Medical Coverage Policy

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

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Related Coverage Resources

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Overview

This Coverage Policy addresses minimally invasive anti-reflux procedures for the treatment of gastroesophageal reflux disease (GERD) and Peroral Endoscopic Myotomy (POEM) for the treatment of esophageal achalasia, gastroparesis or Zenker's diverticula.

Coverage Policy

Peroral endoscopic myotomy (POEM) is considered medically necessary when ALL of the following criteria are met:

- the individual is age 18 years or older
- achalasia type I, II or III is diagnosed using esophageal manometry
- Eckardt symptom score is greater than three

Peroral endoscopic myotomy (POEM) for ANY other indication is considered experimental, investigational and unproven.

Each of the following peroral endoscopic myotomy (POEM) procedures is considered experimental, investigational and unproven:

- Diverticular peroral endoscopic myotomy (D-POEM)
- Gastric peroral endoscopic myotomy (G-POEM)
- Zenker peroral endoscopic myotomy (Z-POEM)

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

- radiofrequency energy to the gastroesophageal junction (e.g., Stretta® System)
- endoluminal gastroplasty/gastroplications (e.g., Medigus Ultrasonic Surgical Endostapler [Muse™] System, GERDx™)
- transoral incisionless fundoplication (TIF) (e.g., EsophyX™)
- injection/implantation of biocompatible material (e.g., plexiglas or polymethylmethacrylate [PMMA], Durasphere™)
- magnetic sphincter augmentation (e.g., LINX™ Reflux Management System)
- resection and plication (RAP) (e.g., Apollo Overstitch)

General Background

Peroral Endoscopic Myotomy (POEM) Procedures

Achalasia is a rare motility disorder of the esophagus and is defined by three elements: the reduction or absence of the primary peristaltic waves in the distal two thirds of the esophagus, incomplete or no relaxation of the lower esophageal sphincter (LES) during swallowing and increased resting LES tone. There is degeneration of the esophageal muscle and the nerves that control the muscles. The cause of primary or idiopathic achalasia is unknown. Secondary achalasia is due to diseases that cause esophageal motor abnormalities (e.g., Chagas disease, esophageal cancer, Fabry disease, amyloidosis). Men and women are affected with equal frequency, with no racial predilection and achalasia is usually diagnosed in patients between the ages of 30 and 60 years. Symptoms of achalasia include dysphagia, heartburn, difficulty belching, chest pain, regurgitation of undigested food and liquid, and weight loss (Spechler, 2021a; Vaezi, et al., 2020a; Tefas, et al., 2018; National Organization for Rare Disorders [NORD®], 2017).

Achalasia is defined by aperistalsis and abnormal LES relaxation (integrated relaxation pressure [IRP] > 15 mmHg). The disorder is characterized manometrically by insufficient relaxation of the lower esophageal sphincter (LES) and loss of esophageal peristalsis; radiographically by aperistalsis, esophageal dilation, with minimal LES opening, “bird-beak” appearance, poor emptying of barium; and endoscopically by dilated esophagus with retained saliva, liquid, and undigested food particles in the absence of mucosal stricturing or tumor (Spechler, et al., 2021a; Vaezi, et al., 2020b).

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

- **Type I (classic achalasia)** – Incomplete LES relaxation, aperistalsis and absence of esophageal pressurization. Swallowing results in no significant change in esophageal pressurization and has 100% failed peristalsis with a distal contractile integral (DCI, an index of the strength of distal esophageal contraction) < 100 mmHg.
- **Type II** – Incomplete LES relaxation, aperistalsis and panesophageal pressurization in at least 20% of swallows. Swallowing results in simultaneous pressurization that spans the entire length of the esophagus. Type II achalasia has 100% failed peristalsis and pan-esophageal pressurization with ≥ 20 percent of swallows.

- **Type III (spastic achalasia)** – Incomplete LES relaxation and premature contractions (distal latency [DL] < 4.5 seconds) in at least 20% of swallows. Swallowing results in abnormal, lumen-obliterating contractions or spasms. Type III achalasia has no normal peristalsis and premature (spastic) contractions with DCI >450 mmHg-sec-cm with ≥ 20 percent of swallows (Spechler, 2021a; Schlottmann, et al., 2017).

The primary treatment objective for achalasia is to relieve obstruction in the distal esophagus by decreasing the resting pressure in the lower esophageal sphincter (LES) to a level at which the sphincter no longer impedes the passage of undigested food and liquid. Established treatment options include pharmacotherapy (e.g., injection of botulinum toxin into the esophagus, use of oral nitrates) or mechanical disruption of the muscle fibers of the LES by surgical interventions (i.e., endoscopic balloon dilation, surgical Heller myotomy [LHM] with or without fundoplication) to reduce the incidence of gastroesophageal reflux disease (GERD). LHM is the treatment of choice and has an 85%–90% effect in treating the condition. When a patient has dysphagia following surgical myotomy, the first suspicion is incomplete myotomy (Spechler, 2021b; Fernandez-Ananin, et al., 2018; Tefas, et al., 2018).

Peroral endoscopic myotomy (POEM)
POEM is a minimally invasive intervention that aims to treat achalasia. It is regarded as the endoscopic equivalent of Heller myotomy. The POEM technique involves guiding an endoscope through the esophagus, making an incision in the mucosa, creating a submucosal tunnel for access to the lower esophagus and gastroesophageal junction, and cutting the muscle fibers in the lower esophagus and proximal stomach. Internal incisions are closed with clips after myotomy is complete. The proposed advantage of POEM is that it can deliver a longer myotomy than pneumatic dilation or the Heller procedure. The length of myotomy from the esophageal to the gastric side can be adjusted on a case-by-case basis while achieving functional durability of traditional surgical myotomy. A longer myotomy may be more effective in controlling symptoms. POEM includes no antireflux procedure and can therefore result in GERD. POEM is a proposed treatment. Reasonable treatment options following a failed surgical myotomy include pneumatic dilation or redo myotomy using either the same or an alternative myotomy technique (POEM or laparoscopic Heller myotomy) (Spechler, 2021b; Khashab, 2019; Inoue, et al., 2018).

POEM is a complex procedure, demanding skilled hands to avoid serious complications. Endoscopists should be able to recognize structures beyond mucosa, including vasculature nerves and the anatomy of the mediastinum. POEM should be performed in highly specialized centers by experienced endoscopists or surgeons (Ahmed and Othman, 2019).

Literature Review – POEM: Randomized controlled trials have compared POEM to laparoscopic Heller myotomy with Dor fundoplication (LHD) for the treatment of achalasia. The study concluded that POEM is noninferior to laparoscopic Heller myotomy with Dor fundoplication with shorter operative times and minimal serious adverse events (Werner, et al., 2019). Another RCT compared the efficacy of POEM to pneumatic dilation as the initial treatment of patients with treatment-naïve achalasia with a clinically significant treatment success rate at two years in the POEM group (Ponds, et al., 2019). Numerous case studies, systematic reviews and systematic reviews with meta-analysis have been published investigating POEM for the treatment of achalasia (Lee, et al., 2019; Li, et al., 2018; Schlottmann, et al., 2018; Akintoye, et al., 2016).

Costantini et al. (2020) conducted a propensity score case-control study that compared POEM to laparoscopic Heller myotomy with Dor fundoplication (LHD) for the treatment of esophageal achalasia. Patients (n=280) that had primary achalasia (types I to III) were enrolled in the study and received either LHD (n=140) or POEM (n=140) at specialized centers. The primary outcome measured treatment success which was defined as an Eckardt score ≤ 3. Secondary outcomes included: basal lower esophageal sphincter (LES) pressure and integrated relaxation pressure (IRP) based on high-resolution manometry (HRM) findings; presence of reflux esophagitis based on endoscopy findings; and esophageal acid exposure. Treatment success was assessed two, six and 12 months after surgery, and every two years. Esophagitis was measured by endoscopy at six (POEM group only) and 12 months after the operation and then recommended every 24 months. Esophageal HR manometry and 24-h pH monitoring (according to DeMeester) were performed six months after the surgical procedure. Study results stated that POEM required a significantly shorter operation time and postoperative stay compared to LHD ($p<0.001$). No mortality was recorded in either group. There was not a significant difference

between groups in severe procedure related complications (p=0.33). At a median follow-up of 24 months for POEM and 31 months for LHD, there was not a significant difference in clinical success (p<0.12). Four years after the treatment, the probability to have symptoms adequately controlled was > 90% for both groups (p=0.2). HR-Manometry showed a similar reduction in the LES pressure; 24-h pH-monitoring showed a significant abnormal exposure to acid in 38.4% of POEM patients, as compared to 17.1% of LHD patients (p<0.01) and esophagitis was found in 37.4% of the POEM and 15.2% of LHD patients (p<0.05). Study limitations included the study design and potential bias due to latent variables that can remain after matching. Additionally, the results may not represent those achievable by centers with less experience with the procedures. The authors concluded that POEM provides the same midterm results as LHD. However, there was a higher incidence of postoperative GERD in the POEM group.

Werner et al. (2019) conducted a prospective, multicenter, randomized, open-label, noninferiority trial that compared peroral endoscopic myotomy (POEM) with laparoscopic Heller's myotomy (LHM) plus Dor's fundoplication in patients with symptomatic idiopathic achalasia. Patients (n=221) in the modified intention-to-treat population were randomly assigned to undergo either POEM (n=112) or LHM plus Dor's fundoplication (n=109). Adults 18 years or older with symptomatic achalasia and a medical indication for surgical myotomy or pneumatic dilation were eligible for inclusion in the trial if they had an Eckardt symptom score > 3 and had findings on preinterventional manometry that were consistent with the diagnosis of achalasia (classified as types I to III). Eligible patients who had previously undergone endoscopic treatment were included. The primary outcome was clinical success at the two year follow-up, defined as an Eckardt symptom score of ≤ 3 without the use of additional treatments; using a noninferiority margin of –12.5 percentage points. Secondary measurements included adverse events, esophageal function, Gastrointestinal Quality of Life Index score and gastroesophageal reflux. Clinical data were collected at three, six, 12, and 24 months follow-up. Patient-reported outcomes were assessed by means of telephone calls, mail, or follow-up appointments by dedicated trial personnel who were aware of the treatment-group assignments. Objective evaluation by means of endoscopy, manometry, and esophageal pH monitoring (at least one week after the discontinuation of a proton-pump inhibitor) was planned at three and 24 months. Clinical success at the two year follow-up was observed in 83.0% of patients in the POEM group and 81.7% of patients in the LHM group, which was not clinically significant (p=0.007 for noninferiority). Serious adverse events occurred in 2.7% of patients in the POEM group and 7.3% of patients in the LHM group. Improvement in esophageal function and Gastrointestinal Quality of Life Index from baseline to 24 months did not differ significantly. At three and 24 months reflux esophagitis was assessed by endoscopy, 57% of patients in the POEM group and 20% of patients in the LHM group had reflux esophagitis and at 24 months, the corresponding percentages were 44% and 29%. Author noted limitations included: the surgeons were more experienced in performing LHM plus Dor's fundoplication than the endoscopists were in performing POEM, treatment effects on postoperative pain or on the use of pain medications was not analyzed and the study was unblinded. Because of the unblinded nature there was a potential source of bias given that the primary end point was based on patients' reports of symptoms; however, objective assessment by manometry corroborated the primary finding. The authors concluded that POEM was noninferior to LHM plus Dor's fundoplication in controlling symptoms of achalasia at two years. Gastroesophageal reflux was more common among patients who underwent POEM than among those who underwent LHM.

Ponds et al. (2019) conducted a multicenter randomized control trial that compared the efficacy of POEM to pneumatic dilation as the initial treatment of patients with treatment-naïve achalasia (types I to III). Patients (n=133) were randomized to receive POEM (n=67) or pneumatic dilation (n=66). The study included adults aged 18–80 years with newly diagnosed achalasia, an Eckardt score > 3, and no previous treatment. The primary outcome measured treatment success at the two year follow-up. Treatment success was defined as a reduction in the patient's Eckardt score to ≤ 3 and the absence of severe complications or need for re-treatment. Secondary outcomes were measured at three months, one year, and two years after initial treatment and included the following: Eckardt score, basal lower esophageal sphincter (LES) pressure and integrated relaxation pressure (IRP) based on high-resolution manometry (HRM) findings, esophageal stasis and diameter evaluated by timed barium esophagogram, complication rate, the rate of endoscopic or surgical re-treatment, presence of reflux esophagitis based on endoscopy findings, esophageal acid exposure, reflux symptoms, PPI use, and general health-related (physical and mental aspects) and achalasia-related quality of life. Of the 133 randomized patients, 130 underwent treatment and were included in the analysis (n=64/POEM, n=66/pneumatic dilation) with 126 (95%) completing the study. Four patients were lost to follow-up. The treatment success rate, after two years of follow-up was 92% in the POEM group and 54% in the pneumatic dilation group, a clinical significant

difference of 38% (p<0.001). Reflux esophagitis occurred significantly more often in the POEM group compared to the pneumatic dilation group (p=0.002). No significant differences were observed in Eckardt score, IRP and basal LES pressure, barium column height and diameter, or quality of life after post hoc adjustment for multiple comparisons. Two serious adverse events, including one perforation, occurred after pneumatic dilation, while no serious adverse events occurred after POEM. Author noted limitations included: a strict intention-to-treat analysis was not performed, the start time for follow-up was treatment initiation rather than randomization resulting in follow-up time differences (24 months for the POEM group vs 24.5 months for the pneumatic dilation group). Additionally, the study was unblinded without long term results beyond two years. The authors concluded that the findings support consideration of POEM as an initial treatment option for patients with achalasia.

Lee et al. (2019) conducted a systematic review and meta-analysis to evaluate the safety and efficacy of peroral endoscopic myotomy (POEM) in children. Studies that conducted POEM in pediatric patients age < 18 years were included. Studies were excluded if they had a non-pediatric population; no clear diagnostic or clinical evaluation of achalasia (e.g., Eckardt scoring system, esophageal manometry, barium X-ray, upper endoscopy); and/or were non-human studies, case-reports, editorials, and review papers. Twelve studies (n=142) met inclusion criteria and included eight case series and four retrospective cohort studies. Three of the studies were published conference abstracts. Primary outcome measures included the Eckardt score and lower esophageal sphincter (LES) pressure before and after POEM. Secondary outcome measures were the clinical success rate and adverse events. Follow-ups ranged from 1-36 months (median 14 months). Compared to baseline, there was a significant reduction in mean Eckardt scores by 6.88 points (p<0.001) and a decrease in LES pressure by 20.73 mmHG (p<0.001). At least 93% of the patients experienced improvement or resolution of achalasia symptoms. Adverse events included mucosal injury (n=7), esophageal tear (n=1), esophageal leak (n=1), focal atelectasis (n=2), pneumoperitoneum (n=13), pneumothorax (n=4), pneumonitis/pneumonia (n=15), pleural effusion (n=9), subcutaneous or mediastinal emphysema (n=25), retroperitoneal CO2 (n=2), fever (n=1), and severe-postoperative pain (n=2). There were also cases of clinical reflux symptoms after POEM such as heartburn (n=2), regurgitation (n=11), and reflux esophagitis (n=5). Most events were minor and self-limiting. Limitations of the studies included: small patient populations; short-term follow-ups; retrospective study designs and conference abstracts; no comparators; missing data; and heterogeneity of the procedure. Randomized controlled trials comparing POEM to established treatment options are needed to establish the safety and efficacy of POEM for the treatment of achalasia in pediatric patients.

Li et al. (2018) conducted a single center study that analyzed the long-term results of POEM, with an emphasis on POEM failures and associated risk factors. Included patients (n=564) had esophageal achalasia which was diagnosed by established methods such as clinical symptoms, barium swallow, EGD, manometry, and/or chest CT scan. The primary outcome measured the clinical success rate of POEM (Eckardt score ≤ 3). The secondary outcomes included procedure-related adverse events (AEs), lower esophageal sphincter (LES) pressure on manometry pre- and post-POEM, reflux symptoms, reflux esophagitis on EGD, and procedure parameters such as operation time, length of hospital stay, and myotomy length. Patients were scheduled to follow-up at one month, three months, six months, one year postoperatively and yearly afterward. Follow-up included a symptom assessment, physical examination, and objective tests including EGD and barium esophagram. A total of 144 patients were lost to follow-up. Major perioperative AEs occurred in 6.4% (36 patients) which included delayed mucosal barrier failure, delayed bleeding, hydrothorax, pneumothorax (all of whom had received air rather than CO2 insufflation). After initiation of CO2 insufflation, the AE rate dropped to 2.4%. After a median follow-up of 49 months (range, 3–68), the Eckardt score and lower esophageal sphincter (LES) pressure were significantly decreased (p<0.05; p<0.05, respectively). Fifteen failures occurred within three months, 23 between three months and three years, and 10 after three years. The estimated clinical success rates at one, two, three, four, and five years were 94.2%, 92.2%, 91.1%, 88.6%, and 87.1%, respectively. Clinical reflux occurred in 37.3% of patients (155/416). Author noted limitations included a high loss-to-follow-up rate, poor patient compliance at diagnostic tests, and difficulties in accessing records from outside hospitals. These limitations resulted in a lack of in-depth analysis of causes of POEM failures, especially regarding the role reflux played. Additionally, the center did not have CO2 insufflator for the entire study resulting in high gas-related AEs.

Schlottmann et al. (2018) conducted a systematic review and meta-analysis to compare the outcomes of oral endoscopic myotomy (POEM) and laparoscopic Heller myotomy (LHM) for the treatment of esophageal achalasia. Studies that investigated POEM or LHM with at least 20 patients and a follow-up greater than nine months were included. The primary outcome measures were improvement of dysphagia and posttreatment

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

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

Akintoye et al. (2016) conducted a systematic review and meta-analysis to assess the safety and efficacy of POEM for the treatment of achalasia. The primary outcome measure was the proportion of patients with an Eckardt score of ≤ 3 after the procedure. Secondary measures were the mean Eckardt score, manometry parameters, timed barium esophagogram, and weight change postoperatively. All studies reporting clinical outcomes after POEM were eligible for inclusion. Exclusion criteria included: animal studies, case reports with <

5 patients, commentaries or general reviews, conference abstracts, and overlapping publications from the same center. Thirty-six studies (n=2373) met inclusion criteria (nonrandomized prospective studies and retrospective reviews). Overall, compared to baseline there was a significant improvement in the Eckardt score, manometry and timed barium esophagogram postoperatively ($p<0.05$). Clinical success (Eckardt score ≤ 3) was achieved in 98% of patients. The mean Eckardt score prior to treatment was 6.9 ± 0.15 compared to 0.77 ± 0.10 at one month, 1.0 ± 0.10 at six months and 1.0 ± 0.08 at 12 months. There was a significant decrease in manometry score within six months post-POEM ($p<0.05$). The average heights of the barium column following a timed barium esophagogram (a simple technique for evaluating esophageal emptying in patients with achalasia) were 14 ± 2.3 and 9.7 ± 1.9 cm at one and five minutes, respectively. The column heights decreased to 4.2 ± 0.77 and 2.6 ± 0.72 cm at one and five minutes, respectively, following POEM. Average weight gain (six studies; n=488) 5.4 ± 0.73 kg after a mean follow-up of 7.4 months. Adverse events included: mucosal injury (4.8%), esophageal perforation (0.2 %), substantial bleeding requiring interventions (0.2 %), subcutaneous emphysema (7.5 %), pneumothorax (1.2 %), pneumomediastinum (1.1 %), pneumoperitoneum (6.8 %) and pleural effusion (1.2 %). After a mean follow-up of eight months the rates of symptomatic gastroesophageal reflux was 8.5%, esophagitis on EGD 13% and abnormal acid exposure following a 24-hour pH monitoring study 47%. Limitations include the heterogeneity of the study populations and POEM techniques, missing data, variable follow-up times and significant heterogeneity in the primary outcomes, limiting the generalizability of the results. The authors concluded that POEM appears to be safe and effective based on the current evidence, and warrants consideration as first-line therapy when an expert operator is available.

Marano et al. (2016) conducted a systematic review and meta-analysis to investigate the efficacy and safety of POEM compared with laparoscopic Heller myotomy (LHM) for the treatment of achalasia. Seven retrospective reviews (n=485) including POEM (n=196) and laparoscopic Heller myotomy (LHM) (n=290) met inclusion criteria. Study populations ranged from 8 to 180 patients per study. All studies with adult patients with a diagnosis of achalasia were included. Studies that did not report the comparison between endoscopic (POEM) and surgical (LHM) treatment, animal studies, single case reports, technical reports, reviews, abstracts, and editorials were excluded. The primary outcome measure was the mean difference in reduction in the Eckardt score. Secondary outcome measures were the mean difference in procedure time, length of hospital stay, postoperative pain score and analgesic requirement, as well as complications and post-procedure symptomatic gastro-esophageal reflux (GER). Follow-ups ranged from 2–12 months. There were no significant differences in reduction in Eckardt score ($p=0.217$) (n=5 studies), operative time ($p=0.36$), and postoperative pain score ($p=4.45$) (n=2 studies). There was a significantly shorter hospital stay in POEM patients ($p=0.049$). There was a significant difference in post-operative gastroesophageal reflux symptoms in favor of LHM ($p=0.017$). Four studies reported data regarding complications. Bleeding and perioperative perforation were indexed as major complications, while urinary retention, splenic capsular injury, atrial fibrillation, vagal nerve injury, and subcutaneous emphysema were listed as minor complications. There was no significant difference in complication rates between POEM and LHM ($p=0.796$). The studies were limited by the small heterogeneous patient populations, short-term follow-ups, duplication of patients in some studies, moderate risk of bias, heterogeneity of the studies, and retrospective study design.

Patel et al. (2016) conducted a systematic review and meta-analysis to assess the efficacy of POEM for the treatment of achalasia. Nineteen case series and three, nonrandomized, prospective comparative studies met the inclusion criteria. Studies were included if they reported outcomes of POEM for the treatment of achalasia. Excluded studies were case series with less than ten patients or results of a patient population reported in a more recent study, case reports, and studies in which adequate details of methodology and outcomes could not be established. Primary outcomes were efficacy, adverse events and incidence of postoperative GERD. Secondary outcome measures were comparison of clinical outcomes and procedural safety of POEM versus laparoscopic Heller's myotomy (LHM). There was a 66% improvement in lower esophageal sphincter pressure and an 80% improvement in timed barium esophagram column height following POEM. Symptom improvement was demonstrated with a pre- and post-POEM Eckardt score of 6.8 ± 1.0 and 1.2 ± 0.6, respectively. Endoscopy showed esophagitis in 0% prior to POEM and 19% following POEM. Minor operative adverse events included capno/pneumo-peritoneum (30.6%), capno/pneumo-thorax (11.0%) and subcutaneous emphysema (31.6%). Major operative adverse events included mediastinal leak (0.3%), postoperative bleeding (1.1%) and one mortality (0.09%). Adequate data was available for a pooled analysis of three, non-randomized comparative studies between LHM and POEM. Analysis showed similar results for adverse events ($p=0.69$), perforation rate ($p=0.69$), operative time ($p=0.4$) and hospital length of stay ($p=0.05$). Author-noted limitations of the studies

included: poor quality of the studies as evidenced by the poor outcomes in the objective study quality assessment; lack of standardization of surgical quality and determination of learning curve; and limited long-term data. Studies were also limited by the small patient populations.

Diverticular peroral endoscopic myotomy (D-POEM)
Esophageal diverticula are rare outpouchings of the esophagus that can cause dysphagia, regurgitation, chest pain and aspiration pneumonia as they progress. Interventional treatment should be considered for symptomatic cases. Surgical resection of the diverticulum has traditionally been considered to be the only curative option. The D-POEM technique is unique in that, through the creation of submucosal tunneling, the cricopharyngeus muscle or the diverticular septum can be methodically exposed, allowing for careful complete septotomy under direct endoscopic visualization. The D-POEM technique for the treatment of esophageal diverticula has only been reported in limited case reports (Yang, et al., 2019).

Literature Review - D-POEM: Studies in the peer-reviewed literature investigating D-POEM are primarily in the form of small prospective studies with patient populations ranging from 11–25 with follow-up of 12 months. Larger prospective studies with longer follow-up are needed to assess the efficacy and safety of D-POEM (Orlandini, et al., 2020; Yang, et al., 2019, Maydeo, et al., 2019; Khashab, 2019).

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

Gastric Peroral Endoscopic Myotomy (G-POEM)
Gastroparesis (GP) is a chronic motility disorder defined as a functional disorder with objective delayed gastric emptying in the absence of a mechanical obstruction. The symptoms of gastroparesis include nausea, vomiting, early satiety, belching, bloating, and/or upper abdominal pain. Initial management of gastroparesis consists of dietary modification, optimization of glycemic control and hydration, and pharmacologic therapy with prokinetic and antiemetic medications. Patients who are refractory to medical therapy may require surgical interventions in the forms of tube gastrostomy, subtotal gastrectomy, or pyloroplasty. Surgical pyloroplasty (eg, Heineke-Mikulicz pyloroplasty) can lead to sustained improvement of symptoms in patients with refractory gastroparesis. The POEM procedure has been adapted to be performed in the stomach (G-POEM) is a proposed, less invasive alternative treatment of severe gastroparesis that is refractory to medical therapy in selected patients. G-POEM consists of creating a prepyloric submucosal tunnel extending to the pylorus before dissecting circular and oblique muscle bundles, as per the peroral endoscopic myotomy (POEM) (Camilleri, 2021; Gregor, et al., 2021; Azzolini, et al., 2020; Spadaccini, et al., 2020; Aghaie Meybodi, et al., 2019; Khashab, 2019)

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

Literature Review – G-POEM: A number of prospective observational studies (n=13–80 patients) and systematic reviews with meta-analysis (n=9–22 studies/196–322 patients) have evaluated the efficacy and safety of G-POEM in treating refractory gastroparesis. These studies have been limited by short-term follow-up of 1–18 months and lack of RCT's. The studies used the Gastroparesis Cardinal Symptom Index (GCSI) and gastric emptying scintigraphy (GES). GCSI measures the following symptoms: nausea, retching, vomiting, stomach fullness, inability to finish a meal, excessive fullness, loss of appetite, bloating and abdominal distension. GES measures half gastric-emptying time, retention at two and four hours. Larger and longer-term studies with active treatment comparators are needed to fully evaluate the effectiveness and safety of G-Poem for refractory gastroparesis (Gregor, et al., 2021; Azzolini, et al., 2020; Spadaccini, et al., 2020; Aghaie Meybodi, et al., 2019).

Vosoughi et al. (2021) conducted an international prospective trial at five tertiary centers (four USA, one South America) that investigated the efficacy and safety of G-POEM in patients with refractory gastroparesis. Adults (n=80) with refractory gastroparesis were included in the study, the mean age was 49.3±14.9 with 57 (71.3%) females. The most common etiology of gastroparesis was idiopathic (n=33, 41.3%), followed by postsurgical (n=28, 35%) and diabetic (n=19, 23.8%). The primary outcome measured clinical success of G-POEM which was defined as at least one score decrease in Gastroparesis Cardinal Symptom Index (GCSI) with ≥ 25% decrease in two subscales, at 12 months. Secondary outcomes evaluated safety, change in quality of life and change in gastric retention over the course of the study. The GCSI Score and subscales, adverse events (AEs)

and 36-Item Short Form questionnaire of quality of life were evaluated at baseline and one, three, six and 12 months after G-POEM. A gastric emptying study was performed before and three months after the procedure. Five patients were lost to follow-up with 75 patients (94%) completing the 12-month follow-up. Clinical success at one month, three months, six months and 12 months following G-Poem were 57.5%, 61.5%, 60.3% and 56%, respectively. At 12 months, the GCSI Score (including subscales) improved moderately after G-POEM ($p<0.05$). Clinical success rate at 12 months was generally not significant across gastroparesis subtypes ($p=0.913$). There was a significant improvement in the majority of the quality of life aspects both at 12 months and over time. Physical functioning, role limitation due to physical health and bodily pain, showed no significant change. Three months after G-POEM, GES was performed in 53 of the 80 patients (66%). Gastric retention at four hours decreased significantly at three months from baseline, which resulted in GES improvement in 64.2% (34 of 53 cases). Mild procedure-related AEs occurred in five (6%) patients. Author noted limitations included the lack of a control group and the inability to sufficiently control important confounding variables, such as the use of prokinetics could be a major threat to the study's internal validity. Lastly, gastric emptying was not evaluated at 12 months after the study and several patients were not available for repeat gastric emptying study at three months post procedure. The authors concluded that G-POEM is a safe procedure, but showed only modest overall effectiveness in the treatment of refractory gastroparesis. Further studies are required to identify the best candidates for G-POEM; unselective use of this procedure should be discouraged. No health disparities were identified by the investigators.

Spadaccini et al. (2020) evaluated the efficacy and safety of G-POEM for refractory gastroparesis (GP) in a systematic review and meta-analysis. The authors noted that symptomatic improvement was achieved after 83.9% of procedures. When comparing the mean values of pre- and post-procedural gastric emptying scintigraphy (GES), there was a significant decrease of the gastric retention percentage at two and four hours 74.9% ± 5.2% versus 52.5% ± 10.8% ($p<0.001$) and 44.1% ± 13.0% versus 20.6% ±9.5 % ($p<0.001$), respectively. The overall adverse events rate was 6.8% ($p=0.006$). Limitations included short term follow-up and the lack of head-to head comparison with either surgical or endoscopic pylorus directed therapies. Additionally, G-POEM is a relatively new technique and long-term data on symptom relief are still lacking. The authors concluded that G-POEM appears to be a promising approach for GP in terms of safety and efficacy outcomes in the short term. Yan et al. (2020) also used a systematic review and meta-analysis that evaluated the efficacy and safety of G-POEM for refractory gastroparesis (GP) using the GCSI scale and GES. The authors noted that the technical success rate was 100%. After G-POEM, patients reported significant changes in GCSI score ($p<0.0001$), GCSI reduction ($p<0.0001$), gastric emptying scintigraphy at four hours (GES-4h) ($p<0.00001$) and GES time (GET) reduction ($p<0.00001$). The intra-procedure complication rate was 5.1 %, including capnoperitoneum (seven cases) and accidental mucotomy (five cases). The post-procedure complication rate was 6.8 %, including abdominal pain (three cases), bleeding (three cases), ulcer (one case), difficulty swallowing (one case) and others (eight cases). Both intra and post-procedure complications were easily managed by conservative or endoscopic treatments. Limitations noted by the authors included: the quality of the included studies was relatively low, studies had a high risk of bias, lack of RCT's, and heterogeneity between studies was significant, probably due to the mismatching of baseline information. The authors concluded that the outcome of this meta-analysis is significant, caution is still needed to draw a conclusion as to whether G-POEM can be a complete treatment for the treatment of gastroparesis. Aghaie Meybod et al. (2019) conducted a systematic review and meta-analysis that concluded that treating refractory gastroparesis with G-POEM results in a high rate of clinical success and low rate of adverse events. The clinical success weighted pool rates (WPR) was 82%. The post procedure mean values of GCSI were reduced significantly at five days ($p<0.001$) when compared to pre-procedure GCSI. The mean values of gastric emptying were significantly decreased 2–3 months after the procedure ($p<0.05$). Author noted limitations included the small patient population of the included studies and high level of heterogeneity in the secondary outcome measures. This finding could be attributed to different inclusion criteria in the studies. The authors also noted that G-POEM is a relatively new technique and the studies that reported outcomes have short follow-up duration.

Zenker peroral endoscopic myotomy (Z-POEM)

A Zenker's diverticulum (ZD), or pharyngeal pouch, is an outpouching that occurs at the junction of the lower part of the throat and the upper portion of the esophagus. The pouch forms because the muscle that divides the throat from the esophagus, the cricopharyngeal (CP) muscle, fails to relax during swallowing. Symptoms of ZD include dysphagia, regurgitation, and its associated complications. Symptomatic ZD is more prominent in males (ratio 1:5) and typically seen in middle-aged adults and older adults in their seventh or eighth decade of life. The

occurrence of ZD shows geographical variation and has been described more frequently in Northern Europe, North America, and Australia than in Southern Europe, Japan, or Indonesia (Schiff and van Delft, 2020; Ishaq, et al., 2018).

The available treatment modalities include open surgery, rigid endoscopy and flexible endoscopy. Z-POEM which is also known as submucosal tunneling endoscopic septum division (STESD) is a modified peroral endoscopic myotomy (POEM) technique. This technique eliminates direct dissection of the CP septum and, instead, involves dissecting a submucosal tunnel around the septum to achieve a complete myotomy. The procedure is indicated for treating small (< 2 cm) ZD because the small pocket may disappear after the myotomy is performed (Brewer Gutierrez, et al., 2019).

Literature Review – Z-POEM: Studies in the peer-reviewed literature investigating Z-POEM are primarily in the form of retrospective studies. Large, well-designed, controlled trials showing long-term safety and efficacy are lacking (Budnicka, et al., 2021; Yang, et al., 2020; Ishaq, et al., 2018).

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

Minimally Invasive Anti-Reflux Procedures

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

According to Richter and Vaezi, 2021, “gender is not a factor in North America and Europe, but women have a 40% higher rate of GERD symptoms compared with men in South America and the Middle East. There is no clear association between gender and peptic stricture, but men are at a greater risk of esophagitis, Barrett’s esophagus, and adenocarcinoma than women. Advancing age has been inconsistently associated with an increase in GERD symptoms but is strongly associated with complications of GERD, including esophagitis, esophageal stricture, and Barrett’s esophagus with cancer. In the US, there appears to be a similar prevalence of GERD symptoms among different races, but whites are at a greater risk for erosive esophagitis, Barrett’s esophagus, and adenocarcinoma of the esophagus”.

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

A variety of endoscopic therapies for the treatment of GERD have been developed and proposed as alternatives to pharmacological therapy or anti-reflux surgery. These techniques include the delivery of radiofrequency energy to the gastroesophageal junction, injection of bulking agents, or implantation of a bioprosthesis into the lower esophageal sphincter, implantation of titanium beads with magnetic cores and suture plication of the proximal gastric folds. These therapies are designed to alter structures at the gastroesophageal junction to prevent reflux of gastric contents (Richter and Vaezi, 2021).

Textbook report that randomized controlled trials with follow-up for at least 5 years with meticulous monitoring of these devices. Furthermore, none of the new devices have been compared in randomized studies with the gold standard, Nissen fundoplication (Richter and Vaezi, 2021).

Radiofrequency Energy

Radiofrequency energy for the treatment of GERD requires a special single-use catheter and radiofrequency energy generator (Stretta® System, Respiratory Technology Corporation [Restech], Houston TX).

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

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

Literature Review - Radiofrequency Energy: Improvements in symptoms, quality of life, reduction in PPI use and decreased acid exposure following treatment with radiofrequency energy have been reported in some studies but outcomes are conflicting. Studies have been limited by small patient populations, short-term follow-ups, high dropout rates, loss of data and/or lack of randomization. In some studies, outcomes were measured solely on patient questionnaires. Adverse events including chest pain, dysphagia, and pneumonia have been reported. Larger randomized controlled trials with longer follow-up are needed to better define the risks and benefits of this procedure (He, et al., 2020; Viswanath, et al., 2019; Liang, et al., 2015; Hu, et al., 2015; Yan, et al., 2015; Noar, et al., 2014; Arts, et al., 2012)

Zerbib et al. (2020) conducted a double-blind, sham-controlled multicenter randomized controlled trial to determine the efficacy of esophageal radiofrequency in patients with PPI refractory heartburn. Sixty two patients were randomized into two groups, the esophageal radiofrequency group (n=29) or to the sham group (n=33). Patients aged 18-78 years, with persistent moderate-to-severe heartburn at least three times per week despite continuous PPI therapy, without esophagitis > grade A were included. The primary outcome measured clinical success at week 24 which was defined as an adequate symptom relief together with a PPI intake of less than seven doses over the two preceding weeks. If clinical success was not reached, the patient was defined as therapeutic failure. The secondary endpoints measured clinical success at week 48, number of days without heartburn and digestive symptoms over the two preceding weeks at weeks 24 and 48, PPI consumption and number of patients not taking PPIs during the last two weeks at weeks 24 and 48. The Gastrointestinal Symptoms Rating Scale (GSRS) and Quality of Life in Reflux and Dyspepsia (QOLRAD) scores at weeks 24 and 48, 24-hour pH-impedance parameters associated with clinical success at week 24 and side effects of the procedure were assessed. In the intention-to-treat population, there was no significant difference in patients that achieved clinical success between the esophageal radiofrequency and sham groups, 1/29 (3.4%) and 5/33 (15.2%), respectively (p=0.158). At week 24, esophageal radiofrequency was proposed to the patients who failed to achieve therapeutic success in the esophageal radiofrequency group (n=24) and a first procedure in the sham group (n=19). There was no significant difference in success rates in patients who received a second procedure compared to patients in whom only one procedure was performed (p=0.285). As a whole, among the 49 patients who completed the week 48 visit, 16 were considered to have a therapeutic success, without significant difference between patients who received one and two (p=0.611). Among the five patients who received no procedure, three were lost to follow-up at 48 weeks, one had a therapeutic success and one had a therapeutic failure. No patient had esophagitis at follow-up endoscopy. There was no significant difference between esophageal radiofrequency 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. No pH-impedance parameter was identified as a predictive factor of therapeutic success. Author noted limitations included: difficulty recruiting patients (70 were recruited over a five year period), small patient population, and pH-impedance monitoring off therapy was not performed. Additional limitations include population only included women and the results may not be applicable to other races or ethnic groups. The authors concluded that the study did not demonstrate any efficacy of esophageal radiofrequency for the treatment of PPI-refractory heartburn regarding symptom relief and PPIs consumption. The technique cannot be recommended for the treatment of refractory heartburn.

Fass et al. (2017) conducted a systematic review and meta-analysis to determine the efficacy of Stretta for the treatment of GERD. Inclusion criteria included: studies with at least three months follow-up; study design was a controlled trial or cohort study; and study had sufficient data for at least one of the six selected outcome variables. Primary outcomes were the relief of associated GERD symptoms. Twenty-eight studies (four randomized controlled trials, 23 cohort studies, and one registry) (n=2468) met inclusion criteria and were

included in meta-analysis. Mean follow-up time ranged from 3–120 months (mean 25.4 months). Pooled results (two studies) showed that Stretta significantly improved health-related quality of life scores ($p<0.001$) and pooled heartburn standardized score ($p<0.001$). Stretta significantly reduced the incidence of erosive esophagitis by 24% ($p<0.001$) and esophageal acid exposure ($p<0.001$). Lower esophageal sphincter (LES) basal pressure was increased following Stretta by a mean of 1.73 mmHg, not significant. A total of 49% of patients required continuation of PPI following Stretta vs. 51% who did not ($p<0.001$). Adverse events for Stretta included small erosions and mucosal lacerations. Subcutaneous emphysema was the most frequent adverse event for LF (3%). Limitations of the studies included: heterogeneity of the studies with respect to inclusion criteria, previous surgeries, protocols for the use of antacids, monitoring of PPI use and follow-up time. Heterogeneity was highly significant ($p<0.001$) in all Stretta subgroups. Additional limitations of the studies include the lack of a comparator; small heterogeneous patient populations; and short-term follow-ups.

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

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

In an open-label, prospective trial (n=149), Noar et al. (2014) evaluated the 10-year safety, efficacy, and durability of response to radiofrequency treatment (Stretta) of the lower esophageal sphincter. The primary outcome measure was normalization of GERD-health-related quality of life (GERD-HRQL) in 70% or greater of patients at 10 years. Secondary outcomes were 50% reduction or elimination of proton pump inhibitors (PPIs) and 60% or greater improvement in satisfaction at 10 years. Successful treatment was defined as achievement of secondary outcomes in a minimum of 50% of patients. Subjects had daily recurring symptoms of heartburn and regurgitation despite twice-daily PPI use. Exclusion criteria included: stenosis, stricture or ulceration of the pylorus, pregnancy, poor surgical risk, achalasia, previous non-Nissen fundoplication (NF) esophageal surgery, scleroderma-type collagen vascular disease, or severe uncontrolled medical illness. A total of 72% of patients

achieved the primary outcome, 64% of patients experienced a 50% or greater reduction in PPI use, and 54% of patients reported a 60% or greater increase in satisfaction. Pre-existing Barrett's metaplasia regressed in 85% of biopsied patients (28/33) and 28 had no further dysplasia. Due to dissatisfaction with first procedure results, 11 patients underwent a second Stretta procedure and one underwent a Nissen fundoplication (NF). Reported adverse events included two patients who had self-limited, minor gastric bleeding. Procedure-related side effects included: short-term chest pain, dyspepsia, increased flatulence and abdominal pain. Limitations of the study include: lack of a comparator; no long-term pH and motility data; number of patients lost to follow-up (n=68) from original study (n=217); missing data from the 149 subjects (50 patients did not complete 10-year follow-up questionnaires; 68 patients had not reached ten-year time point); and not all patients had undergone final endoscopic screening.

Perry et al. (2012) conducted a systematic review and meta-analysis of randomized controlled trials and cohort studies to assess the impact of endoscopic application of radiofrequency energy to the lower esophageal sphincter for the treatment of GERD. The studies included in this meta-analysis were two randomized sham-controlled trials and 18 cohort series, 1441 patients, with a mean follow-up of 15 months. Outcomes analyzed included GERD symptom assessment, quality of life, esophageal pH, and esophageal manometry. There were significant improvements reported in heartburn scores (n=525) (p=0.001), and quality of life as measured by GERD–health-related quality-of-life scale (p=0.001) and quality of life in reflux and dyspepsia scores (n=433) (p=0.001). Esophageal acid exposure decreased from a preprocedure Johnson-DeMeester score of 44.4 to 28.5 (n=267) (p=0.007). The authors reported that the meta-analysis is limited by differences in methodology and definition of criteria for some variables between studies, and absence of blindness in most of the included studies. Additionally, the heterogeneity of the study population across these reports may also influence the interpretation of the pooled results. The author's conclusion suggested that radiofrequency ablation produces significant improvement in GERD symptoms, patient satisfaction, and QOL at short and intermediate term follow-up. However, the definition of the appropriate patient populations for Stretta therapy remains controversial. Larger and longer-term studies are required to establish the durability of the treatment effect, and to identify the patient populations that gain the greatest benefit from this treatment.

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

Aziz et al. (2010) conducted a 12-month randomized, double-blind, sham-controlled trial to assess the Stretta procedure. Thirty-six patients with antisecretory medication-dependent GERD for more than six months were randomized to receive a single-session radiofrequency (RF) procedure, a double-session RF procedure for patients who had < 75% improvement of GERD-HRQL at four months, or a sham procedure. Each patient in the active treatment groups received 56 RF lesions per session. With the double-session group, the authors examined whether 112 lesions created in two sessions several months apart were safer than 112 lesions created during a single session, which was the initial "dose" applied during development of the procedure and resulted in esophageal perforation in a few cases. Ten of 12 patients in the double-session group (83%) underwent both sessions. At 12 months, two of 12 patients (17%) in the single-session group, six of 12 patients (50%) in the double-session group, and zero of 12 patients in the sham group had discontinued antisecretory medication therapy. Within group comparisons showed statistically significant improvements in GERD-HRQL in all three treatment groups: In the single-session RF group, GERD-HRQL scores improved from a mean of 30 at baseline off meds to 14 post-treatment; in the double-session RF group, GERD-HRQL scores improved from 31 to 11; and in the sham group, GERD-HRQL scores improved from 30 to 25. Post-treatment values in the active

treatment groups were significantly greater than the sham group ($p<0.001$), but did not differ from each other ($p>0.05$). Lower esophageal sphincter pressure increased in the active treatment groups to a statistically significant degree (from 12 mmHg to 16 mmHg in the single-session group, and from 12 mmHg to 20 mmHg in the double-session group; $p<0.01$ for both groups) but not in the sham group (14 mmHg at baseline to 16 mmHg post-treatment, $p>0.05$). The total time esophageal pH was less than 4.2 in a 24-hour period decreased to a statistically significant degree in the active treatment groups (from 9.4 minutes to 6.7 minutes in the single-session group ($p<0.01$), and from 8.8 minutes to 5.2 minutes in the double-session group ($p<0.01$) but not in the sham group (9.9 minutes at baseline to 8.2 minutes post-treatment [$p>0.05$]). The clinical relevance of these changes is uncertain. Transient post-procedure adverse events (retrosternal discomfort requiring oral analgesics, mild fever, nausea/vomiting, and dysphagia) were experienced by more patients in the active treatment groups than in the sham groups. Serious adverse events occurred in one patient in the single-session group who developed pneumonia and bilateral pleural. Two patients who received double sessions of RF treatment developed prolonged gastroparesis. During 12 months of follow-up evaluation, one of these two patients showed mild improvement, whereas the other showed no improvement despite high doses of prokinetic medication. The authors reported that “worsening gastroparesis may be due to vagal injury during Stretta treatment, especially with a greater number of RF lesions.”

Endoluminal Gastroplasty/Gastroplication
Basic techniques were designed to place sutures or staples at the cardia, including submucosal stitching devices and deep transmural plicating devices. The technique is proposed to create pleats or plications of tissue just beneath the gastroesophageal junction. Sedation and procedure time vary. An examples of suturing/plication devices included the EndoCinch™ or Bard Endoscopic Suturing System (BESS) (Bard Endoscopic Technologies, Billerica, MA); and the Syntheon ARD Plicator (Syntheon, Miami, FL). The EndoCinch is no longer recommended for use and the manufacturer, Bard, has discontinued distribution of the system. The Endoscopic Plicator System is also no longer available (Trad, 2016; Hayes, 2017; updated 2019).

The Medigus Ultrasonic Surgical Endostapler (Muse™) system formerly the SRS™ Endoscopic Stapling System offers anterior partial fundoplication. The device consists of a flexible endoscope, a video microcamera, an ultrasound sensor, and a surgical stapler. The device is used to clamp and staple the stomach to the esophagus (Hayes, 2017; updated 2019).

Endoscopic full-thickness plication was initially performed using the Plicator device (Ethicon Endo-Surgery) which was withdrawn from the market. A new device, called GERDx, uses the same plicator technology and is meant for single use. The device uses hydraulic elements for control and requires a slim gastroscope that works as a light source (Nabi and Reddy, 2019).

U.S. Food and Drug Administration (FDA): The Medigus Ultrasonic Surgical Endostapler, or MUSE™ system, formerly the SRS Endoscopic Stapling System, FDA indications for use state, “intended for endoscopic placement of surgical staples in the soft tissue of the esophagus and stomach in order to create anterior partial fundoplication for treatment of symptomatic chronic Gastro Esophageal Reflux Disease (GERD) in patients who require and respond to pharmacological therapy” (FDA, 2012, 2015a, 2015b).

The GERDx™ has not received FDA approval.

The EndoCinch™ or Bard Endoscopic Suturing System (FDA, 2000b), NDO Surgical Endoscopic Plication System (FDA, 2003), SRS™ Endoscopic Stapling System (FDA, 2012) and StomaphyX™ (FDA, 2007, 2008, 2009) have been approved through the 510(k) premarket notification process. The Syntheon ARD Plicator is not an FDA-approved device.

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

The EsophyX2 System (K092400) and EsophyX2 HD Device (K142113) are FDA “indicated for use in transoral tissue approximation, full thickness plication and ligation in the GI tract and is indicated for the treatment of symptomatic chronic gastroesophageal reflux disease in patients who require and respond to pharmacological

therapy. It is also indicated to narrow the gastroesophageal junction and reduce hiatal hernia < 2cm in size in patients with symptomatic chronic gastroesophageal reflux disease" (FDA, 2009b, 2014).

The EsophyX Z Device with SerosaFuse Fasteners and Accessories and the EsophyX2 HD Device with SerosaFuse Fasteners and Accessories (K171307 & K172811) are FDA "indicated for use in transoral tissue approximation, full thickness plication and ligation in the GI tract and is indicated for the treatment of symptomatic chronic gastroesophageal reflux disease in patients who require and respond to pharmacological therapy. It is also indicated to narrow the gastroesophageal junction and reduce hiatal hernia ≤ 2cm in size with symptomatic chronic gastroesophageal reflux disease. Patients with hiatal hernias larger than 2cm may be included, when a laparoscopic hiatal hernia repair reduces the hernia to 2cm or less" (FDA, 2017a, 2017b).

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

The StomaphyX system with SerosaFuse Fastener (K073644 & K091832) are FDA "intended for tissue approximation, ligation and full-thickness plication in the GI tract" (FDA, 2008, 2009a).

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

Although FDA approved for GERD in April 2003, the FDA issued an Advice for Patients with Enteryx for Gastroesophageal Reflux Disease, stating Boston Scientific has recalled all Enteryx Procedure Kits and Enteryx Single Pack Injectors because of reports that improper injection procedures can lead to serious patient injury or death (FDA, 2005).

Literature Review - Medigus Ultrasonic Surgical Endostapler (Muse™) System: There is a lack of studies in the peer-reviewed literature investigating the safety and efficacy of the Muse System. The studies in the peer-reviewed literature are primarily in the form of case series with small patient populations (n=14–66). Randomized controlled trials with long term follow-up are needed to determine whether the Muse System improves outcomes compared to alternative treatment modalities (Testoni, et al., 2020; Kim, et al., 2016; Roy-Shapira, et al., 2015; Zacherl, et al., 2014; Danalioglu, et al., 2014).

Literature Review - GERDx™: Kalapala et al. (2021) conducted a single-center, sham randomized controlled trial at the Asian Institute of Gastroenterology (India) to determine the efficacy and safety of an endoscopic full-thickness fundoplication (EFTP) device (GERD-X) in patients with PPI-dependent GERD. The study included patients aged 18–60 on PPI therapy for the last six months with the following: a gastroesophageal flap valve grade I–III (Hill's classification); pathological esophageal acid exposure, abnormal DeMeester score ≥ 14.7 or total reflux episodes > 73; and lower esophageal sphincter pressure (LESP) between 5–15 mm Hg. Seventy patients were randomized to the GERD-X treatment group (n=35) or the sham group (n=35). All patients underwent the EFTP or sham under general anesthesia and endotracheal intubation after overnight fasting. The median (IQR) age was 36 (29–42) years, with 71.4% males. The primary measured outcome was a ≥ 50% improvement in the health-related quality of life (GERD-HRQL) score at three months. Secondary outcome measurements included improvement in GERD-HRQL, reflux symptom scores, PPI usage, esophageal acid exposure and reflux episodes and endoscopic findings at three, six and 12 months. In patients who resumed taking PPIs after the assigned intervention, these assessments were made after stopping PPI therapy for at least three days. A statistically significant improvement in the GERD-HRQL total score at three months post intervention was achieved by the treatment group ($p<0.001$), thus meeting the primary endpoint of the study. There was not a significant difference noted between males and females. The GERD-HRQL total score, the median percentage improvement in the heartburn symptom score and the regurgitation symptom score were significantly higher in the EFTP group compared to the sham group at three, six and 12 months (all $p<0.001$). At 12 months post intervention, a significantly higher proportion of patients in the EFTP group compared to the sham group, had elimination of heartburn and regurgitation ($p<0.001$ and $p<0.001$, respectively). The EGD evaluation conducted on the EFTP group at three, six and 12 months showed Hill's grade 1 in 100%, 91.5% and 77.8%, respectively. The sham group endoscopic Hill's grade did not change from baseline. Mucosal wrap and suture were intact in all patients at 12 months. There was no symptomatic dysphagia nor endoscopic evidence of luminal narrowing at the GE junction. At 12 months, endoscopy showed no esophagitis in the EFTP group (n=18)

and 29.4% (5/17) of the sham group had grade A esophagitis. No major procedure-related adverse events were encountered in either group. Author noted limitations included a small patient population, study was conducted at a single center, initial screening and enrollment of PPI-dependent patients were based on historical details and PPI dependency was not confirmed objectively. Lastly, the reflux was not assessed objectively at the end of 12-month follow-up in all patients. An additional limitation is that the population only included patients at the Asian Institute of Gastroenterology (India) and the results may not be applicable to other races or ethnic groups. The authors concluded that this endoluminal procedure is a promising alternative option to surgery in However, large, prospective trials with long-term follow-up are required to conclude the benefits of this procedure after one year. No health disparities were identified by the investigators.

Weitzendorfer et al. (2018) conducted a prospective one-arm trial that assessed the clinical safety and efficiency of the GERDx™ device by evaluating clinical parameters, reflux symptom scores, and quality of life (QoL). The study included patients (n=40) with at least one typical reflux symptom despite treatment with a PPI for > 6 months, pathologic esophageal acid exposure, hiatal hernia of size < 2 cm, and endoscopic Hill grade II–III. Outcomes measured Evaluation of Gastrointestinal Quality of Life Index (GIQLI), symptom scores, esophageal manometry, and impedance-pH-monitoring which were performed at baseline and at three months after surgery. The authors noted no intraoperative complications, however four out of forty patients experienced postoperative complications requiring intervention. Seven of forty patients were subjected to laparoscopic fundoplication three months after endoscopic plication due to persistent symptoms and were lost to further follow-up. Thirty patients were available at the three month follow-up. There was significant improvements in the GIQLI score, general reflux-specific score, and DeMeester score ($p<0.001$). There was no significant change in manometric data after intervention. Three of thirty patients continued daily antireflux medication. The authors concluded that in well selected patients endoscopic full-thickness plication using the GERDx™ device improves the distal acid exposure of the esophagus, typical reflux-related symptoms and QoL. However, randomized controlled trials with long term follow-up are necessary to compare the outcome of patients treated with PPIs and patients undergoing endoscopic plication with the GERDx™ device.

There is insufficient evidence in the published peer-reviewed scientific literature to support the safety and efficacy of GERDx™ device for the treatment of GERD.

Literature Review - EndoCinch Suturing System: Comparative studies with EndoCinch have failed to show an improvement in acid exposure time when compared to sham. The studies report that there is a high rate of loss of intact sutures at follow-up. Large, well-designed, controlled trials showing long-term safety and efficacy outcomes are lacking. According to Hayes (2017, updated 2019) the EndoCinch has been discontinued.

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

Montgomery et al. (2006) reported data from 46 patients enrolled in a single-center, randomized, sham-controlled trial of EndoCinch plications. There was no difference in the use of PPIs between the sham and the EndoCinch groups at six weeks or 12 months, whereas at three months, there was a significant reduction in the use of PPIs in the treatment group compared to controls ($p<0.05$). Compared to baseline, there was a significant improvement in QOL as assessed by the gastrointestinal symptom rating scale (GSRS) at six weeks, as well as at three and 12 months post-procedure in both groups. At three months (but not at six weeks and 12 months), there was a significant difference in GSRS scores between the groups, favoring the treatment group versus the

control group. Similarly to the sham group, the EndoCinch treatment group had no significant changes in esophageal acid exposure, as indicated by pH monitoring at three and 12 months, in any of the groups. Also noted was a marked loss of sutures, with 67% remaining at 12 months.

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

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

Literature Review - Endoscopic Plication™ System: Studies in the peer-reviewed literature investigating endoscopic plication systems are primarily in the form of case series. Large, well-designed, controlled trials showing long-term safety and efficacy are lacking. The website www.clinicaltrials.gov states that several studies with the NDO Plicator have been terminated, since the sponsoring company (NDO Surgical, Inc.) has ceased business operations.

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

In a multicenter prospective, open-label, postmarket registry study, Birk et al. (2009) assessed full-thickness fundoplication using the Plicator for the treatment of GERD. The study included 131 patients variably responsive to PPI therapy. At 12 months, 50 patients (38%) were lost to follow-up or had not yet reached their 12-month follow-up visit. Sixty-six percent of the remaining 81 patients demonstrated a 50% reduction in their GERD-Health Related Quality of Life (GERD HRQoL) score compared to their pre-fundoplication (off meds) score. No serious adverse events were reported. The lack of a control or comparison group limits the use of these findings.

The safety and efficacy of the Plicator procedure was studied in a prospective multicenter trial and evaluated in four subsequent reports with follow-up of 6, 12, 36 and 60 months, respectively (Pleskow, et al., 2004; Pleskow, et al., 2005; Pleskow, et al., 2007; Pleskow, et al., 2008). Sixty-four patients initially underwent plication to assess the safety and efficacy of endoscopic full-thickness plication. At six months after plication, PPI therapy had been eliminated in 74% of previously medication-dependent patients. Twenty-nine patients completed the 12-month and 36-month follow-up. All procedure-related adverse events occurred acutely, and no new events were observed during extended follow-up. At 36-months post-procedure, 57% of baseline PPI-dependent patients remained off daily PPI therapy. Treatment effect remained stable from 12–36 months, with 21/29

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

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

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

Transoral Incisionless Fundoplication (EsophyX System)
The Esophy®X device (EndoGastric Solutions, Inc., Redmond, WA) creates a transoral incisionless fundoplication® (TIF). The system deploys multiple full thickness serosa-to-serosa fasteners into the gastric wall to form an interrupted suture line at the base of the gastroesophageal junction, thus recreating the gastroesophageal valve (GEV) mechanically. This is sometimes referred to as the endoluminal fundoplication (ELF) technique. The predicate device to the EsophyX system is the StomaphyX™ (EndoGastric Solutions, Inc., Redmond, WA). There are two models of EsophyX devices – EsophyX$_2$ HD and ExophyX Z. Earlier studies used the TIF 1.0 protocol which involved gastro-gastric plications below the gastroesophageal junction and 220 degree of circumference of the re-established valve compared to the current TIF 2.0 protocol which involves esophago-gastric plications above the Z-line and 240 degree circumference.

U.S. Food and Drug Administration (FDA): The EsophyX System (FDA, 2007), EsophyX2™ System (FDA, 2009b) are also FDA 510(k) Class II approved. The EndoGastric Solutions (EGS) EsophyX™ System with SerosaFuse Fastener is "indicated for use in endoluminal, transoral tissue approximation, full thickness plication and ligation in the GI tract and is indicated for the treatment of symptomatic chronic gastroesophageal reflux disease in patients who require and respond to pharmacological therapy. It is also indicated to narrow the gastroesophageal junction and reduce hiatal hernia < 2cm in size in patients with symptomatic chronic gastroesophageal reflux disease" (FDA, 2007). The EsophyX2 HD with SerosaFuse Fasteners and Accessories was approved in 2014. The EndoGastric Solutions EsophyX Device models (EsophyX2 HD and EsophyX Z were 510(k) approved in 2017 for the same indications as the initial device, with one additional statement "patients with hiatal hernias larger than 2 cm may be included, when a laparoscopic hiatal hernia repair reduces the hernia to 2cm or less" (FDA, 2017a, 2017b).

Literature Review - Transoral Incisionless Fundoplication (EsophyX System): Evidence in the published, peer-reviewed scientific literature on the efficacy of transoral incisionless fundoplication (TIF) using the EsophyX system largely consists of case series with small patient populations (n=10–151). While these case series report improvements in outcomes following treatment with EsophyX, the lack of control group precludes the ability to generalize findings and draw strong conclusions regarding the impact on health outcomes (Testoni, et al., 2019; Bell, et al., 2014; Wilson, et al., 2014; Muls, et al., 2013; Trad, et al., 2012; Narsule, et al., 2012; Testoni, et al., 2012; Frazzoni, et al., 2011; Bell, et al., 2011). Randomized controlled trials are needed to determine whether EsophyX improves outcomes compared to the standard of care which is open or laparoscopic Nissen fundoplication.

Bell et al. (2021) conducted a single institution prospective registry that assessed the long term results of transoral incisionless fundoplication (TIF 2). Included patients were age 18 years and older with objective documentation of GERD. Patients (n=151) underwent TIF 2 with the EsophyX2 without hiatal hernia repair. Outcomes measured: GERD-HRQL and regurgitation scores, use of PPI, perioperative complications, and need for re-intervention. At a median of 4.92 years (0.7–9.7 years), 131 of the 151 patients (86%) were available for follow-up. Five years or greater follow-up was obtained on 51% (62) of the 120 total patients. The median GERD-HRQL scores significantly decreased from 21 off PPI and 14 on PPI at baseline to four at 4.92 years and five at 5–9 years post-TIF. The authors reported that (> 50%) reductions in GERD-HRQL scores were seen in 64% at 4.92 years and 68% of patients followed for ≥ 5years. Median regurgitation decreased from 15 off PPI and 11 on PPI at baseline to 0 at 4.92 years and one at 5–9 years post-TIF. Dysphagia and abdominal bloating/distention assessed by GERD-HRQL significantly decreased from baseline to a median of 0 and one respectively at 4.92 years' follow-up ($p<0.0001$). Adverse events reported that two patients experienced localized perforation and recovered uneventfully after laparoscopic surgery. Thirty-three patients (22%) required revision to laparoscopic fundoplication. Long-term quality of life outcomes were equivalent when compared to those patients who did not undergo reoperation. Author noted limitations included: incomplete follow-up on all patients (however a mixed effect model was used to analyze the data to address the potential selective dropout) and the lack of long-term objective outcome data, specifically with regard to esophageal acid exposure. Additional limitations include the small patient population and lack of a comparator. No health disparities were identified by the investigators.

Testoni et al. (2019) conducted a prospective observational study that assessed the long-term clinical efficacy of transoral incisionless fundoplication (TIF 2) with EsophyX for gastroesophageal reflux disease. Patients (n=50)

received TIF 2 with EsophyX with follow-ups occurring at two, three, five, seven and 10 years. There were 35/50 males and 15/50 females enrolled in the study. Included patients had pathological gastroesophageal reflux (GER) with a positive correlation between symptoms and GER, documented by 24-hour pH-impedance. Primary outcomes measured clinical efficacy using Health-Related Quality-of-Life (GERD-HRQL), Gastroesophageal Reflux Disease Quality-of-Life (GERDQUAL), heartburn and regurgitation scores and daily PPI consumption. Outcomes were measured using telephone interview or office consultation. The TIF 2.0 was successful in 49/50 patients. One patient had a pneumothorax and the other case was due to a device malfunction. The latter procedure was repeated with success for a total of 51 TIF procedures were performed in 50 patients. Forty-nine patients were available for follow-up at two and three years, 41 after five years, 30 after seven years and 14 after 10 years. Seven patients were unresponsive to endoscopic fundoplication and underwent surgical fundoplication. The mean scores at two years were significantly lower than before the procedure and did not change substantially during the follow-up. Patients who had stopped or halved antisecretive therapy at two, three, five, seven and 10 years after the procedure were 86.7%, 84.4%, 73.5%, 83.3%, and 91.7%, respectively. Pneumothorax occurred in two of the 51 procedures (3.9%). Author noted limitations included the small patient population clinically assessed at seven and 10 years and there were not any endoscopic and functional evaluations performed. An additional limitation included the lack of a comparator and the disproportionate amount of females included in the study. The results may not be applicable to other sexes, races or ethnic groups.

Janu et al. (2019) examined the safety and efficacy of laparoscopic hiatal hernia repair followed by transoral incisionless fundoplication with the EsophyX device. Data was prospectively collected from patients (n=99) who underwent hiatal hernia repair immediately followed by the TIF procedure (HH + -TIF) at two community hospital settings in Indiana and Wisconsin. Patients aged 18 to 75 years with moderate to severe typical or atypical GERD symptoms for > 1 year, a hiatal hernia between 2 and 5 cm on endoscopy and ongoing daily PPI use for more than six months with either complete or partial symptom control were included in the study. Three validated questionnaires, GERD Health-Related Quality of Life Questionnaire (GERD-HRQL), Gastroesophageal Reflux Symptom Score (GERSS) and laryngopharyngeal reflux (LPR) questionnaire Reflux Symptom Index (RSI) were administered before the procedure and mailed at six and 12 months post-procedure. The questionnaire response rate was 73% at 6 months, 67% at 12 months, and 48%. The average age of subjects was approximately 53 years and 55% of subjects were female. All measures were statistically improved ($p<0.05$) at 12 months. There were no adverse effects reported. Author noted limitations included short-term follow-up, objective evidence of GERD preoperatively and lack of objective outcomes data. Objective longer-term studies with post-procedure testing with either pH testing, endoscopy, or esophagram is needed. No health disparities were identified by the investigators.

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

- LNF was statistically superior to TIF in percent time pH was < 4 and had the highest probability of being the best treatment for improvement in percent time spent in pH < 4 (SUCRA, 0.99), PPI (SUCRA, 0.64), TIF (SUCRA, 0.32), and sham (SUCRA, 0.05).
- LNF was superior to TIF in increasing esophageal sphincter pressure (LESP), but the difference was not significant. LNF had the highest probability of being the best treatment for improvement in LESP (SUCRA, 0.78), followed by TIF (SUCRA, 0.72) and PPI (SUCRA, 0.01).

- TIF was superior to LNF in improved health-related quality of life (HRQOL), but the difference was not significant. TIF had the highest probability of being the best treatment for improvement in HRQOL (SUCRA, 0.96), followed by LNF (SUCRA, 0.66), sham (SUCRA, 0.35), and PPI (SUCRA, 0.042).
- LNF was superior to TIF re incidence of persistent esophagitis, but the difference was not significant. PPI had the lowest probability of being the treatment associated with persistent esophagitis (SUCRA, 0.19), followed by LNF (SUCRA, 0.38), TIF (SUCRA, 0.68), and sham.

Data on harm was not consistently reported and meta-analysis could not be done. The results showed that LNF fundoplication had the highest ability to improve physiologic parameters associated with GERD, including LES pressure and decreasing the percentage of time that the pH < 4. PPIs were superior for reducing esophagitis, possibly due to dose escalation if symptoms persisted. TIF had the highest probability of symptom improvement based on HRQOL likely related to shorter follow-up time compared to LNF or PPIs. Author-noted limitations of this analysis included: lack of data on individual patients, difference in follow-up time and number of subjects (n=875 LNF; n=293, TIF); and moderate to low quality of the included studies. The authors concluded that endoscopic therapy cannot be recommended as an alternative to medical or traditional surgical treatment of GERD.

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

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

term follow-ups, and inclusion of first- and second-generation devices (EsophyX/EsophyX2), as well as heterogeneity by the use of TIF 1.0 and TIF 2.0 protocols. Randomized controlled trials with large patient populations and long-term follow-up are needed to valid the effectiveness of ESOPHX.

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

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

Trad et al. (2017) reported on three-year follow-up data for 52 patients who underwent transoral esphagogastric fundoplication (TF) using the EsophyX device. The initial randomized controlled trial (TEMPO) (n=63) (Trad, et al., 2015) was conducted to assess the safety and efficacy of transoral esphagogastric fundoplication (TF) using the EsophyX device (n-40) vs. high dose proton pump inhibitors (PPI) (n=23). Included patients were ≥ age 18 years, had no hiatal hernia or hiatal hernia < 2 cm, had troublesome GERD symptoms while on proton pump inhibitors (PPI) for at least six month and had abnormal esophageal acid exposure (EAE). Abnormal EAE was defined as pH < 4 for more than 5.3% of total recorded time using 48-h Bravo pH testing. After the six-month evaluation period, the remaining 21 PPI patients elected to crossover to TF. Two patients were included in analysis that had undergone revisional procedures. Outcomes included: GERD symptom resolution using three GERD specific quality of life questionnaires; healing of esophagitis using endoscopy; EAE using 48-h Bravo testing; and discontinuation of PPI use. At the three-year follow-up (n=52), 90% (37/41) of patients reported elimination of troublesome regurgitation, 88% (42/28) patients reported elimination of all atypical symptoms. The mean Reflux Symptom Index score improved from 22.2 on PPIs at screening to 4.0 off of PPIs following TF ($p=0.0001$). The mean total time pH < 4 was improved significantly from 10.5% to 7.8% ($p=0.0283$). Esophagitis was healed in 86% (19/22) of patients and 71% (37/52) of patients had discontinued PPI therapy. Limitations of the study include: the small patient population; short-term follow-up; potential of bias due to the open-label

crossover study design; and 11 patients lost to follow up (17%). According to the authors this 3-year report represents the longest follow-up on the TF procedure performed with the EsophyX device in the US to date.

Huang et al. (2016) conducted a systematic review and meta-analysis to evaluate the safety and efficacy of transoral incisionless fundoplication (TIF) performed with the EsophyX device for the treatment of GERD. A total of 18 studies (n=963) (five randomized controlled trials [RCTs] and 13 prospective observational studies) met inclusion criteria. The study subjects had GERD requiring PPIs and TIF with/without PPIs and primarily had hiatal hernias less than 2–3 cm and BMI < 30 or 35 kg/m^2. The average follow-up duration was more than three months. Outcomes included: esophageal acid exposure time (% time pH< 4); 24-hour total number of refluxes; 24-hour acid reflux episodes; number of patients with complete discontinuation or reduction in proton pump inhibitors (PPIs) usage; overall response rate to TIF; and patient satisfaction. Responsiveness to TIF was defined as an improvement of at least 50% in the GERD health related quality of life (GERD-HRQL) scores or remission of heartburn and regurgitation; and/or complete cessation of PPIs use. The pooled relative risk of response rate (n=4 RCTs) to TIF versus PPIs/sham was 2.44 (95 % CI 1.25–4.79; p=0.0009) in RCTs in the intention-to-treat analysis. Analysis of five RCTs showed no significant difference in percent of acid exposure (p=0.85). Subanalysis of two studies that compared TIF to sham without PPIs, showed a significant improvement following TIF in acid exposure (p=0.02). Analysis of three RCTs (n=73) evaluated the total reflux episodes before and after TIF procedure showing a significant reduction in reflux episode following TIF (p<0.00001). Two RCTs (n=71) reported no significant improvement in acid reflux episodes following TIF vs. PPIs (n=0.16). The effects of TIF decreased over time and PPIs usage led to dependence and increased dosage. Patient satisfaction from ten observational studies ranged from 45%–86% (weighted average 69.15%) at a mean six months. Severe adverse events included: seven perforations, five cases of post-TIF bleeding, and four cases of pneumothorax. One death was reported 20 months after TIF. The authors noted that there was a high degree of heterogeneity of the studies and data analysis was hampered by a lack of standardization in primary and secondary outcomes. Additional limitations of the studies included: variation in exclusion criteria and TIF technique; short-term follow-ups (range 3–36 months); and the small sample sizes used in outcome analysis.

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

number lost to follow-up (19%) (11/87 in study group and 14/42 in sham group); unequal number of patients in each group; and incomplete follow-up data on 12 patients.

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

Trad et al. (2015) conducted a multicenter randomized controlled trial to evaluate the efficacy of transoral incisionless fundoplication (TIF) using EsophyX_2 (n=40) compared to proton pump inhibitors (PPIs) (n=23) for the treatment of GERD. Patients met the following criteria: age 18–80 years; GERD for > 1 year; > 6-month history of PPI use; troublesome atypical symptoms and/or regurgitation, with or without heartburn, while on daily PPI therapy; abnormal esophageal acid exposure (EAE); and Hill grade I or II. Abnormal EAE was defined as pH <◦4 for more than 5.3 % of total recorded time using 48-h Bravo pH testing). Patients were excluded if they had a body mass index (BMI) > 35 kg/m^2; hiatal hernia > 2 cm in axial length and/or > 2 cm in greatest transverse dimensions, esophagitis grade C or D; Barrett's esophagus > 2 cm; esophageal ulcer; fixed esophageal stricture or narrowing. Primary outcome was elimination of daily troublesome regurgitation or extraesophageal symptoms. Secondary outcomes were normalization of esophageal acid exposure (EAE), PPI usage and healing of esophagitis. Symptom assessment was conducted by using Gastroesophageal Health-Related Quality of Life (GERD-HRQL), Reflux Symptom Index (RSI), and the Reflux Disease Questionnaire (RDQ). At six-month's follow-up, per the RDQ questionnaire 97% of TIF patients vs. 50% of PPI patients had elimination of troublesome regurgitation (p<0.001). Overall, 62% of TIF patients vs. 5% of PPI patients experienced elimination of regurgitation and extraesophageal symptoms (p<0.001). EAE was normalized in 54% of TIF patients (off PPIs) vs. 52% of PPI patients on maximum standard dose (p=0.914). Ninety percent of TIF patients were completely off PPIs, 3% were taking PPIs on demand and 8% were on daily PPIs. Endoscopic exam showed complete healing or reduction in reflux esophagitis in 90% of TIF patients compared to 38% PPI patients (p=0.018). In addition, 90% (28/31) of TIF patients (off PPIs) reported elimination of daily troublesome heartburn vs. 13% (2/16) PPI patients (p=0.003). Patient satisfaction with current health condition, as evaluated by GERD-HRQL, improved significantly in the TIF group compared to PPI group (p<0.001). No serious adverse events were reported following TIF. Limitations of the study include: heterogeneous small patient population, short-term follow-up, variety of PPIs used; and 2:1 randomization (TF:PPI). The authors noted that there could have been a potential placebo effect in the TIF group and stated that long-term follow-up was needed.

Witteman et al. (2015) conducted a randomized controlled trial (n=60) to evaluate TIF in patients with GERD who were controlled with PPI but chose TIF over lifelong PPI therapy. Patients remained with PPI (n=20) or underwent TIF (n=40) with EsophyX. Criteria for study participation included: age 18–75 years, hiatal hernia ≤◦2 cm, proven reflux while off PPIs, on daily PPIs for ≥ 1 year, recurrence of GERD symptoms after cessation of PPIs, and normal or reduced lower esophageal sphincter resting pressure (5–40 mm Hg) at manometry. Patients

with body mass index ≥ 35 kg/m^2 and hiatal hernia > 2 cm, esophagitis grade D, Barrett's esophagus and other comorbidities were excluded. At the six-month following-up (n=57) there was a significant improvement in quality-of-life scores in the TIF group (p<0.001) and an increase in lower esophageal sphincter resting pressure (p=0.004). There were no significant differences between the two groups in esophageal acid exposure time (p=0.228), normalization of pH, total number of reflux episodes at impedance measurements (p=0.058) or healing of esophagitis. Following TIF, cessation of PPIs occurred in 74% of patients, 17% used PPIs occasionally and 9% used PPIs daily at six months. At the end of six months the 20 PPI patients crossed over to TIF. Twelve months (n=45) following crossover, quality of life (p<0.05), number of reflux episodes and the increase of lower esophageal sphincter pressure showed a significant improvement compared to baseline. There was no significant improvement in distal esophageal acid exposure (p=0.06). Normalization of pH was accomplished in 44% of TIF patients at six months but dropped to 29% at 12 months. The use of PPIs was discontinued by 39% of patients with 44% needing PPIs on a daily basis at 12 months. At 12-months follow-up, 5% of patients had undergone revisional surgery to control their symptoms. TIF adverse events included an incident of pneumoperitoneum, three cases of pneumonia and a readmission for severe epigastric pain. Milder adverse events (dysphagia and gas bloating) resolved within a short period of time. Limitations of the study include the small patient population; 2:1 randomization; short-term follow-up and number of patients lost to follow-up.

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

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

In a randomized controlled trial, Svoboda et al. (2011) evaluated the safety and efficacy of Natural Orifice Transluminal Surgery (NOTES) TIF procedures. Patients indicated for surgery of GERD were randomly assigned (ratio 2:1) to TIF n=34 and control group, where gold standard Nissen laparoscopic fundoplication (NLF) was performed (NLF group, n=18). For TIF the Plicator® method was initially used for 18 patients, but the company

terminated production in 2008 without a follower. During the last two years the EsophyX® method was used for 16 patients. After the evaluation of 34 TIF patients and 18 NLF patients, similar efficacy of TIF procedures compared with NLF after three and 12 months. The hospital stay was significantly shorter ($p<0.0001$) in TIF group (average, 2.9±0.8 days) than in NLF group (6.4±0.7). There was one serious adverse event in the TIF group and three in the NLF group. The limitations of this study are the small sample size and lack of long-term follow-up.

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

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

- Expandable hydrogel prosthesis (Gatekeeper™ Reflux Repair System; Medtronic, Inc., Minneapolis, MN): It has been reported that the device was withdrawn in late 2005 before U.S. Food and Drug Administration (FDA) approval. A European sham-controlled single-blind multicenter study randomized 118 patients into Gatekeeper or sham treatment. The study was terminated early due to a lack of efficacy (Fockens, et al., 2010).
- Ethylene vinyl alcohol copolymer with tantalum dissolved in dimethyl sulfoxide (Enteryx™; Boston Scientific Corp, Natick, MA).
- Plexiglas polymethylmethacrylate microspheres (PMMA).
- Pyrolytic carbon-coated graphite beads suspended in a water-based carrier gel suitable for suspending the carbon-coated beads (Durasphere™, Carbon Medical Technologies, St Paul, MN). Durasphere is an injectable bulking agent that is being proposed in the treatment of mild-moderate GERD. A small nonrandomized study (n=10) was conducted by Ganz et al. (2009). This study is the first report of Durasphere for the treatment of GERD. On the basis of the findings and limitations of this study, further investigation of this agent is warranted including large controlled studies with long-term outcomes.

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

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

Magnetic Sphincter Augmentation
LINX™ Reflux Management System (Johnson & Johnson, Inc; St Paul, MN): The LINX Reflux Management System is an implant that consists of a small flexible band of interlinked titanium beads with magnetic cores. The magnetic attraction is proposed to help the lower esophageal sphincter (LES) resist opening to gastric pressures, preventing reflux from the stomach into the esophagus. A surgeon uses a laparoscopic incision to implant the device around the patient’s esophagus just above the stomach while the patient is under general anesthesia.

U.S. Food and Drug Administration (FDA): Torax Medical, Inc; obtained FDA Premarket Approval (PMA) in March 2012 to market the LINX Reflux Management System. According to documents submitted to FDA, the device "is intended for people diagnosed with gastroesophageal reflux disease who continue to have chronic symptoms, despite the use of maximum medical therapy for the treatment of reflux" (FDA, 2012). Johnson & Johnson acquired Torax Medical in 2017.

Literature Review - Magnetic Sphincter Augmentation Device (MSDA) (LINX™ Reflux Management System): Overall, studies in the peer-reviewed literature are primarily in the form of systematic reviews with meta-analysis, case series and retrospective reviews. Large, well-designed, controlled trials showing long-term safety and efficacy are lacking (Skubleny, et al., 2017; Schwameis, et al., 2014; Ganz, et al., 2013; Lipham, et al., 2012).

Bonavina et al (2020) reported the three year outcomes for magnetic sphincter augmentation (MSA) and laparoscopic fundoplication (LF) in patients with gastroesophageal reflux disease (GERD). Twenty-two medical centers in four countries (Austria, Germany, Italy, and the United Kingdom) enrolled patients (n=631; 465 MSA and 166 LF) for a prospective, multi-center, observational registry study who were candidates for a surgical anti-reflux procedure. Included patients had a confirmed diagnosis of GERD confirmed and chronic reflux symptoms despite the daily use of medical therapy with PPIs. The type of anti-reflux procedure performed (MSA or LF [Nissen, Toupet or Other/Unspecified]) was determined by the surgeon and patient. If a patient met the labeling requirements for MSA (hiatal hernia ≤ 3 cm, esophagitis less than Grade C, absence of Barrett's esophagus, absence of motility disorders), MSA was recommended. Measured outcomes included clinical effectiveness and Health Related Quality of Life (GERD-HRQL), duration of surgery, length of stay, complications, and healthcare resource use. Baseline characteristics that were statistically significantly different between patients with MSA vs. LF (all p<0.0001) were patient age (LF 56.3 years vs. MSA 46.6 years), BMI (LF 27.8 vs MSA 25.7), frequency of large hiatal hernias (LF 48.1% vs. MSA 1.4%) and the presence of Barrett's esophagus at the time of surgery (LF 12.7% vs MSA 1.7%). Also, a greater proportion of patients with MSA had no esophagitis (p=0.0130). Both MSA and LF resulted in substantial improvements in quality of life and satisfaction over study period. Both groups experienced a decrease in PPI usage and appear to be able to belch as needed. MSA allowed a higher percentage of patients the ability to vomit as needed with 91.2% of patients noting the ability to vomit at 36 months compared to 68% of the LF patients. The mean procedure time was shorter (43.2 min) for MSA compared to LF (79.7 min). Complications and outpatient clinic visits similar between groups. The surgical intervention rate for the MSA group at 3 years was 2.4% (11/459) and the LF group was 1.9% (3/157). Limitations noted by the authors included: the outcomes are not generalizable to all settings of care, implantation of MSA is only available in select centers, the LF group had different procedures performed and the non-randomized study design was not intended to detect statistically significant clinical outcomes between MSA and LF. No health disparities were identified by the investigators.

Bell et al. (2019) conducted a randomized, controlled, prospective, double-arm, crossover study to compare the effectiveness of increased proton-pump inhibitor (PPI) dosing to laparoscopic magnetic sphincter augmentation (MSA). One hundred fifty-two patients with GERD, aged ≥ 21 years with moderate-to-severe regurgitation despite eight weeks of once-daily PPI therapy, were prospectively enrolled at 21 U.S. sites. Participants were randomized 2:1 to treatment with twice-daily (BID) PPIs (n=102) or to laparoscopic MSA (n=50) using the LINX system. The primary outcome measured the percent of patients in both treatment arms who achieved elimination of moderate-to-severe regurgitation at six months, as reported on the Foregut Symptom Questionnaire (FSQ). The secondary outcomes measured the following at six months: (1) changes in baseline scores (while on PPIs) in the GERD–Health-Related Quality of Life (GERD-HRQL) questionnaire, the Reflux Disease Questionnaire (RDQ), and the percentage of patients achieving ≥ 50% decrease in GERD-HRQL score from baseline; (2) differences between treatment arms at six months in esophageal reflux parameters (number of reflux episodes and percentage of time with pH < 4); and (3) PPI use. Three participants withdrew before undergoing the MSA procedure, and one participant failed to start BID PPI therapy, which made up the analysis population for the primary efficacy endpoint (n=101/PPI group; n=47/MSA group). All other analyses were performed with data available at the follow-up visit. Intention-to-treat (ITT) was also performed. At the six month follow-up, 89% of patients treated with MSA reported clinically significant relief of regurgitation compared to 10% of the patients in the BID PPI group (p<0.001). Eighty-one percent of patients with MSA had significant improvement in GERD-HRQL scores (≥ 50%) versus 8% of patients with BID PPI (p<0.001), and 91% remained off of PPI therapy. At six months, a normal number of reflux episodes was clinically significant in 91% of MSA patients compared to

58% of BID PPI patients (p<0.001). Acid exposure did not reach clinical significance (p=0.065). No significant safety issues were observed. Author noted limitations included: the subjective nature of using patient reported questionnaires for outcome measurement, although impedance-pH testing added some objective measure of the control of reflux. Also, there was potential referral bias as recruitment began with patients presenting to a surgical clinic. Another reported limitation could be the use of 20 mg omeprazole BID as the control treatment, given that 40 mg BID PPI is commonly considered for refractory GERD symptoms.

After six months of PPI therapy, MSA was offered to patients with persistent moderate to severe regurgitation and excess reflux episodes during impedance or pH testing on medication. In a separate publication, Bell et al. (2020) reported the outcomes for the crossover portion of the randomized controlled trial. Thirty-one patients met the crossover requirements and were included in the analysis as the MSA crossover arm (n=75). Forty-three patients did not qualify for crossover and were placed on a reduced dose of 20-mg omeprazole daily (the step down PPI cohort). Regurgitation, foregut scores, esophageal acid exposure, and adverse events were evaluated at one year. Patients were assessed by the quality of life metrics and underwent esophagogastroduodenoscopy with telemetry capsule esophageal pH monitoring. Assessments were performed in the MSA patients off PPIs (if being taken) for seven days, and on once-daily PPI in the step-down PPI cohort. Any other GERD medications were stopped seven days before testing, with the exception of antacids which were allowed until the morning of assessment. At study completion, resolution of regurgitation was seen in 96% of MSA patients and in 19% of the PPI group. Among the patients who received MSA, 81% had improvements in GERD health-related quality of life improvement scores (greater than 50%) and 91% discontinued daily PPI use. There was no improvement in these parameters in the PPI group. Proportions of patients with dysphagia significantly decreased from 15% to 7% (p<0.005), bloating decreased from 55% to 25%, and esophageal acid exposure time significantly decreased from 10.7% to 1.3% (p<0.001) from study entry to one year after MSA. Seventy percent of all patients had pH normalization at study completion. MSA was not associated with any peri-operative events, device explants, erosions, or migrations. Author noted limitations included the limited duration of follow-up and use of different pH testing methods at the six and 12 month follow-ups.

Guidozzi et al. (2019) conducted a systematic review and meta-analysis to compare the magnetic sphincter augmentation (MSA) to laparoscopic fundoplication for the treatment of GERD. Six cohort studies (n=1099/patients) that directly compared magnetic sphincter augmentation to fundoplication (n=632/MSA and n=467/fundoplication. Thirteen single-cohort studies (n=11,598/patients) were included that evaluated clinical outcomes from magnetic sphincter augmentation. The primary outcome measured the postoperative requirement for PPI therapy. Secondary outcomes measured the postoperative GERD-health-related quality of life (GERD-HRQOL) score, gas bloating, ability to belch, dysphagia, and the need for reoperation. Outcomes were measured using a random-effects meta-analysis. Following MSA, 13.2% required post-operative PPI, 7.8% dilatation, 3.3% device removal or reoperation, and esophageal erosion was seen in 0.3%. There was no significant differences between the groups in postoperative PPI therapy, GERD-HRQOL score, dysphagia and reoperation. However, when compared to fundoplication, MSA was associated with significantly less gas bloating and a greater ability to belch. The authors concluded that magnetic sphincter augmentation achieves good GERD symptom control similar to that of fundoplication, with the benefit of less gas bloating. The safety of MSA appears acceptable with only 3.3% of patients requiring device removal. Author noted limitations included the potential underreporting of complications associated with device implantation, small patient population and limited follow-up. Well-designed multicenter randomized controlled trials are needed to fully evaluate the effectiveness of MSA in comparison to laparoscopic fundoplication.

Aiolfi et al. (2018) conducted a systematic review and meta-analysis to compare outcomes of laparoscopic Nissen and Toupet fundoplication (LF) to Magnetic Sphincter Augmentation (MSA) using the LINX device. All articles comparing MSA and laparoscopic partial or total fundoplication were included in the systematic review. Six retrospective reviews and one registry study (n=1211) were included. No randomized controlled trials were found. The patient populations of the individual studies ranged from 24 to 415. A total of 686 patients (56%) received the LINX and 525 (44%) patients underwent laparoscopic total (Nissen) or partial (Toupet) fundoplication. The operative time was 42–73 min in the MSA group and 76–118 in the LF group. Overall postoperative morbidity was 0–3% in the MSA group and 0–7% in the LF group. There was no mortality. The hospital length of stay was 13–48 hours in the MSA group and 26–48 hours in the LF group. The postoperative follow-up ranged from 6–12 months. Compared to preoperative baseline, a statistically significant improvement was noted for both procedures. Reoperation was required in 13 MSA patients including 12 device removals, one

for erosion and one crural release. There were 11 reoperations in the LF group. Dysphagia requiring endoscopic dilatation occurred in 9.3% of patients in the MSA group compared to 6.6% of LF patients (p=0.119), not statistically significant. The pooled odds ratio of gas/bloat symptoms, ability to vomit, and ability to belch were 0.39 (p<0.001), 10.10 (p<0.001), and 5.53 (p<0.001), respectively. The postoperative quality of life score was similar between groups (p=0.101). There were no significant differences in the pooled odds ratio of PPI suspension, endoscopic dilation, and reoperation (p=0.548, p=0.119, p=0.183, respectively). Postoperative morbidity was 0%–3% in the MSA group and 0–7% in the LF group. There was no mortality. The author's noted that the difference in outcomes between the two patient groups should be interpreted with caution since no comparative randomized clinical trials existed to provide strong evidence and subgroup analysis according to baseline variables was not possible because all outcomes were aggregated in the analyzed studies. This analysis is also limited by the retrospective and registry study designs, small patient populations and short-term follow-ups. Prospective randomized controlled trials with large patient populations and long-term follow-ups are needed to support the safety and efficacy of LINX.

In the 2018 update of the Hayes Technology Brief on Linx, Hayes concluded that there was an overall low-quality body of evidence that suggested that magnetic sphincter augmentation (MSA) is associated with improved quality of life and GERD symptoms. However, substantial uncertainty exists due to limited follow-up beyond one year and unclear patient selection criteria. Studies were included if they evaluated LINX for the treatment of GERD and compared LINX with alternative treatments (e.g., changes in proton pump inhibitor [PPI] use, patient reported GERD symptoms, quality of life) or harms data. Seven clinical studies (n=66 to 415 patients) met the inclusion criteria. One randomized controlled trial (RCT) that compared MSA with twice-daily PPI treatment and four poor and two very, poor quality cohort studies comparing MSA with laparoscopic fundoplication were included. Outcomes assessed generally included indicators of esophageal acid exposure before and after treatment, changes in PPI usage, patient-reported symptoms, and complications. Hayes also noted that definitive patient selection criteria have not been established for MSA with the LINX. There is a lack of data on patients with moderate-to-severe esophageal disease and moderate-to-severe obesity, a risk factor for GERD. Limitations of individual studies included small patient populations, lack of long-term data, lack of power, analysis, variable follow-up durations among patient populations, and significant differences in baseline characteristics between groups. MSA appeared to be moderately well tolerated; there were no reports of deaths, and serious adverse events were uncommon. MSA resulted in fewer patients experiencing the inability to belch or vomit. Additional prospective comparative studies with large patient populations and long-term follow-up are needed to establish the effectiveness of LINX for the treatment of GERD. In a subsequent literature search (2020), Hayes' conclusions had not changed.

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

Skubleny et al. (2017) conducted a systematic review and meta-analysis to compare the LINX- magnetic sphincter augmentation system to Laparoscopic Nissen fundoplication (LNF) for the treatment of GERD. Randomized controlled trials, non-randomized comparison study and case series with greater than five patients were included. Primary outcomes included: GERD-Health-Related Quality of Life scores, DeMeester scores, operative times, ability to belch, ability to emesis, discontinuation of proton pump inhibitor (PPI), need for endoscopic dilation, procedural satisfaction, presence of gas/bloating and dysphagia. Secondary outcomes included mortality and morbidity. Two retrospective cohort comparative studies and one case series (n=688) met inclusion criteria. Mean duration of follow-up ranged from 7–16 months for LNF and 7–12 months for LINX. There was a statistically significant improvement reported with LINX in preserving the patient's ability to belch (p=0.00001) and ability to emesis (p=0.06). However, there was no statistically significant difference between the groups in gas/bloating (p=0.06), postoperative dysphagia (p=0.43) and discontinuation of PPI use (p=0.68). Six

patients required endoscopic balloon dilation following LINX vs. zero dilations post-LNF. Major morbidity for LNF included one case of intraoperative pleural injury, two cases of retroesophageal abscesses and four cases of revision due to hiatal hernia recurrence. The LINX group morbidity included one pleural injury, two episodes of intraoperative bleeding, one pneumothorax and one gastroesophageal junction obstruction. Two LINX devices were removed due to treatment failure and device erosion 20 months after surgery. Limitations of the studies included: lack of randomization; short-term follow-up; loss to follow-up (7.7%–10.6%); and heterogeneity in the size of hiatal hernia and grade of esophagitis accepted within treatment arms. The authors noted that the validity of many of the primary outcomes was decreased due to their subjective nature and lack of clear medical definition. Additional studies are needed to assess the long-term outcomes of LINX. The long-term implications of reversal of the LINX are unknown.

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

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

Saino et al. (2015) reported five-year data from a multicenter, prospective case series (n=33) of patients with GERD, age 18–75 years, who underwent MSAD with LINX. Patients had abnormal esophageal pH, exhibited typical GERD symptoms, and had been taking daily proton pump inhibitors (PPIs). Patients were excluded if they had a large hernia (> 3 cm), Grade B or higher esophagitis, a body mass index of >35 kg/m2, Barrett's esophagus, motility disorders, gross esophageal anatomic abnormalities or a known allergy to titanium, stainless steel, nickel, or ferrous materials. Outcomes included: gastroesophageal reflux disease (GERD)-Health Related Quality of Life (HRQL) questionnaire score, esophageal pH, PPI use, and complications. Compared to baseline, there were significant improvements in mean total percentage of time with pH < 4 (p<0.001) and mean total

GERD-HRQL score (p<0.001) and 85% of patients achieved pH normalization or at least a 50% reduction. Complete discontinuation of PPIs was achieved by 87.8% of patients. The re-operation rate was 6.8% and due to dysphagia, continued reflux symptoms, and planned MRI imaging. There were no device erosions, malfunctions, or migrations at any point and no other long-term complications. Limitations of the study include the small patient population, lack of a comparator; loss of 12 patients from the original pilot study; failure of all sites to perform pH monitoring after the first year and no manometric evaluations were performed after the first year.

Bonavina et al. (2013) reported on 100 consecutive patients who underwent magnetic sphincter augmentation (MSA) for the treatment of GERD. Implant duration ranged from 378 days to six years (median 3 years). Patients were included if they were age 18 years and older, had GERD for at least six months, had persistent reflux symptoms despite daily proton pump inhibitors (PPIs), and pathologic reflux was confirmed by ambulatory esophageal pH monitoring. Following implant median total acid exposure time was significantly reduced from 8.0% to 3.2% (p<0.001). The median GERD Health Related Quality of Life score improved from 16 on PPIs at baseline to 24 off PPIs and significantly improved to a score of 2 (p < 0.001). A total of 85% of patients achieved freedom from daily dependence on PPIs. There were no reported events of device migrations or erosions. Three patients had the device laparoscopically removed for persistent GERD, painful swallowing (odynophagia), or dysphagia with subsequent resolution of symptoms.

Resection and Plication (RAP)
Resection and Plication (RAP) is a procedure that has been proposed to treat GERD. The procedure utilizes limited mucosal resection and full-thickness plication using the OverStitch device (Apollo Endosurgery). The RAP suturing protocol is proposed to recreate a functional valve that would be seen in patients without GERD or a hiatal hernia. The protocol allows for a tightening of the GEJ to reduce reflux events, which does not prevent normal esophageal motility and distensibility (Raphael, et al., 2020; Bernias, et al., 2017).

U.S. Food and Drug Administration (FDA): The Overstitch Endoscopic Suturing System is FDA approved for "endoscopic placement of suture(s) and approximation of soft tissue." (FDA, 2018). In 2019 the FDA approved OverStitch™ Endoscopic Suturing System for the same indication, but with a modification. "The OverStitch Endoscopic Suturing System has been modified to add a new product code option for the OverStitch 2-0 Polypropylene Suture-Anchor Assembly. The remaining components of the system remain unchanged" (FDA, 2019).

Literature Review - Resection and Plication (RAP): There is currently a paucity of evidence in the published peer-reviewed medical literature evaluating the safety and effectiveness of the resection and plication procedure using the OverStitch device for treatment-of GERD. Benias, et al. (2017) evaluated the success of a novel resection and plication (RAP) anti-reflux procedure. Ten patients with symptoms and objective findings of GERD underwent RAP using the Apollo Overstitch. Follow-up ranged from 5–24 months. The authors reported that all patients had a significant improvement in their GERD-HRQL scores (p<0.0001) and eight patients eliminated daily PPI use. The authors concluded that the RAP method has potential as an effective anti-reflux option, however additional long-term studies are required.

Additional well-designed studies with long-term follow-up are needed to establish safety and effectiveness of the RAP procedure using the OverStitch device for treatment-of GERD.

Technology Assessments/Systematic Reviews of Multiple Systems
In September 2019, Hayes published a Clinical Research Response for gastroesophageal reflux disease (GERD) management devices. The report focused on the comparison of two gastroesophageal reflux disease (GERD) management systems: EsophyX Device (EndoGastric Solutions) and LINX Reflux Management System (Johnson & Johnson). There was a lack of studies that compared LINX with EsophyX head-to-head. A moderate body of evidence was located that evaluated either magnetic sphincter augmentation (MSA) or LINX. Eight abstracts were retrieved and included a randomized controlled trial (RCT), a prospective comparative study, prospective uncontrolled studies, a retrospective uncontrolled study, a systematic review/meta-analysis, a systematic review, and a review article. Hayes concluded that the published literature failed to provide sufficient evidence to determine the superiority of either the LINX or the EsophyX. Larger, well-designed comparative trials

with long-term follow-ups are needed to guide evidence-based decisions regarding the superiority of either of these products.

Coronel et al. (2018) conducted a systematic review and meta-analysis of randomized controlled trials (n=16) to evaluate the safety and efficacy of endoscopic treatment for GERD. Endoscopic therapies included: transoral incisionless fundoplication (TIF2) using EsophyX; surgical plication by NDO surgical device; Stretta radiofrequency therapy; EndoCinch endoscopic suturing system; injectable esophageal prostheses by Gatekeeper device, and biocompatible non-resorbable copolymer Enteryx device. Controls included: sham procedure, proton pump inhibitors (PPIs) or laparoscopic anti reflux surgery (LARS). Inclusion criteria were randomized controlled trials with patients over 18 years of age, undergoing endoscopic procedures for chronic GERD (symptoms ≥ 6 months in duration), and follow-ups of ≥ 3 months. Sixteen RCTs (n=1085) met inclusion criteria. The primary outcome measure was overall efficacy of endoscopic treatments versus controls. A total of 221 patients underwent TIF2, 145 surgical plications, 81 Stretta; 42 endoscopic suturing, 32 injectable esophageal prostheses and 75 biocompatible non-resorbable copolymer. Control groups (n=312) included 294 patients who underwent a sham procedure, 120 received PPIs and 63 underwent LARS. Overall, there was a statistically significant difference in treatment efficacy in favor of endoscopic treatment (p<0.00001). At three months follow-up, three trials (n=263) showed a significant difference in two endoscopic groups (p<0.00001). At six months, six trials (n=377) also showed a statistically significance difference for endoscopic subjects (p<0.00001). At 12 months follow-ups in two trials (n=67) showed no statistically significant difference (p<0.06). Regarding efficacy of endoscopic treatments (ET) versus pharmacological (PPI) four studies (n=320) were analyzed. At six months (n=277) statistically significant difference was seen in favor of ET (Stretta, TIF2) (p<0.00001). One trial (n=43) showed no difference at the 12-month follow-up. In studies comparing ET with sham, at six months two RCTs (n=100) showed a significant difference (p<0.0001) but at 12 months there was no significant difference (1 RCT; n=24). The outcomes of normalization of esophageal acid pH (*p*<0.03); lower esophageal sphincter resting pressure (LESRP) (p<0.00001); mean percent of total time of esophageal pH < 4 (p<0.00001); and mean number of reflux episodes (p<0.00001) were statistically significant in favor to the ET. Overall, there was high heterogeneity between the trials in up to 12 months of follow up. The time in remission (p<0.00001), number of patients with GERD HRLQ score >50 % improvement (p<0.00001), elimination of troublesome regurgitation (*p*<0.00001) were statistically significant in favor of ET with very low heterogeneity between the trials at six and 12 months follow up. The mean GERD HRQL score (p<0.00001), the heartburn score (p<0.00001) and DeMeester score (p<0.00001) showed statistically significance improvement following ET up to six and 12 months but there was high heterogeneity. The SF-36 score showed improvement in favor of controls at 12 months follow up, but also with high heterogeneity between studies. When comparing endoscopic therapies only to sham, the results were similar. Most studies reported clinically significant moderate to severe post-procedure related adverse events (n=312 events) such as epigastric pain, musculoskeletal pain, dysphagia, sore throat, chest pain, nausea and vomiting, bloating and flatulence that were treated clinically, with complete resolution and no major sequelae. The event rate was 38% for ET, 24% for sham, 4% for PPI and 2% for the LARS group. Author noted limitations included a high degree of heterogeneity in outcomes, short-term follow-ups (< 6 months) and many patients were offered alternative interventions during follow-ups and the actual benefit of the endoscopic intervention was compromised. The authors noted that to date, there are no randomized studies evaluating the efficacy of endoscopic procedures with over 12 months of follow up. The role of ET for the treatment of GERD remains unclear.

Hayes (2017) conducted a comparative effectiveness Directory Report on endoscopic therapy for GERD. The report included Stretta, EsophyX and Medigus Ultrasonic Surgical Endostapler (MUSE). Fourteen comparative studies of which five were randomized and five were noncomparative studies met inclusion criteria. The report included comparative studies with follow-up ≥ 6 months and noncomparative studies with ≥ 100 patients and ≥◦12 months follow-up. A total of 12 Stretta studies (n= 36–217), five EsophyX studies (n=44–129) and two MUSE studies (n=27–66) were reviewed. There was insufficient evidence to support the use of MUSE for GERD patients. Although findings for Stretta and EsophyX suggested improvement in clinical and patient-reported outcomes compared to baseline for GERD patients who were unsatisfied with or uncontrolled on PPIs, the evidence was of low quality. Long-term data are lacking for these two procedures. Limitations of the studies included: lack of randomization and/or blinding, small sample size, short-term follow-up, lack of and inconsistent comparators, loss to follow-up (especially for pH measures), retrospective study designs, inconsistent use of outcome measures and potential lack of generalizability. Hayes updated the technology assessment in 2019 with no change in recommendation.

Chen et al. (2009) conducted a systematic review of 33 studies examining seven endoscopic treatments for GERD. A total of 33 studies examining seven endoscopic procedures (Stretta procedure, Bard EndoCinch, Wilson-Cook Endoscopic Suturing Device, NDO Plicator, Enteryx, Gatekeeper Reflux Repair System and Plexiglas) were included in the review. Of the three procedures that were tested against sham controls (Stretta procedure, Bard EndoCinch and Enteryx), patient outcomes in the treatment group were either as good as, or significantly better than, those of control patients in terms of heartburn symptoms, quality of life and medication usage. However, for the two procedures that were tested against laparoscopic fundoplication (Stretta) procedure and Bard EndoCinch, outcomes for patients in the endoscopic group were either as good as, or inferior to, those for the laparoscopic group. The authors concluded that, despite the potential benefits of these procedures, there was insufficient evidence to establish their safety and efficacy, particularly in the long-term.

Professional Societies/Organizations
American College of Gastroenterology (ACG): In the 2020 clinical guideline for the diagnosis and management of achalasia, the American College of Gastroenterology (ACG) stated the following (Vaezi, et al., 2020a):

- POEM or LHM is more effective for type III achalasia when compared to PD
- POEM and PD have comparable symptom improvement in patients with types I or II achalasia
- POEM and LHM have comparable symptom improvement in patients with achalasia
- POEM is a safe option in patients with achalasia who have failed PD or LHM
- POEM is associated with a higher incidence of GERD when compared to LHM with fundoplication or PD

In 2013, the ACG updated their Practice Guidelines for GERD. Under the section on surgical options for GERD the authors state, “The usage of current endoscopic therapy or transoral incisionless fundoplication cannot be recommended as an alternative to medical or traditional surgical therapy (Strong recommendation, moderate level of evidence)” (Katz, et al., 2013).

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

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

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

American Society for Gastrointestinal Endoscopy (ASGE): The 2020 ASGE guideline on the management of achalasia focused on the treatment modalities currently used for managing most patients with achalasia. The ASGE suggested the following:

- Laparoscopic Heller myotomy, pneumatic dilation, and POEM are effective treatments for patients with achalasia. Achalasia type, local expertise, and patient preference should be used to decide between these treatments (strong recommendation based on high-quality evidence).

- POEM is the preferred treatment for management of patients with type III achalasia (weak recommendation, very-low quality evidence).
- Patients with failed initial myotomy (POEM or laparoscopic Heller myotomy), should undergo pneumatic dilation or redo myotomy using either the same or an alternative technique (weak recommendation based on very-low quality evidence).
- POEM patients should be counseled regarding the increased risk of postprocedure reflux compared with pneumatic dilation and laparoscopic Heller myotomy (weak recommendation based on low-quality evidence).
- POEM and laparoscopic Heller myotomy are comparable treatment options for management of patients with achalasia types I and II (weak recommendation based low-quality evidence).

The guideline noted that 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, such as bleeding, perforation, and leakage (Khashab, et al., 2020).

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

American Society of General Surgeons (ASGS): The ASGS issued a position statement on transoral fundoplication in 2016 stating that “the ASGS supports the use of transoral fundoplication by trained General Surgeons for the treatment of symptomatic chronic gastroesophageal reflux disease (GERD) in patients who fail to achieve satisfactory response to a standard dose of Proton Pump Inhibitor (PPI) therapy or for those who wish to avoid the need for a lifetime of medication dependence.”

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

Society of American Gastrointestinal Endoscopic Surgeons (SAGES): In 2021 SAGES published guidelines for the use of peroral endoscopic myotomy (POEM) for the treatment of achalasia. The panel recommended that peroral endoscopic myotomy should be done over pneumatic dilatation in patients with achalasia. If there is concern about the continued use of PPI post-operatively, POEM or pneumatic dilatation can be used (Kohn, et al., 2021).

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

In 2017, SAGES updated the Clinical Spotlight Review on Endoluminal Treatments for Gastroesophageal Reflux Disease (GERD). The Clinical Spotlight review is intended to indicate preferable approaches to medical problems as established by experts in the field. These recommendations are based on existing data or a

consensus of expert opinion when little or no data are available. A 4-tiered system for denoting the quality of evidence (very low [+], low [+ +], moderate [+ + +], or high [+ + + +] and a 2-tiered system for strength of recommendation (weak, or strong) were used. The devices and techniques selected for this Clinical Spotlight Review include EsophyX and Stretta (SAGES, 2017a).

- Recommendation - EsophyX: “Based on existing evidence, TIF [i.e., EsophyX] can be performed with an acceptable safety risk in appropriately selected patients. The procedure leads to better control of GERD symptoms compared with PPI treatment in the short term (six months), but appears to lose effectiveness during longer term follow-up and is associated with moderate patient satisfaction scores. Objective GERD measures improve similarly after TIF 2.0 compared with PPI. No comparative, controlled trials exist between TIF and surgical fundoplication, but preliminary evidence suggested that the latter can be used safely after TIF failure.” (Level of evidence +++, strong recommendation). SAGES did not define the criteria for “appropriate selected patients”. Quality of Evidence: (++). GRADE Recommendation: Weak.
- Recommendation - Stretta: “Based on existing evidence, Stretta significantly improves health related quality of life scores, heartburn scores, the incidence of esophagitis, and esophageal acid exposure in patients with GERD, but does not increase lower esophageal sphincter basal pressure. In addition, it decreases the use of PPI by approximately 50%. The effectiveness of the procedure diminishes some over time, but persistent effects have been described for up to 10 years after the procedure in appropriately selected patients with GERD. Stretta is more effective than PPI, but less so than fundoplication. Stretta is safe in adults and has a short learning curve”. Level of Evidence: (+++); Strong Recommendation.

In 2009 SAGES published a position statement addressing endolumenal therapies for gastrointestinal diseases. The authors discuss the current gastrointestinal applications for endolumenal surgery including endolumenal therapies for GERD. The authors state that “endolumenal techniques, either existing or still in development, may well represent the procedure of choice for selected patients with GERD in the future.” The authors state that, “to facilitate progress in endolumenal therapy, several key issues still need to be addressed beyond the needed technology development. These include defining criteria for patient selection, defining the requisite skill set needed by the treating physician, defining the setting for these procedures to be performed in, and addressing reimbursement/coding issues” (SAGES, 2009). There has been no update to this statement since 2009.

Use Outside of the US
The 2021 European Society of Neurogastroenterology and Motility (ESNM) and American Neurogastroenterology and Motility Society (ANMS) joint consensus paper: Diagnosis and management of refractory gastro-esophageal reflux disease included stated the following for surgical and interventional management of GERD (Zerbib, et al., 2021):

- Laparoscopic fundoplication and magnetic sphincter augmentation, improves refractory GERD symptoms, particularly regurgitation, in patients with proven GERD.
- Transoral incisionless fundoplication (TIF) in carefully selected patients demonstrated short-term and limited longer-term evidence for benefit in improving regurgitation, but acid exposure times are not normalized.
- The benefits from radiofrequency application (Stretta) in refractory GERD has variable symptom improvement, but limited objective improvement in acid burden or manometric EGJ features.

The European Society of Gastrointestinal Endoscopy (ESGE) 2020a clinical practice guidelines on endoscopic management of gastrointestinal motility disorders (part 1) recommended (Weusten, et al., 2020a):

- POEM is effective and relatively safe treatment for esophageal achalasia (conditional recommendation based on moderate evidence)
- POEM should be used cautiously when treating spastic motility disorders other than achalasia (strong recommendation based on very low quality of evidence)
- POEM can be used to treat recurrent or persistent dysphagia after LHM with pneumatic dilation, POEM, or redo surgery (conditional recommendation based on very low quality of evidence)

- POEM can be used to treat recurrent or persistent dysphagia after POEM with either re-POEM, LHM, or pneumatic dilation (conditional recommendation based on very low quality of evidence)

Additionally, the guidelines noted that G-POEM is an emerging procedure and can be considered in carefully selected patients in an expert center, preferably in the context of a clinical trial. There is limited data on effectiveness, safety, and durability (strong recommendation, low quality of evidence).

The European Society of Gastrointestinal Endoscopy (ESGE) 2020b clinical practice guidelines on endoscopic management of gastrointestinal motility disorders (part 2) recommended (Weusten, et al., 2020b):

- TIF should not be used as an alternative to PPI therapy or antireflux surgery in the treatment of GERD, because of the lack of data on the long-term outcomes, , the inferiority of TIF to fundoplication, and its modest efficacy in only highly selected patients (strong recommendation based on moderate evidence)
- MUSE should not be used in clinical practice because of insufficient data showing its effectiveness and safety in patients with GERD, MUSE should only be used in clinical trials (strong recommendation based on low quality of evidence)
- Stretta may be considered in patients needing symptom relief and without erosive esophagitis and a hiatal hernia (weak recommendation based on moderate level of evidence)
- Z-POEM is an emerging treatment for Zenker's diverticulum and can be considered experimental and only offered in a research setting (strong recommendation, low quality of evidence)

The 2020 United European Gastroenterology (UEG) and European Society of Neurogastroenterology and Motility (ESNM) joint guideline on achalasia included the following recommendations for the treatment of achalasia:

- Per-oral endoscopic myotomy is an effective and relatively safe treatment for oesophageal achalasia (strong recommendation based on high certainty of evidence).
- Recurrent or persistent dysphagia after laparoscopic Heller myotomy can be treated with PD, POEM or redo surgery (conditional recommendation based on very low evidence).
- Treating recurrent or persistent dysphagia after POEM can be done with either re-POEM, laparoscopic Heller myotomy or pneumatic dilation (conditional recommendation based on very low evidence).

The guideline stated that treatment decisions should be made based on patient specific characteristics, patient preference, possible side effects and/or complications and a center's expertise (Oude Nijhuis, et al., 2020).

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

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

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

The National Institute for Clinical Excellence (NICE, United Kingdom), issued an interventional procedure guidance document on laparoscopic insertion of a magnetic titanium ring for the treatment of GERD. The authors concluded that there was no safety concerns but evidence is limited to short-term efficacy. Therefore, this

procedure should only be used with special arrangements for clinical governance, consent and audit or research (NICE, 2017).

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

The 2011 Gastroenterological Society of Australia Clinical Update on Gastroesophageal Diseases in Adults reports under the section on management and endoscopic therapies noted that a number of therapies have been developed for the treatment of GERD including: suturing devices, injection of inert substances, plication devices and devices that deliver radiofrequency energy to the Gastro-esophageal junction. GSA stated that experience with these techniques is relatively limited. They do not significantly reduce exposure of the distal esophagus to acid, and many have already been removed from the market because of lack of efficacy or complications (including death). These treatments should not be used by inexperienced operators or outside a program (e.g. a clinical trial) where complications can be reported.

Medicare Coverage Determinations

	Contractor	Policy Name/Number	Revision Effective Date
LCD	CGS Administrators, LLC	Stretta Procedure (L34540)	9/26/2019
LCD	National Government Services, Inc.	Select Minimally Invasive GERD Procedures (L35080)	4/15/2021
LCD	Palmetto GBA	Stretta Procedure (L34553)	12/27/2020
LCD	Palmetto GBA	Upper Gastrointestinal Endoscopy and Visualization (L34434)	10/24/2019
LCD	Palmetto GBA	Peroral Endoscopic Myotomy (POEM) (L38747)	2/28/2021
LCD	Wisconsin Physicians Service Insurance Corporation	Endoscopic Treatment of GERD (L34659)	2/14/2021

Note: Please review the current Medicare Policy for the most up-to-date information.

Coding/Billing Information

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

Peroral endoscopic myotomy (POEM)

Considered Medically Necessary for the treatment of achalasia when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
43497	Lower esophageal myotomy, transoral (ie, peroral endoscopic myotomy [POEM])

Considered Experimental/Investigational/Unproven when used to represent: D-POEM, G-POEM, Z-POEM:

CPT®* Codes	Description
43180	Esophagoscopy, rigid, transoral with diverticulectomy of hypopharynx or cervical esophagus (eg, Zenker's diverticulum), with cricopharyngeal myotomy, includes use of telescope or operating microscope and repair, when performed
43499	Unlisted procedure, esophagus
43999	Unlisted procedure, stomach

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

CPT®* Codes	Description
43192	Esophagoscopy, rigid, transoral; with directed submucosal injection(s), any substance
43201	Esophagoscopy, flexible, transoral; with directed submucosal injection(s), any substance
43210	Esophagogastroduodenoscopy, flexible, transoral; with esophagogastric fundoplasty, partial or complete, includes duodenoscopy when performed
43236	Esophagogastroduodenoscopy, flexible, transoral; with directed submucosal injection(s), any substance
43253	Esophagogastroduodenoscopy, flexible, transoral; with transendoscopic ultrasound-guided transmural injection of diagnostic or therapeutic substance(s) (eg, anesthetic, neurolytic agent) or fiducial marker(s) (includes endoscopic ultrasound examination of the esophagus, stomach, and either the duodenum or a surgically altered stomach where the jejunum is examined distal to the anastomosis)
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 (ie, magnetic band), including cruroplasty when performed
43289	Unlisted laparoscopy procedure, esophagus
43499	Unlisted procedure, esophagus
43659	Unlisted laparoscopy procedure, stomach

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