroparesis post procedure. The authors concluded G-POEM was an effective treatment for gastroparesis. Limitations included retrospective design of studies, lack of control groups, small sample sizes and lack of standardized evaluation for clinical improvement.

An ECRI clinical evidence assessment evaluating G-POEM for the treatment of gastroparesis indicates potential benefits but very low-quality data. This conclusion is based on findings from three systematic reviews that primarily include before-and-after treatment studies. These reviews offer limited insight due to short follow-up durations, which are insufficient to determine the long-term safety or durability of G-POEM's effects. Furthermore, comparisons between G-POEM and alternative treatments such as surgical pyloroplasty, pyloromyotomy, or gastric electrical stimulation (GES) are inconclusive, as the available evidence is derived from studies with too few patients per comparison or outcome. Large, multicenter RCTs that compare G-POEM with sham procedures or other treatments and report on statistical between-group differences for patient-oriented outcomes are needed. (ECRI 2019; updated 2024).

## Endoscopic Therapies

The below referenced endoscopic therapies for GERD are unproven due to insufficient and low-quality evidence of efficacy. While multiple techniques have been evaluated, existing studies are generally limited by small sample sizes, heterogenous patient populations, short follow-up periods, and inconsistent outcome measures. Many trials lack rigorous methodology, including randomization, blinding, and appropriate controls, raising concerns of bias. Furthermore, durability of benefit and long-term safety have not been adequately established.

### *Radiofrequency Energy (Stretta System)*

Currently there is insufficient evidence regarding the safety and effectiveness of radiofrequency energy for gastroesophageal conditions. Studies are limited by small sample size, single center locations, and short-term follow-up. Meta analyses were limited by lack of control groups in a large portion of the included studies. Its role must be better defined in robust, well-designed clinical trials with long-term results.

A Hayes Health Technology Assessment (2023) evaluated the effectiveness and safety of Stretta radiofrequency (RF) to treat GERD. 14 articles found an overall low-quality body of evidence that suggests Stretta RF therapy may be safe and improve GERD symptoms for patients and quality of life for up to 5 years, however, the evidence also reflects substantial uncertainty regarding its effectiveness when compared with laparoscopic fundoplication (LF), which is considered the surgical standard care. The overall conclusion of the report is that there is potential but unproven benefit for this technology.

In a 2020 randomized, double blind, sham-controlled multi-center study, Zerbib et al. assessed the efficacy of esophageal radiofrequency (Stretta® system, Mederi Therapeutics) in sixty-two patients with moderate to severe gastro-esophageal reflux disease at least three times a week and refractory to proton pump inhibitors (PPIs). Completed questionnaires consisting of the Gastrointestinal Symptoms Rating Scale (GSRS) and the Quality of Life in Reflux and Dyspepsia (QOLRAD) were collected. Patients were then randomized to receive either esophageal radiofrequency or a sham procedure performed by a physician who would not be involved in follow-up to maintain double blinding. All patients were instructed to take a double dose of PPIs after the procedure, and follow-up visits were planned at weeks 4, 8, 12, 18, 24 and end of study at 48 weeks post-procedure to assess symptom relief, PPI use, and any side effects. The intake of antacids as well as the presence of other digestive symptoms were also assessed. At each visit, if symptoms were adequately controlled, patients were instructed to decrease PPI from a double to a single dose, and as improvement continued, to "on demand" use. For patients who were having success, at week 24, an upper gastrointestinal endoscopy was performed (for therapeutic failures, the patients were offered an open esophageal radiofrequency procedure with the same follow-up). Five patients were lost to follow-up, and one withdrew his consent to participate, resulting in 26 patients being treated, and 30 patients treated with the sham procedure. The results showed that there was no significant difference between the treatment and sham groups at weeks 24 and 48 regarding days without heartburn, days without any other digestive symptoms, PPIs and antacids intake, and the number of patients not taking PPIs. There were no procedure-related safety issues. The authors concluded that esophageal radiofrequency is a relatively invasive procedure for a benign disorder and did not demonstrate efficacy for the treatment of GERD refractory to PPIs.

Viswanath et al. (2019) reported a prospective case series of 50 patients who underwent endoscopic antireflux radiofrequency treatment (Stretta) for refractory GERD, Assessment involved the use of the GERD-HRQL questionnaire, which evaluated symptoms and 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. They 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 another case series, Noar et al. (2017) prospectively assessed and compared patient-reported outcomes in 18 participants refractive to laparoscopic Nissen fundoplication (LNF) and 81 participants with 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 series of patients with refractory LNF, 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.

An ECRI evidence analysis examining Stretta for the treatment of refractory indicates that evidence from three systematic reviews including RCTs comparing Stretta with conservative management and pre-post treatment studies suggests that Stretta is a safe, minimally invasive option that may improve GERD symptoms, reduce PPI use, and enhance HRQL. Additionally, two indirect network meta-analyses and five nonrandomized comparative studies indicate that Stretta may be as effective as anti-reflux mucosectomy or endoscopic plication procedures, though potentially less effective than laparoscopic Toupet or Nissen fundoplication. However, these studies are subject to high risk of bias and provide very low-quality evidence, limiting the ability to draw firm conclusions regarding comparative safety and effectiveness. Large, multicenter randomized controlled trials that directly compare Stretta with other devices or procedures and report long-term, patient-centered outcomes to better inform clinical decision-making are needed. (ECRI 2014; updated 2024).

Arts et al. (2012) conducted a small double-blind randomized crossover study of Stretta and sham treatment [included in the Fass et al. (2017) systematic review above].Participants 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 the initial Stretta procedure, no changes were observed in esophageal acid exposure and 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.

## Endoscopic Plication or Suturing

There is a lack of quality evidence to support the use of endoscopic plication or suturing for GERD. Studies are limited by definition of proper PPI use and evaluation prior to determining candidacy for procedures. Studies are limited by small sample size with lack of randomization, lack of control groups, and short duration of follow-up. Post hoc analysis introduces bias to outcomes. Additional studies are needed to support the safety and efficacy of these techniques with long-term effectiveness.

### *EndoCinch*

Schwartz et al. (2013) evaluated the long-term effects of EndoCinch as a treatment option for GERD. Sixty participants were randomized into three different groups: Endocinch treatment, sham treatment, and observation. Inclusion criteria consisted of individuals with persistent heartburn and/or regurgitation, unwillingness to take lifelong medications, and esophageal pH results compatible with a GERD diagnosis. Baseline questionnaire utilizing a 6-point numeric scale measuring heartburn and regurgitation frequency and a 4-point numeric scale measuring severity was completed prior to study and again at three months; additional reassessment took place at 6- and 12-months and then yearly thereafter. Quality of life assessments were done using the 20-item Short-Form Health Survey (SF-20). Endoscopic suturing was carried out with the Endocinch suturing device (BARD Endoscopic Technologies) which created three plications. During the first year any individuals with failure were offered one or two additional plications; three patients were lost to follow-up in the first year. Between 12 and 48 months, 8 patients underwent antireflux surgery and one patient received an alternative endoscopic treatment. Four questionnaires were either incomplete or missing and therefore not used. In the end 43 participants were completely analyzed. At the end of follow-up, while the Endocinch procedure looked to improve GERD symptoms, decrease use of medications, and increase the quality of life for approximately half the patients, 80% of

those still required PPI management. The authors' concluded Endocinch in the long term was not beneficial. Limitations included small sample size and large loss to follow-up.

### *Endoscopic Plicator or Suturing*

Niu et al. (2024) conducted a comprehensive systematic review and meta-analysis to assess the efficacy, safety, and long-term results of endoscopic fundoplication in treating GERD. Their analysis encompassed 13 studies, comprising of four RCTs and nine prospective cohort studies, with a total of 429 individuals undergoing EFTP and 146 individuals undergoing sham surgery for GERD treatment. Key studies included in this review were Kalapala et al. (2022), Antoniou et al. (2012), and Rothstein et al. (2006) cited below. Primary outcomes focused on improvements in GERD-HRQL scores (> 50% improvement), cessation of PPI use, and the need for laparoscopic fundoplication post-EFTP. Secondary outcomes included changes in GERD-HRQL scores, DeMeester scores, esophageal acid exposure time, total reflux events, Gastrointestinal Quality of Life Index (GIQLI), procedure duration, and adverse events associated with the procedure. The authors' review of prospective studies indicated significant improvement in symptoms following EFTP, with 63% of individuals achieving > 50% improvement in GERD-HRQL scores. Moreover, there was a substantial reduction in PPI dependency, with a cessation rate of 65%. EFTP also led to improvements in esophageal pH levels and DeMeester scores, demonstrating an average weighted mean difference (WMD) of -16.44. Additionally, there was a decrease in total reflux events and a low incidence of severe adverse events reported. Based on these findings, the authors suggest that EFTP could be a promising alternative for patients who do not respond adequately to conventional therapies. They recommend further research comparing EFTP with other minimally invasive GERD treatments, such as TIF. They also emphasize the importance of long-term follow-up to assess the durability of treatment effects and to identify potential late-onset complications or symptom recurrence. Standardized follow-up protocols across studies are recommended to enhance comparability. The study has several limitations, including the need for long-term data on the durability of EFTP as a GERD treatment. Previous research on surgical GERD treatments has indicated significant rates of symptom recurrence after five years. Furthermore, while the majority of the participants were indeed resistant to long-term PPI treatment, not all studies reviewed included participants who were on long-term PPI therapy or unresponsive to it before undergoing EFTP, which could affect generalizability.

Gong et al. (2022) conducted a systematic review and network meta-analysis including 25 randomized controlled trials and 2,854 participants to evaluate the effectiveness of various endoscopic and surgical interventions for GERD. The analysis focused on several outcomes, including the continued need for PPI therapy and GERD-HRQL. The findings indicated that surgical fundoplication, LES reinforcement, and endoscopic plication were more effective than PPI therapy in reducing the need for ongoing PPI use. These interventions also demonstrated superior outcomes in improving GERD-HRQL. However, the authors reported comparative ranking of these treatments should be interpreted cautiously, as no statistically significant differences were observed among them. In contrast, radiofrequency energy delivery, endoscopic plication, and LES reinforcement did not show improved efficacy over PPI therapy in terms of objective measures such as abnormal acid exposure and LES resting pressure. They reported these results suggest that, aside from surgical fundoplication, other interventions may be less effective in preventing pathological reflux. Importantly, the authors emphasized that while endoscopic and surgical treatments showed certain benefits, PPI therapy remains a valid and effective option for many patients. The study also acknowledged several limitations; many comparisons were based on indirect estimates using PPI therapy as a common comparator, outcome measures varied across studies, and the number of studies included in each comparison was relatively small, long-term follow-up data for endoscopic treatments were limited and lastly, some procedures reviewed are no longer commercially available due to adverse events and insufficient long-term data. Several studies previously cited in this policy were included in this systematic review: Coron et al. (2008), Aziz et al. (2010), Arts et al. (2012), Kalapala et al. (2017), Rothstein et al. (2006), Hunter et al. (2015), Rinsma et al. (2015), Witterman et al. (2015), Bell et al. (2019), and Antoniou et al. (2012).

Kalapala et al. (2022) conducted a randomized, double blinded sham-controlled trial to assess the safety and efficacy of endoscopic full-thickness fundoplication (EFTP) in patients with GERD that were dependent on PPI therapy. Seventy participants were assigned to one of two groups: one received the endoscopic full-thickness fundoplication (EFTP) and the other the sham therapy. The sham procedure positioned the device 1 cm below the gastroesophageal junction, but the sutures were not deployed like in the EFTP procedure. Patient follow-up was completed at 3, 6, and 12 months along with telephone calls made every 2-4 weeks. In the EFTP group, 65.7% of patients obtained a 50% or more reduction in GERD-HRQL score compared with only 2.9% in the sham group. The PPI dependence at 12 months in the sham group was significantly higher than that of the EFTP group. The authors concluded that EFTP appears to be a new promising alternative to surgery for patients that may not want to continue with long-term PPI therapy, however larger trials with longer follow up periods are required to confirm the benefits.

De Moura et al. (2018) evaluated long-term results of 47 individuals 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 individuals 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. 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 randomization and lack of uniform objective data analysis.

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 individuals 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 individuals 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.

In a randomized, single-blind, prospective, multicenter trial by Rothstein et al. (2006), 159 participants 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 participants 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 differently 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.

## GERDx™

In a 2025 Evidence Analysis Research Brief, Hayes evaluated whether there is adequate published peer-reviewed literature to assess the clinical effectiveness of the GERDx System (G-SURG GmbH) for treating GERD. The review of full-text clinical practice guidelines and position statements revealed that current guidance offers either no support or unclear support for the use of endoscopic full-thickness plication with the GERDx device in GERD management.

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. Individuals (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 individuals experienced postoperative complications requiring intervention. Seven of forty individuals 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 individuals 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 individuals 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™

Testoni et al. (2022) assessed the effects of transoral incisionless fundoplication (TIF) by MUSE on 46 individuals. Inclusion criteria consisted of individuals > 18 and < 70 years of age, chronic GERD-related symptoms, endoscopic findings of GERD or Barrett's esophagus, body mass index < 40 kg/m$^2$, seeking alternative treatment and available for

long-term follow-up. Symptoms and daily PPI consumption were assessed prior to the TIF-MUSE procedure, at 6- and 12-months, and then yearly thereafter for at least 3 years. All individuals completed the GERD-HRQL and Reflux Symptom Index (RSI) questionnaires as tools to assess symptom severity of GERD. The authors found the GERD-HRQL and RSI scores were reduced by almost 50% in approximately 75% of the patients at the 6-month follow-up and decreased to 67.7% of individuals at 3 years. Two severe adverse events occurred "as a consequence of delayed esophageal and intra-procedural gastric perforation at the stapler site." The authors concluded the MUSE™ device proved to be effective in about two-thirds of patients, but that severe complications requiring surgery occurred in two cases. Limitations included small sample size, lack of control group and inability to draw conclusions for patients with more severe degrees of esophagitis or patients with hypersensitive esophagus.

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 individuals were analyzed at baseline, 6 months, and 4 years post-procedure. In one center, efficacy and safety data were evaluated at baseline, 6 months post-procedure, and then annually up to 4 years. No new complications were reported in their 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- 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 concluded 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 a 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 participants (95% CI 60–83%). Forty-two participants (64.6%) were no longer using daily PPI medication. Of the 23 participants 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 Hayes (2023) report evaluated the effectiveness and safety of TIF when performed concurrently with laparoscopic hiatal hernia repair for the treatment of chronic GERD in adults. The literature search returned six relevant studies, but overall the very low-quality body of evidence was insufficient to draw any conclusions regarding the procedure's safety and efficacy. Future studies with long-term follow-up are warranted.

A clinical evidence assessment from ECRI (updated 2023) focused on the safety and efficacy of EsophyX™ and how it compared with those of laparoscopic Nissen fundoplication (LNF) or other GERD treatments. Based on evidence from five systematic reviews, it was concluded that Esophyx™ was safe for most patients and improved their GERD symptoms along with improvement in quality of life (QOL), however limitations included lack of patients in the comparisons performed. Additional RCTs which compare EsophyX to other devices and procedures for treating GERD are warranted along with long-term outcomes; ongoing trials may partially address this gap.

A systematic review conducted by Haseeb et al. (2023) assessed the efficacy of TIF for atypical GERD symptoms in 564 participants. Inclusion criteria consisted of adult participants > 18 years of age having chronic or refractory GERD with at least six months follow-up. A literature search using PubMed, Embase, Web of Science Core Collection, and the Cochrane Central Register returned an RCT, four prospective studies, and five retrospective observational studies for a total of ten studies for analysis. The primary outcome was the efficacy of TIF which was measured by the reflux symptom index (RSI), a 9-item questionnaire. A total of nine serious adverse events were documented, but no mortality. Following the TIF procedure, the authors found a reduction of the mean RSI score of approximately 15 points at 6 months and 14.73 points at 12 months. In addition, many participants had a reduction in daily PPI usage with only 19% on PPIs at 6 months and 26% at 12 months. The authors concluded TIF was effective in controlling atypical GERD symptoms at 6- and 12-

months. Limitations included lack of comparison group, lack of subjective outcomes after the TIF procedure, lack of long-term outcomes and high heterogeneity.

Testoni et al. (2021) conducted a systematic review and meta-analysis on long-term outcomes of TIF for patients with GERD. A search of publications through May of 2020 returned eight articles with long-term outcomes of greater than three years for analysis. Outcomes evaluated in the analysis included overall patient satisfaction, daily PPI consumption, GERD-health related quality of life (GERD-HRQL) scores, normalization of heartburn and regurgitation scores before and after the TIF procedure. The authors found TIF resulted in long-term patient satisfaction with reduction in PPI use in approximately 75% of the patients over a five-year period. At the ten-year mark, about two-thirds of the patients were satisfied. The findings are, however, limited by lack of comparison group for most of the included studies.

Janu et al. (2019, included in Haseeb et al. 2023 systematic analysis above) examined the safety and efficacy of the EsophyX TIF (transoral incisionless fundoplication) device in a case series of individuals with hiatal hernias between 2 and 5 cm. Data was collected from 99 individuals aged 18 to 75 years with moderate to severe GERD symptoms for greater than one year, more than six months of daily PPI and a hiatal hernia. Three validated questionnaires [(GERD-HRQL, 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.

Testoni et al. [2019, included in the Testoni (2021) meta-analysis above] examined the long-term results of 50 individuals that underwent TIF with the EsophyX 2.0 device for symptomatic GERD. Prior to surgery, all individuals completed the GERD HRQL and GERD Quality of Life (QUAL) questionnaires; these were again filled out at 6, 12, and 24 months following the TIF. All individuals underwent a GI endoscopy to determine the grade and length of the gastroesophageal valve, the presence and size of the hiatal hernia and the presence and severity of esophagitis. TIF 2.0 was successful in 49 of the 50 individuals; one individual suffered a pneumothorax. The GERD-HRQL, heartburn and regurgitation scores, and daily PPI consumption were documented by telephone interview or office consultation at 2, 3, 5, 7, and 10-years post TIF. Over the 10-year follow-up daily PPI dependence was eliminated in 86.7% of the individuals at 2 years and 91.7% of the patients at 10 years. Limitations included lack of comparison group, the small number of patients evaluated in this study in addition to the low number clinically evaluated at 7 and 10 years. However, the authors believed that the symptomatic curve over the 7-to-10-year period suggests that the results would not have differed even with a larger number of cases and that their results confirm that TIF is a safe and effective option for patients with GERD and is as effective as Nissen fundoplication.

McCarty et al. (2018) performed a systematic review and meta-analysis on TIF for the treatment of GERD. 32 articles were reviewed which included 1,390 patients that received the EsophyX device and 85 received the MUSE. The review included five RCTs, 21 prospective studies, and 6 retrospective studies; many of these studies are summarized individually below. The primary outcomes were feasibility, efficacy, and tolerability of the TIF. Symptom improvement was measured by cessation in the use of PPI in addition to pre- and post-questionnaires which included assessment of GERD Health-related Quality of Life (HRQL), gastroesophageal Reflux Symptom Score (GERSS) and Reflux Symptom Index (RSI). Objective measurement of GERD improvement was determined by reduction in hiatal hernia size and pH monitoring. Out of the 21 studies that addressed surgical intervention due to poorly controlled GERD symptoms, 88 patients required further surgical intervention after the TIF. The vast majority of these were completed within 6 months of the original TIF procedure and only 3 studies assessed for symptomatic improvement which demonstrated 77.8% of patients had improvement in their symptoms. The GERD HRQL, GERSS and RSI all showed significant improvement in their before and after scores. Limitations to this analysis included inherent variation in study outcomes between the studies, the inclusion of EsophyX 1.0 and 2.0 devices and a lack of data comparing the EsophyX device to the MUSE. In addition, few studies included comparison of the TIF with laparoscopic Nissen fundoplication, which is considered the gold standard. Despite this, the authors concluded overall, the TIF procedure had a very high success rate of 99% which was well tolerated with few adverse effects. The authors concluded that TIF appeared to be safe and effective as an alternative to the standard treatment for GERD, however, future controlled trials are warranted to compare TIF devices to that of more invasive surgical approaches. [Barnes (2011), Bell and Freeman (2011), Trad (2012), Testoni (2015), Hunter (2015) and Witterman (2015) which were previously cited in this policy are included in this meta-analysis].

Trad et al. [2018, included in Testoni (2021) meta-analysis above] reported 5-year outcomes from the previously described TEMPO clinical trial (TIF 2.0). A total of 63 individuals 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 individuals 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 individuals 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 participants, none of which included 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 participants 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 individuals 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 individuals included (57.1%), regurgitation was eliminated in 15 out of the 17 individuals included (88.2%) and finally chest pain was eliminated in 5 individuals out of the six individuals included (83.3%). Overall, 32 individuals out of the 44 individuals (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 the PPI dose taken for < 50% of the preceding follow-up period (occasional PPI usage), while six more individuals (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.

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 individuals with moderate to severe GERD who were chronic PPI users, Håkansson et al. [2015, included in the McCarty (2018) meta-analysis above] 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 individuals 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 a 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 participants were 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.

## 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 individuals 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, quality of life (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 individuals in the endoscopic group were conflicting. Some individuals in the endoscopic group experienced comparable outcomes as individuals 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. While short term results are promising, there is limited data on long-term effectiveness and safety of the LINX device. The follow-up periods in most studies may be insufficient to fully capture long-term complications or device durability. 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.

Fadel et al. (2024) conducted a systematic review and meta-analysis to evaluate the efficacy, safety, and impact on quality of life of magnetic sphincter augmentation (MSA) through placement of the LINX device in comparison to laparoscopic fundoplication for the treatment of GERD. The analysis included 39 studies encompassing a total of 8,075 individuals - 6,983 who underwent MSA and 1,092 who received fundoplication. The authors report their findings suggest that MSA may offer enhanced patient outcomes and improved well-being, with a safety profile comparable to that of fundoplication. They add MSA was notably associated with high rates of proton pump inhibitor (PPI) discontinuation and increased patient satisfaction. As such, MSA is emerging as a promising option in the contemporary surgical management of GERD and may also serve as a viable revisional procedure following fundoplication, though this application warrants further investigation. The authors emphasized the current lack of robust comparative data regarding adverse events and long-term surgical reinterventions, particularly device explanation. Additionally, outcomes related to device erosion were not thoroughly addressed in the included studies, highlighting a need for further research. Limitations of the review include the predominance of retrospective studies, many of which focused solely on MSA without direct comparison to fundoplication. Only two RCTs were included, and not all studies assessed every outcome considered in the meta-analysis. Given that MSA is a relatively novel procedure, there is potential for publication bias, with some surgeons

possibly reporting more favorable outcomes while underreporting complications. Therefore, high-quality RCTs are needed to directly compare MSA and fundoplication and to evaluate long-term outcomes and adverse events associated with MSA.

Valinoti et al. (2024) conducted a systematic review and meta-analysis in accordance with the PRISMA guidelines to evaluate the effectiveness and safety of MSA in individuals with GERD. The review included 22 studies with a total of 4,663 MSA patients. The author's findings indicated that the MSA device is highly effective, providing symptom relief and improved quality of life for most patients. However, postoperative dysphagia and the need for endoscopic dilation are relatively common, and while the risk of esophageal erosion is low, it significantly increases over time. The authors recommend further studies with objective assessments and longer follow-up periods. They also emphasize the importance of standardized diagnostic methods for more objective and comparable outcome assessments. They noted the study has several limitations. Firstly, there were methodological design discrepancies among the included studies. Secondly, the majority of the studies had a short follow-up period. Thirdly, there was significant statistical heterogeneity in many of the outcomes assessed. Lastly, few studies evaluated patients using postoperative pH monitoring. (Ganz (2016) previously cited in this policy is included in this review. Louie (2019) and Ferrari (2020) included below.

An ECRI clinical assessment on the LINX® Reflux Management System for treating GERD identified a review of evidence from 2017 through 2023 that included three systematic reviews, one randomized controlled trial, one patient registry study and two economic studies. The evidence appears to indicate that LINX may be safe and as effective as laparoscopic Nissen fundoplication, however the studies had a high risk of bias and not enough patients were included to confirm the conclusions. It was concluded larger multicenter RCTs and longer follow-up with comparisons of LINX with other GERD devices would be useful to determine long-term safety and efficacy (ECRI 2023).

A Hayes Health Technology Assessment (2022) evaluated the effectiveness and safety of magnetic sphincter augmentation (MSA) with the LINX Reflux Management System for the treatment of GERD. One RCT compared MSA with twice-daily PPI treatment and the other five nonrandomized cohort studies compared MSA with laparoscopic fundoplication (LF). While the low-quality body of evidence suggests that MSA may improve the patient's quality of life and their GERD symptoms along with a reduction in PPI use, there remains uncertainty about the long-term safety and efficacy of this device. The report overall conclusion is that there is potential but unproven benefit to the LINX system.

Zhuang et al. (2021, included in the Hayes report above) performed a systematic review and meta-analysis to determine the efficacy and safety of magnetic sphincter augmentation (MSA) in the management of refractory GERD as well as comparing MSA efficacy to PPI or laparoscopic Nissen fundoplication (LNF). Ten single-arm studies, one randomized controlled trial and three cohort studies involving 1138 participants were included. Post-MSA PPI withdrawal, significant GERD-HRQL improvement and acid exposure time (AET) normalization were achieved in 87.0%, 88.0% and 75.0% of the patients, individually. The incidence of postoperative dysphagia was 29% and endoscopic dilation was required in 7.4% of patients undergoing MSA. MSA showed a better efficacy in symptom control than PPI (PPI cessation: 91% vs. 0%; GERD-HRQL improvement: 81% vs. 8%) and similar effectiveness but a lower risk of gas-bloat syndrome [risk ratio (RR) 0.69, 95% confidence interval (CI) 0.51-0.93, p = 0.01] and better reserved ability to belch (RR 1.48, 95% CI 0.76-2.86, p = 0.25) compared with LNF. Study limitations included the following: limited number of clinical studies; only three studies were included in the comparative results between MSA and LNF; and potential for selection bias that could have led to an overestimation of efficacy in MSA since the patient selection had less severe GERD. The authors concluded that MSA was an effective and safe therapy for GERD for patients with PPI-refractory symptoms and pathological reflux. There was only one randomized comparative trial that presented an advantage over a double dose of PPI. Therefore, there is a need for additional randomized trials that compare the efficacy of MSA with other therapies. [Bonavina (2010), Lipham (2012), Ganz (2013 and 2016), Riegler (2015), Saino (2015), Ganz (2016), and Warren (2016) previously cited in this policy are included in this meta-analysis].

Chandan et al. (2021) conducted a systematic review and meta-analysis on patients undergoing treatment for refractory GERD and compared the efficacy of MSA with that of transoral incisionless fundoplication (TIF2). Twenty-four articles were included in the analysis which consisted of 1,074 patients that underwent MSA, and 868 patients underwent TIF2. In the MSA cohort, six studies were prospective, and three studies were retrospective; in the TIF cohort, eleven studies were prospective and four were retrospective. The authors found the clinical success rate, demonstrated by improvement of scores in GERD HRQL, was 80% for MSA and 77% for TIF. It was concluded that both procedures have a similar efficacy, but MSA seems to outperform TIF2. Overall, 91.3% of the MSA patients were able to discontinue PPI therapy compared to 63.8% of the TIF2 patients. Limitations included lack of long-term data.

Bell et al. (2020, included in Hayes report above) compared the effects of MSA versus PPI in a randomized trial. 152 participants with moderate to severe regurgitation symptoms across twenty-one U.S. clinical sites were randomized into two groups. Additional inclusion criteria for the participants were once daily PPIs for at least 8 weeks, body mass index <

35 kg/m2, abnormal pH testing (DeMeester score < 4), hiatal hernia < 3 cm by endoscopy and absence of Barrett's esophagus or Los Angeles Classification Grade C or D esophagitis. Participants were assessed at 6 and 12 months with the Reflux Disease Questionnaire (RDQ) and the GERD-HRQL standard assessments along with specific questions concerning bloating, diarrhea, flatulence, and medication use. One group (n = 102) received PPI (20 mg of omeprazole twice daily) and the other group (n = 50) received laparoscopic MSA. The authors found that MSA controlled regurgitation in 96% of patients versus only 19% of patients receiving PPIs reported control of regurgitation. The regurgitation had been sustained over 12 months. The second portion of the study allowed eligible patients (39%) from the PPI group to crossover and receive the laparoscopic MSA if they had not demonstrated improvement with the twice-daily medication. The authors concluded MSA is an effective surgical treatment option for patients with medically refractory regurgitative GERD. The study is limited by limited follow-up.

Ferrari et al. (2020) followed a cohort of 124 individuals who underwent laparoscopic implantation of an MSA device. The goal was to assess the long-term safety and efficacy of the Linx Reflux Management System for 6-12 years. Prior to surgery, all patients completed a diagnostic assessment that included the GERD-HRQL questionnaire, upper GI endoscopy, barium swallow study, ambulatory esophageal pH monitoring and esophageal manometry. Success was defined as ≥ 50% improvement in the GERDHRQL total score and discontinuation of PPI medication. During follow-up, over a five-year period, eight patients (2.4%) required a single endoscopic pneumatic dilation due to persistent dysphagia. Thirty-one patients (9.2%) required removal of the device for various reasons; erosion and regurgitation were the top two reasons with six patients each. The average total GERD-HRQL score decreased from 19.9 (baseline) to 4.01. The authors found eighty-one percent of the patients had a successful clinical outcome and were able to discontinue their PPI use. Long-term results in thirty-two patients past 10 years found zero dysphagia, seven individuals with occasional PPI use and only three with daily PPI use. The total overall patient satisfaction rate was 92.5%. The authors concluded MSA allows control of GERD symptoms and improvement in patient quality of life without significant safety issues. However, it was also concluded that additional RCTs could provide more definitive conclusions. Limitations included no comparison group and possible selection bias with a large loss to follow up overtime.

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 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. [Asti (2016), Ganz (2016), Desart (2015), Reynolds (2015), Bonavina (2008 and 2010), Louie (2018), and Warren (2018) previously cited in this policy are included in this systematic review].

A prospective, multicenter, randomized controlled 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 participants 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 participants 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.

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 five 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 participants, of whom 273 and 415 underwent Nissen fundoplication and MSA, respectively. MSA was statistically superior to LNF in preserving patients' ability to belch (95.2 vs. 65.9%, $p < 0.00001$) and the 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 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.

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.

## *Clinical Practice Guidelines*

### American College of Gastroenterology (ACG)

In a ACG clinical guideline (Camilleri, et al. 2022) for gastroparesis, the ACG suggests pyloromyotomy over no treatment for patients with gastroparesis that have not responded to medical therapy and continue to experience symptoms (conditional recommendation, low quality of evidence). The preferred myotomy method (laparoscopic or endoscopic) is, however, not specified.

In a 2021 ACG published clinical guideline (Katz, et al. 2021) for the diagnosis and management of GERD, the following recommendations are cited:

- Recommend antireflux surgery as an option for long-term treatment of patients with objective evidence of GERD, (strong recommendation; moderate level of evidence).
- Recommend consideration of magnetic sphincter augmentation (MSA) as an alternative to laparoscopic fundoplication for patients with regurgitation who fail medical management (strong recommendation, moderate level of evidence).
- Consideration of transoral incisionless fundoplication (TIF) for patients with troublesome regurgitation or heartburn who do not wish to undergo antireflux surgery and who do not have severe reflux esophagitis or hiatal hernias (conditional recommendation; low level of evidence).
- Do not recommend radiofrequency energy (Stretta) as an antireflux procedure due to inconsistent data on the efficacy of the device (conditional recommendation; low level of evidence).

### American Gastroenterological Association (AGA)

An AGA clinical practice update (Khashab et al., 2023) on gastric peroral endoscopic myotomy for gastroparesis offered expert advice regarding cognitive, procedural, and post-procedural aspects on performance of gastric peroral endoscopic myotomy for the treatment of refractory gastroparesis. After review of the available evidence, it was concluded G-POEM is safe with a high technical success rate when performed by an experienced endoscopic specialist.

An AGA clinical practice update offers guidance on best practices for personalized diagnosis and treatment of gastroesophageal reflux disease (GERD). The AGA recommends a stepwise approach for individuals presenting with GERD symptoms, aimed at identifying underlying mechanisms. When symptoms persist despite lifestyle changes and optimal medication use, management strategies should be tailored based on factors such as the integrity of the anti-reflux barrier, presence of visceral hypersensitivity and hypervigilance, confirmation of PPI-refractory GERD, symptom patterns, body mass index, and esophageal (and gastric) motor function (Yadlapati et al., 2022).

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).

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 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 our members

with the procedure, we do 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).

## National Institute for Health and Care Excellence (NICE)

The National Institute for Health and Care Excellence (NICE, 2023) conducted a rapid review of the published literature on the efficacy and safety of laparoscopic insertion of a magnetic ring for gastro-esophageal reflux disease (GORD). They evaluated evidence from three systematic and meta-analyses, one RCT, three non-randomized comparative studies, and two case series. The committee noted that the magnetic ring use has evolved over time and is considered adequate. In addition, it was stated that the use of the device should be performed by clinicians that have specific training in the procedure.

The 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).

## Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)

SAGES guidelines (Kohn et al., 2021) on the use of POEM for the treatment of achalasia make the following recommendations:

- The panel suggests that adult and pediatric patients with type I and II achalasia may be treated with either POEM or laparoscopic Heller myotomy based on surgeon and patient's shared decision-making (conditional recommendation, very low certainty evidence).
- Based on the panel's collective experience, they suggest POEM over laparoscopic Heller myotomy for type III adult or pediatric achalasia (expert opinion).

The following recommendations are made by SAGES (Auyang et al., 2013) on endoluminal treatments for GERD:

- Results for EsophyX appear to be mixed and lacking long term data. Further studies are required to define optimal techniques and to further evaluate the device and its safety [Quality of Evidence: (++)]. GRADE Recommendation: Weak.
- The evidence for the Stretta device demonstrates it is considered appropriate therapy for patients > than 18 years of age with GERD and show symptoms of heartburn, regurgitation, or both for 6 months or more, have been partially or completely responsive to anti-secretory pharmacologic therapy, and have declined laparoscopic fundoplication [Quality of Evidence: (++++)]. GRADE Recommendation: Strong.

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 explanation appears to be persistent dysphagia with a rate in larger series from 3-6%.
- Erosion appears to be rare, with one case reported in the 1st 1,000 patients, one additional published case report, a large series reporting two 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 explanation (Telem et al., 2017).

## U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

The only gastric electrical stimulation (GES) device for gastroparesis treatment approved for marketing in the United States is the Enterra™ Therapy System, manufactured by Medtronic, Inc. On March 31, 2000, the FDA approved a Humanitarian Device Exemption (HDE) for the marketing of the Enterra gastric electrical stimulation system for the treatment of chronic, intractable (drug-refractory) nausea and vomiting secondary to paresis of diabetic or idiopathic etiology. Enterra is indicated for the treatment of chronic intractable (drug refractory) nausea and vomiting secondary to gastroparesis of diabetic or idiopathic etiology in patients aged 18 to 70 years. Based upon the FDA label, the Enterra device should not be used for patients with gastric obstruction or pseudo-obstruction, prior gastric resection, fundoplication, eating disorders, history of seizures, primary swallowing disorders, chemical dependency, or psychogenic vomiting. Refer to the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=376493. (Accessed April 2, 2025)

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 August 14, 2025)

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 August 14, 2025)

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: https://www.accessdata.fda.gov/cdrh_docs/pdf7/K071553.pdf. (Accessed August 14, 2025)

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.

Refer to 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 August 14, 2025)

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. Refer to the following website for additional information: https://www.accessdata.fda.gov/cdrh_docs/pdf14/k143634.pdf. (Accessed August 14, 2025)

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

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. Refer to the following website for more information using PMA number P100049: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm. (Accessed August 14, 2025)

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. Refer to the following website for more information, using PMA number P980053: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm. (Accessed August 14, 2025)

FDA 510(k) Premarket Notification was received on May 24, 2024 for the GERDx-System under 510(k) Number K233240. Refer to the following website and search using either the product name or the Product Code of ODE for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed August 14, 2025)

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# Policy History/Revision Information

| Date | Summary of Changes |
|---|---|
| 02/01/2026 | **Title Change**<br>• Previously titled *Minimally Invasive Procedures for Gastric and Esophageal Diseases*<br>**Coverage Rationale**<br>• Added language to indicate:<br>  ○ Gastric electrical stimulation (GES) therapy is proven and medically necessary for treating refractory Gastroparesis that has failed other therapies, or chronic intractable (drug-refractory) nausea and vomiting secondary to Gastroparesis of diabetic or idiopathic etiology; refer to the *U.S. Food and Drug Administration (FDA)* section for information regarding FDA labeling and Humanitarian Device Exemption (HDE) for GES (relocated from the Medical Policy titled *Gastrointestinal Disorders Diagnostic Procedures*)<br>  ○ Surgical pyloroplasty (open or laparoscopic) is proven and medically necessary for treating refractory Gastroparesis that has failed other therapies, or chronic-intractable (drug-refractory) nausea and vomiting secondary to Gastroparesis of diabetic or idiopathic etiology<br>• Removed language indicating functional lumen imaging probe technology is unproven and not medically necessary for diagnosing Achalasia<br>**Medical Records Documentation Used for Reviews**<br>• Added language to indicate:<br>  ○ 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<br>  ○ Medical records documentation may be required to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the service requested; refer to the guidelines titled Medical Records Documentation Used for Reviews<br>**Definitions**<br>• Updated definition of "Gastroparesis"<br>**Applicable Codes**<br>• Added CPT codes 43647, 43648, 43659, 43881, 43882, 64590, and 64595<br>**Supporting Information**<br>• Updated *Description of Services*, *Clinical Evidence*, *FDA*, and *References* sections to reflect the most current information<br>• Archived previous policy version 2026T0322KK |

# Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, check the member specific benefit plan document and any applicable federal or state mandates. 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.

This Medical Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.