Amerigroup

Medical Policy

Subject:	Transendoscopic Therapy for Gastroesophageal Reflux Disease, Dysphagia or Gastroparesis		
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Description/Scope

This document addresses selected transendoscopic therapies for the treatment of gastroesophageal reflux disease (GERD), dysphagia or gastroparesis. This document does not address procedures that approach the esophagus through abdominal laparoscopic or open surgical approaches.

Note: For additional information, please see the following related documents:

- CG-MED-59 Upper Gastrointestinal Endoscopy in Adults
- CG-SURG-101 Ablative Techniques as a Treatment for Barrett's Esophagus
- SURG.00131 Lower Esophageal Sphincter Augmentation Devices

Position Statement

Medically Necessary:

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

1. The individual is 18 years of age or older; **and**
2. Has a diagnosis of primary achalasia; **and**
3. POEM is being proposed as an alternative to pneumatic dilation or myotomy (open or laparoscopic); **and**
4. Eckardt symptom score is greater than 3; **and**
5. There is no history of previous open surgery of the stomach or esophagus.

Not Medically Necessary:

POEM is considered **not medically necessary** when the criteria above are not met, and for all other indications.

Investigational and Not Medically Necessary:

The following transendoscopic treatments for gastroesophageal reflux disease, dysphagia or gastroparesis are considered **investigational and not medically necessary** for all indications:

1. Endoluminal gastric plication;
2. Endoscopic submucosal injection of bulking agents, beads or other substances;
3. Gastric peroral endoscopic myotomy or peroral pyloromyotomy;
4. Transendoscopic gastroplasty;
5. Transesophageal radiofrequency therapy (note: this does NOT include treatment of Barrett's Esophagus with radiofrequency energy);
6. Transoral incisionless fundoplication.

Rationale

Transendoscopic Therapy for GERD

Randomized, placebo-controlled trials with clinically relevant and self-reported outcomes are ideally required to validate the effectiveness and clinical utility of transendoscopic therapies for GERD for the following reasons:

- Medical treatment of GERD is associated with a placebo effect (Fennerty, 2003; Fry, 2007; Pace, 2007), and a similar placebo response is expected for transendoscopic therapies.
- Studies have shown an inconsistent relationship between esophageal acid exposure and GERD symptoms. Therefore, changes in esophageal acid exposure are considered intermediate health outcomes. Key final health outcomes are the self-reported outcomes of symptom relief. Other outcomes of interest include resolution of esophageal erosions, if present.

A search of the literature initially focused on randomized, placebo-, or sham-controlled, trials. The durability of treatment response to transendoscopic therapies is another important outcome that has been reported in case series. It is important to note that since proton pump inhibitor (PPI) therapy is a well-established, effective therapy for GERD, transendoscopic therapies have been positioned as an alternative to open or laparoscopic surgical treatments (for instance, fundoplication) for individuals who either fail or who are intolerant of PPI therapy. Thus, while results of sham-controlled trials are an initial measure of the feasibility and efficacy of transendoscopic procedures, ultimately these techniques would ideally be compared to established surgical therapies and include long-term outcomes.

Another consideration is whether symptoms are truly reflux related and PPI-refractory. In 2019, Spechler and colleagues published a randomized trial on PPI therapy versus Nissen fundoplication surgery for refractory heartburn. They found that among 366 participants in the study, GERD was the true cause of PPI-refractory heartburn in a minority of the participants. For 42 individuals referred to surgery because of "PPI-refractory" heartburn, heartburn was relieved during a 2-week trial of omeprazole twice a day. After a systematic preoperative workup that included endoscopy with esophageal biopsy, esophageal manometry, and MII-pH monitoring, they found that GERD was not the likely cause of heartburn for 122 individuals. Only 78 individuals were found to have reflux-related, PPI-refractory heartburn and could be included in the study. After randomizing the participants to receive surgery (n=27), PPI treatment (n=25), or control medical treatment (n=26), the researchers found that Nissen fundoplication outcomes at 1 year were significantly superior to PPIs or control. They concluded that "systematic workup including esophageal MII-pH monitoring can identify a subgroup of patients with PPI-refractory heartburn, including those with reflux hypersensitivity, who can have a response to antireflux surgery." This study highlights the importance of proper PPI use and systematic workups prior to determining candidates for GERD procedures.

Radiofrequency Ablation (for example, Stretta®)

According to the manufacturer, the Stretta procedure "delivers low power, low temperature radiofrequency (RF) energy to the LES [lower esophageal sphincter] muscle and gastric cardia, which remodels the tissue, resulting in improved barrier function and fewer random relaxations that cause GERD symptoms."

A randomized controlled trial (RCT) was identified that enrolled 64 participants with GERD who were partially responsive to PPI therapy and randomized to either a sham or active Stretta procedure (Corley, 2003). Outcomes consisted of symptoms, GERD-related quality of life (GERD HRQOL) and general quality of life (QOL)

questionnaires, medication usage, and esophageal acid exposure. At 6 months, active treatment participants had improvement in heartburn scores and both GERD-related and general QOL scores, and a greater proportion reported absence of daily heartburn symptoms (61% vs. 33%). However, there were no differences between groups in daily use of PPIs or any other medications. Both active treatment and sham-treated groups substantially reduced their medication usage after intervention. There was also no change in esophageal acid exposure times. Therefore, this study reports inconsistent results; in terms of the objective measures of GERD, the findings were equivocal. The large proportion of sham-treated participants who successfully reduced medication use suggests a possible placebo effect of the procedure. An accompanying editorial highlighted discrepancies between the study's objective and subjective findings and hypothesized that the possible mechanism of action of the Stretta procedure is neurolysis resulting in decreased esophageal sensitivity to acid exposure, rather than reduction in acid exposure (Kahrilas, 2003).

Richards and colleagues (2003) reported on their findings from a nonrandomized controlled trial of individuals undergoing treatment with either the Stretta device (n=65) or laparoscopic fundoplication (n=75). They report that at 6 months post-procedure, 58% of Stretta participants discontinued PPI treatment, and an additional 31% had reduced their dose significantly. They also reported that 97% of fundoplication participants discontinued PPIs. No statistical data was provided for this comparison. At a mean of 7.2 ± 0.5 months, 22 Stretta participants (33.8%) returned for 24-hour pH testing and there was a significant reduction in esophageal acid exposure time. However, with such a large drop-out rate, the significance of this finding is unclear. The results of this study seem to indicate that laparoscopic fundoplication is superior to the Stretta procedure, but due to the limitations of the statistical analysis, no definitive conclusions can be made based on the data.

Coron and colleagues (2008) reported the results of a small RCT that involved 20 participants who received treatment with the Stretta device and 16 who received standard treatment with PPIs followed for 6 months. The authors reported a significant decrease in PPI use in the Stretta group compared to the control group ($p=0.001$). As with the study addressed above, the small sample size does not provide results sufficiently robust to adequately demonstrate the efficacy of the Stretta device.

An RCT by Aziz and colleagues (2010) involved 36 participants randomized to one of three groups on a 1:1:1 basis: the first group underwent sham radiofrequency ablation, the second underwent a single radiofrequency ablation with the Stretta device, and the third group underwent a single radiofrequency ablation Stretta procedure followed by a second if their GERD HRQOL measure was not improved by 75% following the first procedure. The authors reported that after the 12-month follow-up period, there was statistically significant improvement in all groups in relation to the primary outcome measure of GERD HRQOL and improvement was significantly better in both Stretta groups when compared to the sham group ($p<0.05$). For secondary outcomes of GERD medication use, LES basal pressure and esophageal acid exposure, the Stretta-treated groups had significantly improved results when compared to the sham procedure ($p<0.01$, $p<0.01$, $p<0.01$, respectively). These results are promising; however, the small sample size limits the generalizability of these findings to larger populations.

A randomized controlled crossover study involved 22 participants who received treatment with either the Stretta device (n=11) or sham treatment (n=11) (Arts, 2012). Participants were followed for 3 months and then underwent the opposite treatment, followed by another 3-month follow-up period. The authors reported good results with regard to esophageal acid exposure and LES pressure. However, the small group sizes and short follow-up period weaken the value of these results.

A meta-analysis of the available literature addressing the Stretta device was published in 2012 by Perry and colleagues. A total of 20 studies were included. The authors reported that Stretta treatment improved heartburn scores (p=0.001), produced improvements in QOL as measured by GERD HRQOL scale (p=0.001), and improved QOL in reflux and dyspepsia score (p=0.001). Esophageal acid exposure was reported to have decreased from a Johnson-DeMeester score of 44.4 to 28.5 (p=0.007). Of the 20 studies included in the analysis, only 2 were RCTs, the remainder being uncontrolled, unblinded case series. Data from such studies are subject to bias and are generally not considered to be high-level evidence. Combining the data from such studies does not mitigate this flaw, nor does adding data from RCTs. If anything, it dilutes the impact of the findings from the RCTs.

A trial was reported by Liang and colleagues in 2014 which enrolled 215 participants who underwent either laparoscopic Nissen fundoplication (n=102) or Stretta (n=113). At 5-year follow-up, 179 evaluable participants were available (n=87, Nissen group and n=92, Stretta group). Post-treatment scores with regard to outcome measures including symptom scores of regurgitation, heartburn, chest pain, belching, hiccup, cough and asthma were statistically lower compared with the pre-treatment scores in both groups, while those for the Stretta group were significantly lower than those for the Nissen group ($p<0.05$). Complete PPI therapy independence was 91% in the Nissen group (81/87) and 51.1% in the Stretta group (47/87; $p<0.05$). No significant differences in post-treatment complications were observed except for abdominal distention. The authors concluded that even though laparoscopic Nissen fundoplication and the Stretta procedure are capable of controlling GERD symptoms effectively in selected individuals, the Nissen procedure could provide more improvement in symptoms and a greater degree of PPI independence.

The results of two long-term, follow-up studies were published in 2014. The larger study by Noar and colleagues involved 217 participants, of which 149 (68.7%) reached the 10-year follow-up. An additional 50 participants were lost to follow-up, leaving 99 evaluable participants or 45.6% of the original subject pool. No serious adverse events were reported. The primary endpoint of the study was normalization of HRQOL in greater than or equal to 70% of participants which was achieved in 72% of participants at 10 years. A 50% reduction in PPI use was reported in 64% of participants with 41% reporting complete cessation of PPI treatment. The other study was a continuation of an earlier report by Dughera and colleagues in 2007, which began with 86 total participants. This new report includes data from 26 participants (30.2%) who were followed for 8 years. Of those participants not completing the study, 5 were lost to follow-up, and treatment efficacy was lost in 7, 5 of whom underwent successful laparoscopic treatment. At 8 years, the mean heartburn scores and HRQOL were both still significantly improved over baseline (p=0.003 and p=0.0003, respectively). PPI use was completely discontinued in 20 of the 26 participants (76.9%). The authors reported that 8-year LES pressures did not show significant amelioration compared to baseline values. Mean esophageal acid exposure did initially improve at 4 years but had returned to baseline at 8 years. A single severe adverse event was reported, when 1 subject experiencing transient severe gastric paresis required hospitalization. The study methodology and large loss to follow-up in these trials significantly impairs the generalizability of these findings.

Additional literature addressing the Stretta procedure consists of small to moderate sized case series studies (Arts, 2012; Coron, 2008; Dughera, 2011; He, 2020; Liang, 2014a, 2014b; Lufti, 2005; Lui, 2011; Meier, 2007; Noar, 2007; Reymunde, 2007; Torquati, 2004; Triadafilopoulos, 2001, 2002; Wolfsen, 2002). While this evidence is informative, it is not adequately rigorous to allow appropriate conclusions regarding the efficacy, clinical utility, or longevity of the Stretta procedure.

A nonrandomized controlled trial enrolled 137 individuals with severe asthma and coexisting GERD, who received treatment with Stretta (n=82) or Nissen fundoplication (n=55). All participants were followed for 5 years. At 1 and 5 years post-procedures, participants were asked to complete a Reflux Diagnostic Questionnaire (RDQ) and self-report medication usage. Significant decreases in digestive, respiratory and otolaryngological symptom scores on the RDQ were reported at both 1 and 5 years in both groups ($p<0.001$). Reductions were noted to be better at 1 vs. 5 years ($p<0.05$), but outcomes in the fundoplication group were significantly better at both 1 year and 5 years than those found in the Stretta group in terms of digestive ($p<0.001$, $p=0.001$), respiratory ($p=0.006$, $p=0.001$), and ENT symptoms ($p=0.006$, $p=0.003$). No major adverse events were reported (Hu, 2015).

Liang and colleagues (2015) reported on the results of a nonrandomized controlled study involving 165 participants who underwent Stretta (n=80) or Toupet fundoplication (n=85) and were followed for 3 years. At the 3-year follow-up, 125 (75.8%) participants were available, including 60 (70.6%) Stretta participants and 65 (81.3%) fundoplication participants. At 1 year, both groups reported significant improvements in the rate of heartburn, belching, hiccup, cough or asthma, but no differences between groups were noted. These benefits were continued through the 3-year follow-up. Also, at that time point, 68.3% of Stretta and 72% of fundoplication participants were free from PPI use, with no differences between groups. No serious adverse events were reported for either group, but 8 Stretta participants required revision surgery due to treatment failure.

In 2015, Lipka and colleagues published the results of a meta-analysis of the available literature addressing the RCTs involving the Stretta device. The analysis included four trials with a total of 165 participants. Sham controls were used in one study and PPI therapy was used as the controls in the remaining three trials. The authors stated that overall, the quality of the evidence was very low, and that the pooled results demonstrated no differences between the Stretta procedure and controls with regard to mean esophageal exposure time at less than pH of 4 over a 24-hour period, LES pressures, the ability to stop PPI treatment, or HRQOL measures. They concluded that the Stretta procedure did not produce significant changes compared to sham therapy.

Fass and colleagues (2017) performed a systematic review and meta-analysis to determine the efficacy of the Stretta procedure. The researchers included 28 studies (n=2468) in the meta-analysis including 4 RCTs, 23 prospective cohort studies, and 1 registry study. The study outcomes analyzed were PPI usage, HRQOL scores, heartburn scores, erosive esophagitis, esophageal acid exposure, and LES pressure. Before the Stretta procedure, 1743 participants were using PPIs, and after the procedure 850 participants resumed using PPIs (risk ratio [RR] 0.49, 0.40 to 0.60; $p<0.001$). Of the participants who reported HRQOL (n=507), the Stretta procedure improved the score by a mean of –14.60 (–16.48, –12.73; $p<0.001$). For the participants with heartburn (n=637), the Stretta procedure improved the heartburn standardized score by –1.53 (–1.97, –1.09; $p<0.001$). For participants with erosive esophagitis (n=486), the Stretta procedure only marginally reduced the frequency (RR 0.76, 0.56 to 1.04; $p=0.08$). When the fixed effects model was used, the effect of Stretta on esophagitis was found to be statistically significant ($p<0.00001$). For esophageal acid exposure (n=364), Stretta improved the pooled estimate of esophageal acid exposure by –3.01 (–3.72, –2.30; $p<0.001$). For lower esophageal sphincter basal pressure (n=269), Stretta changed the basal pressure by +1.73 mmHg (–0.29, 3.74; $p=0.09$). The rate of adverse events for Stretta was 0.93%, the most frequent being small erosions and mucosal lacerations. The researchers concluded that the Stretta procedure significantly improved HRQOL, heartburn, and erosive esophagitis, but it had no significant effect on LES pressure. After Stretta, 49% of participants resumed PPIs. The meta-analysis was limited by a lack of control groups in most of the included studies.

Kalapala and colleagues (2017) performed a prospective, randomized study that compared the Stretta procedure (n=10) to a sham procedure (n=10). Inclusion criteria included > 18 years old, GERD with persistent symptoms despite PPIs (twice daily) for at least 5 years, abnormal esophageal acid exposure (≥ 4%) in a 24-hour pH study while off medication, DeMeester score of more than 14.7, endoscopically confirmed Los Angeles grade A or B esophagitis, small hiatus hernia (< 2–3 cm), and LES pressure (LESP) between 5 and 15 mm Hg detected by esophageal manometry. Exclusion criteria included > 60 years old, underlying coagulation disorders, previous esophageal or gastric surgery, cardiovascular diseases such as coronary artery disease, American Society of Anesthesiologists (ASA) physical status > II, LESP < 5 or > 15 mmHg or GE flap valve grade IV (Hill's classification), Barrett's esophagus, and esophageal dysmotility. The primary outcome was the proportion of participants showing improvement in QOL and in the frequency and severity of GERD. Secondary outcomes included LES pressure at esophageal manometry, reduction of medication use, and satisfaction. After 3 months post-procedure, the QOL score increased from 20% to 80% in the Stretta group compared to 20% to 30% in the sham group ($p<0.05$). There was a significant decrease in the score for heartburn, regurgitation, chest pain, and cough in the Stretta group but not the control group ($p<0.05$). There were no significant differences in LES pressure between the groups. PPI therapy was eliminated in 60% of the Stretta group, whereas there was no change in the control group. Overall, 80% of the Stretta group was satisfied compared to 30% of the control group. The authors concluded that Stretta was effective short-term for the management of refractory or PPI dependent GERD. The study was limited by a small sample size, single-center location, and short follow-up duration.

Endoscopic Suturing (for example, EsophyX® Z, Medigus Ultrasonic Surgical Endostapler [MUSE™])

Currently, there are two endoscopic suturing devices available. The EsophyX Z system (formerly EsophyX$_2$® and EsophyX®) is used with transoral incisionless fundoplication (TIF® 2.0 [formerly TIF and ELF]) and has evolved to include partially wrapping the fundus 270 degrees around the esophagus in a manner similar to fundoplication surgery. TIF 2.0 has several significant improvements over older versions of the procedure, including the securing of fasteners 1-3 cm above the Z-line. The MUSE system is also used during an incisionless transoral fundoplication procedure and designed to perform a 270 degree wrap similar to fundoplication surgery. Older endoscopic suturing devices, such as the Plicator and EndoCinch, are no longer on the market.

There have been several small case series on the use of EsophyX devices with TIF (Antoniou, 2012; Barnes, 2011; Bell, 2010, 2012; Cadiere, 2008a, 2008b, 2009; Demyttenaere, 2010; Ihde, 2011; Muls, 2013; Rinsma, 2014; Testoni, 2012; Velanovich, 2010). The vast majority of these uncontrolled case series studies involved small numbers of participants and had short follow-up times (under 1 year). Most studies report positive results for the majority of participants, but a significant number of serious complications, including gastric mucosal and esophageal tears requiring transfusions, were reported.

A case control study reported enrolling 3 cohorts of 20 participants each undergoing TIF with the EsophyX device, laparoscopic Nissen fundoplication or laparoscopic Toupet fundoplication (Toomey, 2014). The authors reported that TIF participants were more likely to have undergone prior fundoplication procedures ($p<0.01$). No significant differences between groups were reported with regard to post-procedure symptom frequency or severity; although, it was stated that all participants had a "remarkable and profound resolution of symptoms," with heartburn scores going from 8 pre-operatively to 0 post-operatively ($p<0.05$) and a majority of participants experiencing symptoms less than once per month ($p=0.12$). No complications associated with TIF were reported, and no conversions to other procedures occurred. This study was the first to directly compare TIF and fundoplication for the treatment of GERD.

Due to the small sample sizes and lack of randomization, further investigation with more rigorous methodology is warranted.

Wilson and colleagues (2014) published the results of a retrospective case series of 100 participants treated with the $EsophyX_2$ device with 12-month follow-up. Esophageal acid exposure was normalized in 52% (n=14) of the 27 participants who underwent 12-month pH testing. A total of 74% of all participants were off PPIs vs. 92% on daily PPIs before TIF 2.0 ($p<0.001$). Daily bothersome heartburn and regurgitation symptoms were eliminated in 66/85 (78%) and 48/58 (83%) of participants, respectively. Median Reflux Symptom Index (RSI) score was reduced from 20 (0 to 41) to 5 (0 to 44), ($p=0.001$). Only 2 participants reported de novo dysphagia, and 1 reported bloating (scores 0 to 3). Revision surgery was done in 6 participants. No major complications were reported. Comparison with a randomized control group and longer-term results are warranted.

Bell and colleagues (2014) reported the results of a case series involving 127 participants who underwent TIF 2.0 with the $EsophyX_2$ device and were followed for 2 years. Revision surgery occurred in 8 participants who were considered treatment failures and 19 participants were lost to follow-up. No serious adverse events were reported. The authors reported 50% or greater improvement in GERD HRQOL and regurgitation scores in 66% (63/99) and 70% (62/88) of participants with elevated cores at baseline. RSI scores normalized in 56% of participants and daily PPI use decreased from 91% to 29%. In the participants available for evaluation, esophageal acid exposure normalized in 57% of participants (8/14). Study limitations include lack of a comparison group.

In a prospective, single-center study by Testoni and colleagues (2015), 50 carefully selected participants frustrated with medication therapy (mean age 45 ± 16 years, mean BMI 22 ± 3 kg/m^2) with symptomatic chronic GERD symptoms had undergone the TIF 2.0 procedure and were subsequently followed for 6 years (January 2007 to December 2012). The goal of this study was "to assess the long-term effect of TIF 2.0 on pathological reflux and symptoms in GERD patients with daily dependence on proton pump inhibitors (PPI)." Prior to enrolling in this study, all of the participants experienced heartburn and/or regurgitation and were prescribed PPI therapy for at least 3 months. The exclusion criteria for the TIF 2.0 procedure included atypical GERD symptoms; Barrett's esophagus diagnosed by biopsy, hiatal hernia ≥ 3 cm, previous major thoracic or abdominal surgery and severe co-morbidities. Pre-operatively, the participants completed the GERD HRQOL and GERD-QUAL questionnaires, medication and medical histories, underwent upper GI endoscopy (to assess Hill's grade and Jobe's length of the gastroesophageal valve), esophageal manometry, 24-hour ambulatory pH impedance monitoring and assessment of gastric emptying time. Post-operatively, GERD HRQOL and GERD-QUAL questionnaires were obtained, PPI therapy, upper GI endoscopy, esophageal manometry and 24-hour ambulatory impedance results were monitored at 6, 12 and 24 months post TIF 2.0. Questionnaires and PPI use were documented at 3 years and continued monitoring occurred every year by telephone or office interviews. A total of 51 TIF 2.0 procedures were performed on 50 participants; there was 1 treatment failure. Severe complications (pneumothorax) occurred in 2 participants, but both recovered with prompt response to treatment. The results of this study revealed that TIF 2.0 by EsophyX reduced daily PPI use at 6, 12, 24, and 36 months; 83.7, 79.6, 87.8, and 84.4% of the participants respectively stopped or halved their PPI therapy, and 3-year figures remained stable up to 6 years. The authors concluded that 3- and 6-year post TIF 2.0 results were inferior to surgical Nissen fundoplication, but in well-selected symptomatic GERD patients, "TIF 2.0 by Esophyx achieved long-lasting elimination of daily dependence on PPI in 75-80% of cases for up to 6 years, and about 50 and 30% of patients could stop PPI medication in, respectively, 3 and 6 years." This study is limited by the lack of a control group, small sample size, and a single-institution case series. The authors acknowledge that RCTs are warranted to further demonstrate clinical utility of TIF 2.0 a therapeutic option for prudently selected individuals with refractory GERD.

In 2015, Trad and colleagues published the results of the TEMPO trial, an RCT involving 63 participants undergoing TIF 2.0 treatment with the EsophyX$_2$ device. Participants were followed for 6 months following randomization to either TIF 2.0 (n=39) or optimal medical therapy (n=21). The reported results showed that troublesome regurgitation, as evaluated by RDQ, was eliminated in 97% (29/30) of TIF 2.0 participants vs. 50% (9/18) of participants in the control group (p<0.001). Globally, at 6 months follow-up, complete elimination of all daily troublesome GERD symptoms other than heartburn was observed in 62% (24/39) of TIF 2.0 participants vs. 5% (1/21) of control participants (p<0.001). At 6 months follow-up, 90% of TIF 2.0 participants had completely stopped taking PPIs, another 3% were taking PPIs on demand and the remaining 8% were back on daily PPIs. All participants underwent endoscopic evaluation at 6 months follow-up and complete healing or reduction in reflux esophagitis at 6 months was achieved in 90% (18/20) of TIF 2.0 participants vs. 38% (5/13) of control participants (p=0.018). A single subject with short segment Barrett's (< 2 cm) before TIF 2.0 treatment was reported to have healed esophageal erosions. This subject was off PPIs at 6 months, with the percentage of total time with a pH less than 4 reduced from 9% to 1.5%. The elimination of daily troublesome heartburn was reported in 90% (28/31) of TIF 2.0 participants vs. 13% (2/16) of controls (p=0.003). The median total RSI score in the TIF 2.0 group decreased significantly from 23 (range, 0-43) on PPIs before procedure to 3 (range, 0-25) off PPIs at 6 months follow-up (p<0.001). A minor improvement in the median total RSI score was reported in the control group, but this difference did not reach statistical significance (p=0.205). No major complications were reported. The authors concluded their report by stating, "Despite encouraging results from this study, longer-term follow-ups are warranted."

Hunter and colleagues published the results of the double-blind, sham-controlled randomized RESPECT trial in 2015. This study involved 87 participants treated with the EsophyX$_2$ device followed by 6 months of sham medical therapy vs. 42 participants treated with sham surgery and 6 months of PPI medical therapy. The per-protocol analysis included 81 TIF 2.0 and 38 control participants. At 3 months follow-up, 36% (15/42) of control group participants met criteria for early treatment failure, and 12 were crossed over to the treatment group. At the same time point, 11% (10/87) of the TIF 2.0 group participants were considered early treatment failures and all were returned to PPI therapy. In total, 76 TIF 2.0 and 28 control participants completed the 6-month study period. The intent-to-treat analysis resulted in 68% (58/87) TIF 2.0 group participants reporting elimination of troublesome regurgitation vs. 45% (19/42) of the control participants (p=0.023). Similar findings were reported in the per-protocol analysis, 67% (51/81) vs. 45% (17/38), respectively (p=0.028). The authors reported that esophageal acid exposure was significantly improved following surgical treatment, with the mean number of episodes falling from 135 to 94 (p<0.001). Mean total time pH < 4 and DeMeester score were also significantly improved (p<0.001 for both). No significant changes in these measures were reported in the control group. Of the 17 participants with esophagitis at baseline, 13 (76%) underwent re-evaluation at 6 months, with 77% (10/13) having complete healing. An additional 2 participants had improvement from grade B to grade A esophagitis. In the sham group, only 2 (33%) of the 6 participants with esophagitis at baseline underwent 6-month re-evaluation, with healing reported in 1 subject. A total of 7 participants experienced adverse events in the intervention group (3 severe reports of pain, 2 moderate reports of pain and dysphagia and 2 mild reports of dysphagia and nausea), whereas only 1 in the sham group experienced an adverse event (severe nausea). Longer-term follow-up is warranted to determine if the outcomes experienced in this trial are durable.

Witteman and colleagues (2015) described the interim results of a non-blinded RCT involving 60 participants assigned to either TIF 2.0 treatment with the EsophyX$_2$ device (n=40) or continuation of PPI therapy (n=20). Control participants were allowed to cross over to TIF 2.0 treatment at the end of the 6-month trial period, and all 20 participants did undergo TIF 2.0. At the end of the initial 6-month follow-up point, 37 TIF 2.0 participants and 20

control participants were available, and the authors reported that QOL measures improved significantly better in the TIF 2.0 group vs. controls (p<0.001). No differences were reported between groups with regard to esophageal acid exposure (p=0.228). The TIF 2.0 group had a significantly lower esophageal resting pressure vs. the control group (p=0.004), but no differences in total number of reflux episodes were detected (p=0.058). Cessation of PPI use was reported in 74% of TIF 2.0 participants and none of the controls. Serious adverse events (SAEs) included pneumoperitoneum (n=1), pneumonia (n=3), and severe epigastric pain (n=1). One death was reported, but not considered associated with the experimental treatment. Treatment failure and subsequent treatment with fundoplication occurred in 1 TIF 2.0-group subject, and an additional 2 control-group participants following crossover treatment with TIF2.0. TIF 2.0-group participants reported significantly better Gastrointestinal Symptom Rating Scale (GSRS) scores vs. controls (p=0.001). Distal esophageal acid exposure was not found to be significantly improved in the TIF 2.0 group at 6 months, or at 12 months follow-up. The original non-inferiority study design called for an enrollment of 120 participants for an 80% power to detect a difference between groups, the under enrollment and short follow-up are limitations of this trial's design.

Hakansson and colleagues (2015) reported the results of an RCT. This study involved 44 participants assigned to receive treatment with TIF 2.0 with the EsophyX device (n=22) or continuation of PPI therapy (n=22). At the 6-month follow-up, 21 and 18 participants were available, respectively. The primary endpoint, time in remission, was reported to be significantly longer in the TIF 2.0 group vs. controls (mean 192 days vs. 107 days, p<0.0001). At 6 months, QOL scores indicated significant improvements in the TIF 2.0 group (p=0.0005), but none in the control group. Similarly, GSRS scores improved significantly in the TIF 2.0 group (p=0.004) but not in the control group. Cessation of PPI use occurred in 59% (13/22) of TIF 2.0 participants and 18% (14/22) of controls. Ambulatory pH monitoring was done in 68% (15/22) of TIF 2.0 participants and 50% (11/22) of controls. Total acid reflux time was significantly reduced in the TIF 2.0 group (p=0.003), but not in the controls. Time with esophageal pH < 4 was also reported to be better in the TIF 2.0 group vs. controls (69% of TIF 2.0 participants vs. 20% of controls, p=0.04). No serious adverse events were reported.

A systematic review and meta-analysis on TIF and TIF 2.0 using EsophyX was performed by Huang and colleagues (2017). A limitation of this study is that long-term outcomes and adverse events are based on pooled data including both TIF and TIF 2.0 procedures without differentiation. The authors analyzed the results of 18 studies (n=963), including 5 prospective observational studies that used TIF, and 13 studies (8 prospective observational and 5 RCTs) that used TIF 2.0. Most of the study participants required the daily use of PPIs or were unsuccessful with PPI therapy before the procedure, and the majority of participants had hiatal hernias less than 3 cm and a BMI less than 35 kg/m^2. Based on the 5 included RCTs, the researchers determined that TIF 2.0 diminished acid reflux incidents when compared to PPIs and diminished acid exposure time when matched to a sham group. However, long-term outcomes in the 13 prospective observational studies showed decreased efficacy over time leading to PPI treatment. Based on this analysis, the authors concluded that the results of TIF and TIF 2.0 procedures decrease in efficacy in the long term and necessitate the resumption of PPI therapy. The researchers reported that adverse events had an incident rate of 2.4% which included 7 perforations, 5 post-procedure bleeds, 4 pneumothorax and 1 death (reported 20 months post-procedure). Limitations noted by the authors included an excessive degree of heterogeneity in the included studies and lack of data analysis for the standardization with primary and secondary outcomes (no statistical difference between the two groups in the effectiveness for decreasing acid exposure time and acid reflux occurrences).

Trad and colleagues (2017) presented follow-up data from the 3-year TIF 2.0/EsophyX_2 versus Medical PPI open-label randomized trial with a crossover arm (TEMPO trial). They stated:

> Randomization was to the transoral esophagogastric fundoplication (TF) group (n=40) or to PPI (n=23). Following evaluation at 6 months, all remaining PPI patients (n=21) elected to undergo crossover to TF. Fifty-two patients were assessed at 3 years for (1) GERD symptom resolution using three GERD specific quality of life questionnaires, (2) healing of esophagitis using endoscopy, (3) esophagus acid exposure (EAE) using 48-h Bravo testing, and (4) discontinuation of PPI use. Two patients who underwent revisional procedures by year 3 were included in the final analysis.

The significant outcomes of the study Included regurgitation reduction as evaluated by the RDQ calculated at 90% (37/41) at 3 years, at 90% (41/44) at 2 years and at 88% (42/48) at 1 year. These improved findings were substantiated by the total regurgitation score which was from 3.0 on PPIs at screening to 0.5 off PPIs at 3 years. Atypical symptom relief as documented by the RSI was detected in 82% (45/55) of participants at 1 year, in 84% (43/51) of participants at 2 years and in 88% (42/48) at the 3-year follow-up. There were no statistical improvements in the GERD-HRQL scores at any of the yearly intervals; however, at the 3-year follow-up, the score decreased from 26.4 (9.4) on PPIs at screening to 5.0 (9.2) ($p<0.0001$) off PPIs. The authors commented:

> Of patients available for 1-, 2-, and 3-year follow-ups, 98% (59/60) underwent endoscopic evaluation at 1-year, 91% (50/55) at 2-year, and 79% (41/52) at 3-year follow-up. Esophagitis was diagnosed in 55% (33/60) of patients at pre-TF screening, in 5% (3/59) at 1-year, in 10% (5/50) at 2-year, and in 12% (5/41) of patients at 3-year follow-up. Of 33 patients with esophagitis at screening, esophagitis healed in 94% (31/33) with one patient presenting new onset grade A esophagitis at 1 year. At 2-year follow-up, esophagitis healed in 93% (26/28) of patients, three patients presented with new onset of esophagitis compared to screening (two grade A and one grade B). At 3-year follow-up, esophagitis healed in 86% (19/22); two patients who had esophagitis at 2 years were noted to have persistent esophagitis.

The percentage of participants who discontinued PPI therapy at 1 year was 78% (47/60), 76% (42/55) at 2 years and 71% (37/52) at 3 years. TIF 2.0 performed with the EsophyX in well-chosen symptomatic GERD participants provided sustained relief of symptoms at 3 years follow-up. Authors recommended that TIF 2.0 should be considered in the management of GERD due to its demonstrated efficacy. Larger, blinded trials are warranted.

Stefanidis and colleagues (2017) conducted a small, retrospective study to evaluate the long-term efficacy and durability of TIF 2.0. A total of 45 participants (all were on PPIs) underwent TIF 2.0 with EsophyX. One subject was removed from the study due to a pneumothorax during the procedure. Another subject was returned to the endoscopy unit the next day to stop bleeding on the anterior site of the fundoplication. Other adverse events included epigastric pain (39 participants; 86.7%) and pharynx irritation (22 participants; 48.9%). After a follow-up period of 36-75 months (mean 59), the average HRQOL scores improved from 27 to 4 ($p<0.001$). Heartburn was eliminated in 12 out of 21 participants (57.1%), and regurgitation was eliminated in 15 out of 17 participants (88.2%). Of the 44 participants that completed the study, 32 (72.7%) reported the elimination of their main symptom and could stop using PPIs. A total of 3 participants chose to have an additional procedure: 2 Nissen fundoplication surgeries with excellent results and 1 repeat TIF with unfavorable results.

Ebright and colleagues (2017) reported an intermediate follow-up study that examined TIF 2.0 using the EsophyX$_2$ device. All participants (n=80) had a mean follow-up of 24 months, with a minimum of 6 months. Participants were

included who had typical or atypical symptoms of GERD, Hill grade 1-4, a hiatal hernia 2 cm or less, and nonspecific esophageal motility disorder. The researchers found that satisfaction scores improved, going from 2.95 to 1.77 ($p<0.001$). There was a significant reduction in postoperative HRQOL scores for participants with a Hill grade of 3 or 4 compared to Hill grade 1 or 2; however, there was not a significant difference in those with a Hill grade 4 compared to those with Hill grade 1 to 3. Compared to 87% of participants who were using PPIs before the procedure, 56% of participants were still using PPIs at follow-up. A total of 63% of participants were off PPIs or were taking a reduced dosage. Of the participants who were dissatisfied with the procedure, 6 had a degraded wrap, 4 had to undergo a repeat TIF procedure, and 5 underwent a Nissen fundoplication surgery. The authors concluded that "although the TIF is successful in some patients, the dissatisfaction rate of 16% was higher than would typically be seen after a Nissen fundoplication at intermediate follow-up." The authors stated that comparative studies are needed.

Trad and colleagues (2018) reported on the 5-year outcomes from the TEMPO trial. Of the original randomized participants, 44 out of 63 (70%) completed the 5-year follow-up. A total of 37/43 participants had elimination of troublesome regurgitation (95% confidence interval [CI], 72% to 94%). Troublesome atypical symptoms were eliminated in 31/39 participants (95% CI, 64% to 89%). The total regurgitation score improved from 3.0 (on PPIs at screening) to 0.7 ($p<.001$). The total RSI score improved from 22.2 at screening to 6.3 ($p<0.001$). Complete cessation of PPI therapy was achieved in 20/44 participants (95% CI, 32% to 60%). The satisfaction score improved from 2% (1/60, 95% CI, 0% to 10%) to 70% (31/44, 95% CI, 56% to 82%) at 5 years ($p<0.001$ vs screening in all cases). The authors concluded the following:

> Five years after undergoing TIF 2.0, the great majority of TEMPO trial patients experienced durable elimination of all types of troublesome GERD manifestations, including regurgitation and atypical symptoms. There were no SAEs or any safety concerns associated with the TIF 2.0 procedure.

Richter and colleagues (2018) conducted a systematic review and network meta-analysis on the efficacy of TIF 2.0 compared to laparoscopic Nissen fundoplication (LNF). Since RCTs have not been conducted that directly compare TIF 2.0 to LNF, the researchers reviewed RCTs that compared TIF 2.0 or LNF to sham or PPI therapy. They selected 7 RCTs (n=1128) that met inclusion criteria (2 RCTs that compared TIF 2.0 to PPI [n=123], 2 RCTs that compared TIF 2.0 to sham [n=173], and 3 RCTs that compared LNF to PPIs [n=875]). The primary outcomes were decrease in proportion of a 24-hour time period spent at $pH < 4$ and augmentation of the LESP. The secondary outcomes were symptom scores and SAEs. The probability of best treatment was ranked using the Surface Under the Cumulative Ranking (SUCRA). Compared to LNF, the researchers found that TIF 2.0 had a higher probability of improving HRQOL scores (0.66 vs. 0.96); however, a meta-regression showed a shorter follow-up time for TIF 2.0 as a significant confounder. LNF had a higher probability of increasing percent time at $pH < 4$ (0.99 vs 0.32) and increasing LES pressure (0.78 vs 0.72). LNF also had a lower probability for persistent esophagitis (0.38 vs. 0.69). Because data on harm was not reported consistently, the authors were not able to perform a meta-analysis on safety. The study was limited by a network meta-analysis design that was based on probability and the ranking of LNF, TIF, and PPI therapy. The authors concluded the following:

> LNF is superior to TIF and PPIs for the treatment of chronic GERD. TIF only approaches equivalency with the LNF for short-term symptom relief, but durability is a major issue with most patients back on PPIs in 5 years. Furthermore, this technically demanding procedure has relatively higher rates of severe complications, especially esophageal perforations, the harm from which might outweigh any potential risk of long-term PPI use. These findings based on the

> synthesis of all available evidence from RCTs beg for a well-designed and executed RCT with adequate power to conclusively address the question on the efficacy of TIF vs LNF for long-term management of GERD.

McCarty and colleagues (2018) performed a systematic review and meta-analysis on the efficacy of TIF for refractory GERD. The researchers included 32 studies (n=1475) published between 2001 and March 2017. The study was limited by the mix of ELF (n=20), TIF 1.0 (n=138), TIF 2.0 (n=1232) and MUSE (n=85) devices in the primary research, although a subgroup analysis was performed on the individual devices. Participants who had previous anti-reflux surgery or a hiatal hernia > 2 cm were not excluded. The researchers found that TIF was feasible with an immediate success rate of 99% and few SAEs. There were significant improvements in HRQOL scores from baseline (mean difference 17.72, 95% CI, 17.31 to 18.14; p<0.001). At a mean follow-up of 15.5 months, complete discontinuation of PPI therapy was seen in 89% of participants (n=1407; 95 % CI, 82 to 95; p<0.001). In the participants who were tested, there was a significant improvement in esophageal acid exposure scores (n=722; mean difference 3.43%, 95% CI, 2.98 to 3.88; p<0.001), number of reflux episodes in a 24-hour period (mean difference 51.57; 95 % CI, 47.96 to 55.18; p<0.001), and DeMeester scores (n=647; mean difference 10.22; 95% CI, 8.31 to 12.12; p<0.001). In the studies that reported repeat procedures (21 studies; n=1176), a total of 7.5% of participants required a repeat TIF procedure (n=19) or surgery (n=69). In a subgroup analysis that looked at the individual devices, the researchers found TIF 2.0 to demonstrate a significant improvement in HRQOL scores from baseline (n=997; mean difference 17.62, 95% CI, 17.19 to 18.05; p<0.001). The MUSE device also had a significant improvement in HRQOL scores from baseline (n=85; mean difference 19.93, 95% CI, 17.74 to 22.13; p<0.001). For the TIF 2.0 and MUSE devices, significant improvements were seen from baseline in mean percent acid exposure time (TIF 2.0: mean difference 53.18 %, 95% CI, 49.49 to 56.87; p<0.001; MUSE: mean difference 70.40 %, 95% CI, 21.84 to 118.96; p=0.004) and number of reflux episodes (TIF 2.0: mean difference 3.61, 95 % CI, 3.14 to 4.08; p<0.001; MUSE: mean difference 3.97, 95 % CI, 1.236 to 6.59; p=0.003). The authors concluded:

> The longevity of TIF vs. conventional PPI treatment modalities is, and should continue to play, a factor when deciding between surgical and endoscopic treatments. The minimally invasive approach and significantly improved outcomes following TIF procedures suggest an increasing role for TIF. At present, laparoscopic Nissen fundoplication is still the gold standard for the surgical treatment of GERD, though TIF appears to be an emerging option for patients with refractory GERD.

Gerson and colleagues (2018) performed a meta-analysis to determine the efficacy and long-term outcomes of TIF 2.0 in individuals with chronic long-term refractory GERD. The authors included three RCTs (n=233): Trad, 2015; Hunter, 2015; and Hakansson, 2015. The primary outcomes were 3-year-post procedure esophageal pH scores, PPI utilization in milligrams (mg), and HRQOL scores. The researchers found that a higher proportion of individuals with an esophageal pH < 3 were in the PPI group (65%) compared to the TIF 2.0 group (52%); however, the results were not significant. The mean dose per day of PPIs was 15.8 mg in the PPI group (95% CI, 6.42 to 25.15) compared to 8.0 mg in the TIF 2.0 group (95% CI, 0.54 to 15.45), but the probability value was not found to be significant. The HRQOL scores while off PPIs was not significantly different between the TIF 2.0 group (6.93 [95% CI, 0.51 to 13.34]) and the PPI group (10.1 [95% CI, 1.73 to 18.39]). When comparing the changes from baseline, there was a significant improvement in HRQOL that favored the TIF 2.0 group at 1 year post-procedure (p<0.0001). The authors concluded that TIF 2.0 offers "excellent short and long-term symptomatic relief for the majority of chronic GERD patients who are appropriate candidates for the procedure."

Chimukangara and colleagues (2018) conducted an 8-year cohort study on the outcomes of TIF (n=57). However, the differentiation of TIF 2.0 and predicate devices (ELF and TIF 1.0) was not addressed. The authors stated the procedures were done between 2007 and 2014 and represented their institution's early experience with the procedure. They found that at long term follow-up, HRQOL scores improved from 24 to 10 ($p<0.01$), 27% of individuals were no longer taking PPIs, and 73% of individuals who resumed PPIs were able to decrease the dosage. However, the study was limited by a significant loss-to-follow-up of 34 participants, including 12 participants who underwent subsequent traditional laparoscopic surgery at a median interval of 24 months after having the TIF procedure. The authors concluded that "TIF can produce durable improvements in disease-specific quality of life in some patients with GERD" and further studies are needed to identify populations who may benefit from the procedure.

In a small case series, Puri and colleagues (2018) retrospectively evaluated the outcomes of surgical remediation for symptomatic or anatomic failure after TIF. They studied 11 participants with intractable foregut symptoms after TIF who underwent surgical remediation between June 2011 and September 2016. A total of 5/11 participants had a combined laparoscopic hiatal hernia repair in addition to TIF. All participants had remedial surgery after a median of 35.8 months (range 10-72 months). After remediation surgery, 8 participants had incorporation of the left crural pillar with at least one fastener. A total of 6 participants had very dense adhesions and 4 participants had severe anatomic distortion of the gastroesophageal junction (GEJ) from the prior TIF procedure. The study was limited by the small sample and retrospective design. The researchers noted that due to dense adhesions, "simultaneous hiatal hernia repair and TIF should be strongly discouraged." They also stated the following:

> We recommend that all patients with symptomatic failure of TIF undergo a comprehensive evaluation, looking for anatomic distortion of the GEJ. Remediation of patients with symptomatic TIF failure using LNF is effective for reflux symptoms, but may be less effective for post-TIF dysphagia.

Testoni and colleagues (2019) published 10-year outcomes of individuals who had TIF 2.0 for the treatment of GERD. Out of 49 participants, 14 (28.6%) were evaluated after 10 years. At 10 years, 41.7% completely stopped PPI therapy to be responders to TIF 2.0; the complete response rate of TIF 2.0 fell 20% at 10 years compared to 2 years but was not statistically significant. In the intention-to-treat analysis at 10 years, 73.3% of individuals stopped or halved PPI therapy and 33.3% completely discontinued it. A total of 7 individuals unresponsive to TIF 2.0 underwent Nissen fundoplication during the study. The researchers concluded that TIF 2.0 appears to be an effective and reasonably safe treatment long term. The study was limited by a small subject sample and loss to follow-up. The available data addressing the use of EsophyX/TIF 2.0 for the treatment of GERD is of moderate quality, with some methodological weaknesses present in most reported studies, including lack of blinding and small study populations. Further investigation continues to be needed to address the safety and efficacy of EsophyX/TIF 2.0.

Results of a single-center prospective study of individuals undergoing TIF 2.0 and followed up to 9 years were reported by Bell and colleagues (2021). A total of 151 participants underwent TIF 2.0; 131 participants were available for follow-up at a median of 4.92 years (range 0.7-9.7 years). Of the participants followed for the median 4.92 years, 64% had successful (> 50%) reductions in GERD HRQOL scores. At 4.92 years, median regurgitation scores decreased from 15 (8–20) off PPI and 11 (5–20) on PPI at baseline to 0 (0–4). In 62 participants followed for 5-9 years, mean regurgitation remained at 1 (0-3). Daily PPI use decreased from 93% to 32% at 4.92 years, and 22% at ≥ 5 years post-TIF. A total of 33 participants (22%) underwent revision to laparoscopic fundoplication due to failure of TIF to control GERD at a median of 14.7 months after TIF. Two participants had laparoscopic surgery for localized

perforation due to the TIF procedure. The authors concluded that "long-term outcomes of 151 patients undergoing modified TIF 2.0 with the EsophyX2 device demonstrate durability of the procedure out to 9 years." However, less than half (41%) of the 151 participants received follow-up between 5-9 years, so the number of participants participating in long-term follow-up was far smaller than the original cohort. Another limitation is the lack of long-term objective outcome data (for example, esophageal acid exposure) after the TIF procedure.

In 2021, Testoni and colleagues published a systematic review and meta-analysis of long-term outcomes of TIF for GERD. A total of eight studies published up to May 2020 were included involving 418 participants with a mean follow-up of 5.3 years (range 3-10 years). Two studies used the EsophyX/TIF 1.0 procedure, four used EsophyX/TIF 2.0 and two MUSE. Data on proton pump inhibitor (PPI) daily consumption, PPI use reduction, GERD health-related quality-of-life (GERD-HRQL) score, and overall participant satisfaction were pooled and analyzed. Pooled rates of participants on occasional PPIs and completely off PPIs and were 75.8% (95% CI: 67.6-82.6) and 53.8% (95% CI: 42.0%-65.1%), respectively. "The pooled estimated mean GERD-HRQL scores off PPI before and after TIF were 26.1 (95% CI: 21.5-30.7; range: 20.0-35.5) and 5.9, respectively (95% CI: 0.35.1-11.4; range: 5.3-9.8; P<0.001)." Patient-reported satisfaction before and after TIF was 12.3% (95% CI: 12.3-35.1%, I^2 = 87.4%) and 70.6% (95% CI: 51.2-84.6, I^2 = 80%), respectively. The authors concluded that TIF appears to offer an effective long-term therapeutic option for selected patients with GERD. However, this study had limitations. Follow up was only carried out in a portion of study participants (range 24-100% by study) and rarely included a complete clinical assessment (i.e., endoscopic and/or functional evaluations), so follow-up was based only on subject-reported parameters. Furthermore, regarding subject-reported overall satisfaction after TIF, a high heterogeneity across studies was found as judged by an I^2 statistic greater than or equal to 80%.

Snow and colleagues (2022) published the results of a prospective multicenter study assessing subject-reported and clinical outcomes after TIF 2.0 or concomitant TIF (cTIF; TIF 2.0 with hiatal hernia repair) in individuals with laryngopharyngeal reflux (LPR) symptoms and proven GERD. A total of 49 participants had TIF (n=26) or cTIF (n=23); follow-up was for at least 6 months (median of 10.5 months). At follow-up, 90% of participants had improved GERD HRQOL score, 85% normalized RSI, 75% normalized esophageal acid exposure time, and 80% discontinued PPI. There were no procedure-related SAEs. The researchers concluded that TIF and cTIF are safe and effective in controlling LPR symptoms. Nevertheless, this study is limited by small sample size, lack of a control group, and short duration of follow-up.

In 2023, Haseeb and colleagues performed a systematic review and meta-analysis of outcomes of the second-generation TIF technique using the EsophyX device. Ten studies (1 randomized control trial, 4 prospective studies, and 5 retrospective observational studies) involving a total of 564 participants were included. Participants were treated with either TIF 2.0 or cTIF (for hiatal hernia > 2 cm). The primary outcome was the efficacy of TIF measured by RSI score at 6 and 12 months of follow-up. At the 6-month follow-up, data from 474 participants were available from 8 studies; at 12 months, follow-up data from 287 participants were available from 6 studies. Results showed a mean reduction of RSI of 15.7 (95% CI, 12.2-19.3) and 14.7 (95% CI, 11.7-17.7) points at 6 and 12 months, respectively. The proportion of participants using PPI post-TIF was 19% at 6 months and 26% at 12 months. The researchers concluded that TIF 2.0 is safe and effective in reducing symptoms of GERD. However, this study has several important limitations including lack of objective outcomes after the TIF procedure, instead relying on subject-reported results. The data mainly consisted of lower quality observational evidence with only 1 RCT. There was also considerable heterogeneity among the studies, with an I^2 statistic of 88% using a random-effects model. The

authors acknowledge that the scarcity of data available on the long-term effectiveness of TIF limited the scope of their analysis to short-term follow-up.

Results of a systematic review and meta-analysis comparing outcomes between endoscopic plication (TIF) and laparoscopic fundoplication (LAP) for the treatment of GERD were reported by Hajjar and colleagues (2023). Five studies were included comparing 105 (46.1%) individuals receiving TIF to 123 (53.9%) undergoing LAP. Follow-up periods were variable but all were less than or equal to 12 months. The primary outcome demonstrated that at follow-up, 89.2% of individuals undergoing LAP discontinued PPI compared to 69.4% for those receiving TIF. Meta-analysis of the primary outcome demonstrated that those undergoing TIF had reduced odds of PPI discontinuation compared to LAP (odds ratio [OR] 0.27; 95% CI, 0.12–0.64; p=0.003). Secondary outcomes showed that complication rates and the odds of postoperative dysphagia were similar. The authors noted that few long-term or prospective studies are available which is a limitation of this analysis, and that studies with optimized TIF approaches and longer term follow-up data are needed. However, for individuals with GERD who have failed medical therapy, current evidence suggests that "laparoscopic fundoplication remains the gold standard."

Use of the Medigus Ultrasonic Surgical Endostapler (MUSE System) has been described in a few small studies. Zacherl and others (2014) performed a prospective case series study involving 69 participants who were treated with the MUSE System and followed for 6 months. A total of 66 participants completed the trial, at which time GERD-HRQOL scores improved by 50% in 73% of participants (p<0.001). PPI use was discontinued in 64.6%, and a 50% reduction in dose was reported in 56.5% of participants who continued to take PPIs (p<0.001). The percent of time with esophageal pH less than 4.0 was decreased from a mean of 170.8 episodes to 100.4 episodes (p<0.001). Serious adverse events were reported in 10 participants, 6 of which required no intervention. One incidence each of pneumomediastinum and pneumoperitoneum were reported. Two severe adverse events were reported that required intervention, including one with empyema and pneumothorax and one upper gastrointestinal hemorrhage. Both participants recovered with treatment. An interim analysis of these events led to revisions to the protocol and device after the first 24 participants.

Roy-Shapira (2015) reported a pilot case series study of 15 participants. Clinical evaluation was conducted at 6 months post-treatment with the MUSE System and telephonic follow-up was done for 5 years. In 2 participants, the MUSE procedure was abandoned, leaving 13 evaluable participants. GERD HRQOL measures improved significantly with 92% of participants achieving greater than 59%. Mean esophageal pH exposure was significantly reduced from 13.3 to 8.6 (p<0.002), and 54% had normalization as defined by pH less than 4 for 5% of the time, or less. Daily PPI use was eliminated in 92% of participants and 69% were off PPIs completely. One case of benign pneumoperitoneum was reported.

Kim and colleagues (2016) performed a retrospective analysis of participants who were included in the previous study on MUSE by Zacherl and colleagues (2014). Of the small sample of participants (n=36) who completed the HRQOL questionnaire at 4 years post-procedure, 69.4% remained off of PPIs. No long-term adverse effects were reported. The authors stated that "although the patients remaining on daily acid suppression therapy after 4 years of MUSE treatment were still substantial, they had lower symptom scores, and most had reduced dose of PPI medication." They noted that further studies are needed.

A prospective study enrolled 37 individuals with symptomatic GERD for at least 6 months, who underwent therapy with TIF via the MUSE System. Technical success was achieved in all but 1 subject whose intubation was not

possible due to altered anatomy. At 12-month follow-up, there was significant loss to follow-up (n=17; 46%); therefore the intention-to-treat analysis was calculated in just 23 individuals. At 12 months, GERD-HRQL, RSI, heartburn, and regurgitation scores were significantly improved from baseline measures (p=0.001 for each of the four measures). Authors report that 90% of enrolled participants evaluable at 12 months stopped or halved their PPI dose. Functional evaluation was only possible in 13 individuals; due to the small sample, the statistical analysis is unreliable, and significance was not reached in evaluation of change in functional outcomes (total and proximal reflux, the length and basal pressure of the LES, and De Meester score). During the procedure, 1 esophageal perforation requiring surgical repair occurred and at 6 months, 1 subject, who was unresponsive to TIF, underwent Nissen fundoplication (Testoni, 2020). Limitations of this study include the small sample size and significant loss to follow-up.

The case-series addressing the MUSE System are promising, but the incidence of serious adverse events, specifically pneumomediastinum, pneumoperitoneum, and pneumothorax, warrant additional research to establish the safety and efficacy of the device.

Kalapala and colleagues (2022) introduced results of a randomized, sham-controlled, single-blinded clinical trial using a new endoscopic full-thickness fundoplication device, the GERD-X (a competitor of EsophyX and MUSE). A total of 70 individuals with PPI-dependent GERD were randomized to either GERD-X treatment or a sham procedure. The primary end point was ≥ 50% improvement in GERD-HRQL score at 3 months. This outcome was more frequently achieved in the GERD-X group vs. sham (65.7% vs 2.9%; p<0.001). In the GERD-X group, 62.8% of participants were off-PPI at 12 months compared with 11.4% in the sham group (p<0.001). Overall, the procedure using the GERD-X device was found to be effective at reducing GERD symptoms and improving quality of life. However, in this small, short-term study, reflux was not assessed objectively at the end of 12-month follow-up in all participants. The authors stated that "large, prospective trials with long-term follow-up are required to conclude the benefits of this procedure after 1 year."

Injection Therapy (for example, Enteryx®, PMMA beads; the Gatekeeper® Reflux Repair system, and Durasphere®)

Enteryx was voluntarily removed from the U.S. market in September 2005 after serious adverse events involving unrecognized transmural injections. Medtronic, the manufacturer of the Gatekeeper Reflux Repair System (an expandable hydrogel prosthesis), has suspended further research on this product prior to FDA approval. Only one small case series describing injection of polymethylmethacrylate (PMMA) beads was identified in a literature search (Feretis, 2001).

Durasphere was originally developed and approved as a bulking agent for the treatment of urinary incontinence. At this time, the results of only one small pilot study have been published on the use of this product for the treatment of GERD (Ganz, 2009). This case series study involved 10 participants, 9 of whom completed the 12-month follow-up. The authors report that 70% of participants discontinued all antacid medications, and 90% reduced their PPI use by greater than 50%. Normal esophageal pH was detected in 4 participants. These results are promising, but further data from large-scale trials is warranted before the clinical utility of this product can be fully assessed.

Other Considerations for GERD Treatments

In 2011, the Agency for Healthcare Research and Quality (AHRQ) published a technology assessment entitled "Management Strategies for Gastroesophageal Reflux Disease: An Update. Comparative Effectiveness Review." This document details the evaluation of various technologies used to treat GERD, including endoscopic surgical methods and technologies. They conclude that, "The effectiveness of endoscopic procedures remains substantially uncertain."

In 2011, the American Society of General Surgeons (ASGS) published a position on the coverage of transoral fundoplication and stated the following:

> The ASGS continues to support the adoption of this procedure by trained General Surgeons as a less invasive alternative to more conventional surgical techniques. However, ASGS believes that in patients who are candidates for fundoplication, the preferred surgical technique for creating the fundoplication should be left to the discretion of the General Surgeon and should be based on the surgeon's independent medical judgment and the individual patient's clinical circumstances.

The American College of Gastroenterology (ACG) states the following in their guideline (Katz, 2013) on GERD: "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)."

In 2015, the American Society for Gastrointestinal Endoscopy (ASGE) published a guideline on the role of endoscopy in the management of GERD and made the following statement:

> Endoluminal antireflux techniques represent potentially new therapeutic indications for GI endoscopy. Prospective trials comparing these therapies with existing medical and surgical options by using objective measures of GERD as the primary endpoint could be useful in further defining the clinical role of these procedures. Appropriate patient selection and endoscopist experience and training should be carefully considered before pursuing these therapies.

In 2018, an expert panel of 14 esophagologists assessed management options for individuals with GERD refractory to PPIs (Yadlapati, 2018). They applied the RAND/UCLA Appropriateness Method to evaluate management options in the context of nine hypothetical scenarios of individuals with GERD refractory to medical therapy. According to the publication, "An appropriate intervention is one in which the expected health benefit exceeds the expected negative consequences by a sufficiently wide margin that the procedure is worth doing, exclusive of cost." The appropriateness of laparoscopic fundoplication, the LINX device, transoral incisionless fundoplication, radiofrequency energy delivery and pharmacologic/behavioral therapy were each evaluated in the context of the hypothetical scenarios. The expert panel made the following recommendations:

- Invasive therapy requires abnormal reflux burden in the form of elevated EAE (with or without a large hiatal hernia), or positive symptom-reflux association for regurgitation with large hiatal hernia (laparoscopic fundoplication for all three scenarios; magnetic sphincter augmentation for small/absent hiatal hernia);
- Transoral incisionless fundoplication and radiofrequency energy delivery are not endorsed in any of the evaluated PPI unresponsive profiles;
- Overall, medical/behavioral therapies are preferred for the other scenarios.

In 2022, the American Gastroenterological Association (AGA) issued a report entitled *AGA Clinical Practice Update on the Personalized Approach to the Evaluation and Management of GERD: Expert Review*. This article presented Best Practice Advice statements developed by participants in the AGA Center for GI Innovation and Technology GERD Consensus Conference. One of the statements was that "transoral incisionless fundoplication is an effective endoscopic option in carefully selected patients" in the absence of a hiatal hernia. However, criteria for selecting appropriate patients for this procedure were not addressed. Furthermore, it was stated that further research is needed into risks/benefits, durability, effectiveness, and treatment outcomes in order for this technique to be optimally utilized.

In their current guideline on GERD (Katz, 2022), the ACG suggests that TIF should be considered for patients with troublesome regurgitation or heartburn who do not wish to undergo anti-reflux surgery and who do not have severe reflux esophagitis (conditional recommendation, low level of evidence). However, the guideline also states that while randomized trials have shown that TIF is effective for treating troublesome regurgitation, the long-term benefit of TIF is not established and is questionable. The authors reference a recent systematic review and meta-analysis on the use of TIF for the treatment of GERD (Testoni, 2021) in which "although symptoms responded to TIF significantly more often than to PPIs/sham, TIF did not result in significant improvement in esophageal acid exposure and most patients resumed PPIs at reduced dosages during long-term follow-up."

In the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) multi-society guideline on the treatment GERD, the expert panel suggested that individuals with GERD may benefit from surgical fundoplication over TIF 2.0 (Slater, 2023). This recommendation is largely due to the lack of sufficient trials directly comparing TIF 2.0 to fundoplication. Among the drawbacks of using TIF 2.0 is that it is not useful as a standalone procedure in individuals with a hiatal hernia of greater than 2 cm, thus limiting TIF 2.0 as an option for many persons with GERD. In addition, TIF 2.0 is an advanced endoscopy procedure that requires specialized training, which may contribute to the low level of adoption of this technique worldwide. However, the panel did recommend that individuals with GERD might benefit from TIF 2.0 over continued PPI therapy. The panel deemed the undesirable effects of TIF 2.0 compared to PPI use to be small. The authors concluded that additional long-term prospective comparative studies of TIF 2.0 versus fundoplication are needed.

Similar recommendations were made by the expert panel in the SAGES guideline with regard to the Stretta procedure (Slater, 2023). The panel suggested that adult participants with GERD may benefit from surgical fundoplication over Stretta. The panel deemed there to be small desirable effects and moderate undesirable effects of Stretta compared to fundoplication. Undesirable effects included lower QOL, higher reflux recurrence and reoperation required after Stretta. However, the panel did recommend that individuals with GERD might benefit from Stretta over continued PPI therapy. Conclusions were that "Stretta is a still evolving technology that has not been widely adopted. Increased training and proctoring in the technique are needed world-wide before the technology will improve." In addition, comparative trials (especially randomized controlled trials and long-term durability studies) are needed in order to strengthen recommendations for this technology.

Transendoscopic Therapy for Dysphagia and Related Conditions

The use of peroral endoscopic myotomy (POEM) has been proposed as an alternative to laparoscopic Heller myotomy (LHM) for achalasia and other conditions related to dysphagia (e.g., diffuse esophageal spasm [DES], non-

relaxing LES). While endoscopic treatment for dysphagia has been proposed for over 20 years, it was only recently that renewed interest has resulted in clinical studies.

Ren and colleagues (2012) published a case series study involving 119 participants who received POEM treatment. The authors reported a high incidence of intraoperative complications, including subcutaneous emphysema (27/119, 22%), mediastinal emphysema (12/119, 10.1%) and pneumothorax (3/119, 2.5%). Complications in the immediate post-operative period were also reported to be very high, including subcutaneous emphysema reported to be 55% (66/119), mediastinal emphysema 29.4% (35/119), pneumothorax 25.2% (30/119), thoracic effusion 48.7% (58/119), segmental atelectasis 49.06% (47/119), aeroperitoneum 39.5% (47/119), and delayed hemorrhage 0.8% (1/119). During the 1-month follow-up, 1 subject (0.8%, 1/119) suffered dysphagia that was successfully treated with balloon dilation. Another subject (0.8%, 1/119) had dysphagia, vomiting and edema of the gastric cardia. Surgical intervention was conducted, but the report only provides outcome from the fifth post-operative day when the subject tolerated a liquid diet. It is unknown whether a return to a standard diet was successful. The large incidence of complications in this study is not in line with those in previously reported studies. This may be due to surgical technique or some other factor. However, with the limited data overall addressing the use of POEM, this is a source of concern which requires further investigation.

Stavropolous and colleagues (2013), in a review article of endoscopic approaches to achalasia, provides a discussion of the role of myotomy in the treatment of achalasia. Among the discussion of the peer-reviewed literature, they describe the results of a study done by their group, which to date has only been published in abstract form. They also discuss the results of an unpublished survey study of the opinions of surgeons who conduct POEM surgery. Unfortunately, such evidence is of little value in determining the efficacy of the POEM technique. They further compare the POEM endoscopic approach with historical publications of alternative methods, but since this argument is based upon the existing limited data for POEM, the utility of this evidence is poor. Addressing the available evidence, they state that the data regarding adverse events with POEM are limited. They also state that very little data exist in the published literature regarding POEM in individuals with nonachalasia hypercontractile conditions of the esophagus, age extremes, sigmoid and megaesophagus or in individuals with prior treatment with botulinum toxin injection (BTI), pneumatic dilation (PD) or LHM. This only highlights the need for more data addressing the use of POEM for a wide array of indications.

von Renteln and colleagues (2013) published a brief report on a case series study involving 70 participants with achalasia. They reported that at 3 months after POEM, 97% of participants were in remission with no symptoms. At the 3-month, 6-month, and 12-month time point symptom scores, as measured using the Eckardt scale, scores were reduced from 7 to 1, 1.3, and 1.7 respectively ($p<0.001$). At 3 months, LES pressures were measured in 87.1% of participants (61/70) and were reduced from 28 to 9 mm Hg ($p<0.001$). No LES pressure data was provided at 6 and 12 months. At the 6- and 12-month evaluations, the percentage of participants meeting the definition of treatment success was reported as 88.5% and 82.4%, respectively. No conversions to laparoscopic or open procedures were reported. Without a comparison group the value of these results are unclear.

A significant number of small case series studies have also been published addressing the use of POEM for achalasia and other conditions (Chan, 2016; Inoue, 2011; Jones, 2016; Kurian, 2013; Minami, 2013; Swanstrom, 2011; Ujiki, 2013; Verlaan, 2013; von Renteln, 2012). While these reports provide some data suggesting significant benefits, they also report a significant rate of serious adverse events including penetration of the cardiac mucosa, exposure of mediastinal tissue, pneumoperitoneum, esophagotomy, gastric mucosal perforation, capnoperitoneum, capnothorax associated with hemodynamic instability, and development of GERD and esophagitis. There is also significant

variation in the reported studies with regard to how the actual procedure is conducted, with the length of myotomy and whether to do a partial or complete myotomy of the cardia.

A large controlled study on the use of POEM for achalasia was reported by Bhayani and colleagues in 2014. This study involved 101 participants, 37 who underwent POEM and 64 who underwent LHM (42% Toupet and 58% Dor fundoplication). The authors reported that rates of post-operative morbidity were comparable. Eckardt scores at 1 month post-treatment were significantly better for POEMs vs. myotomy (1.8 vs. 0.8, p<0.0001). At 6 months, both groups were reported to have similar improvements in their Eckardt scores (1.7 vs. 1.2, p=0.1). Both groups had significant improvements in post-myotomy lower esophageal sphincter profiles. Post-myotomy resting LES pressures were higher in the POEM group vs. the myotomy group (16 mm Hg vs. 7.1 mm Hg, p=0.006). Postmyotomy relaxation pressures and distal esophageal contraction amplitudes were not significantly different between groups. Routine post-operative 24-hour pH testing was obtained in 76% POEM participants and 48% myotomy participants and the authors reported that 39% of POEM participants and 32% myotomy participants had abnormal acid exposure (p=0.7). They concluded that POEM is comparable with LHM for effective treatment of achalasia. However, is should be noted that this study was not powered or designed as a non-inferiority study.

Ling and colleagues (2014) reported on a prospective case series study involving 87 treatment-naive participants with achalasia and treated with POEM. Postoperatively, Eckardt scores declined to less than or equal to 3 in 97.7% of participants, from a pre-operative mean of 7.1 to post-operative mean of 0.04 (p=0.001). Symptom relief and QOL were measured using the SF-36 physical component summary (PCS) and mental component summary (MCS). PCS improved from 32.6 to 68.5 at last follow-up (p<0.001) and MCS improved from 44.1 to 67.4 at last follow-up (p=0.003). Mean LES decreased significantly from 32.4 mm Hg to 3.8 mm Hg (p<0.001). Post-operative timed barium esophagogram indicated no retention and complete flow into the stomach, with mean barium column height at 1 minute post-swallow decreasing from 11.7 cm pre-operative to 3.2 cm post-operative (p<0.001). The 5-minute column height went from 9.1 cm to 2.3 cm (p<0.001). Cutaneous emphysema occurred in 11.5% of participants (10/87), mucosal injury was reported in 2.3% (2/87), and pneumothorax in 1.1% (1/87). At 3 months follow-up, 5 participants were found to have symptomatic esophagitis, 3 with Los Angeles classification grade A and 2 with grade B. These findings are promising, but in the absence of a comparator group of participants who underwent standard therapy, the clinical meaning is unclear.

Kumbhari and colleagues (2015) reported on the results of a retrospective, nonrandomized, comparative study that involved 49 participants who were treated with POEM for type III achalasia compared to 26 participants who underwent LHM. POEM participants were followed for a mean of 8.6 months vs. 21.5 months. Statistically significant differences between groups were reported at baseline, including exposure to prior therapy and baseline Eckardt stage (p<0.01 for both). The authors reported that clinical response was significantly more frequent in the POEM group vs. the LHM group (98.0% vs. 80.8%; p=0.01). The median length of myomectomy was twice as long in the POEM group vs. the LHM group (16 cm vs. 8 cm; p<0.01). Rate of adverse events was significantly less in the POEM group (6% vs. 27%; p<0.01), with no severe events reported in either group. The adverse events reported were considered moderate grade and included ileus, wound infection, arrhythmia and urinary tract infection in the LHM group and pulmonary embolus in the POEM group. In univariate analysis, the rate odds for clinical failure were greater in the LHM group vs. the POEM group (odds ratio [OR]=11.4; p=0.031); however, this difference was not found in multivariate analysis (OR=11.32; p=0.6). The authors note several limitations in their study, including the significant differences between groups at baseline and significantly longer follow-up in the LHM group. Other limitations noted include different diagnostic criteria used to evaluate the groups, with the LHM group participants not undergoing high-resolution esophageal manometry while the POEM group did.

Several moderately sized case series studies have been reported on the use of POEM. The largest to date was reported by Ramchandani in 2015. This retrospective study involved 200 consecutive participants with achalasia who were followed for 1 year following treatment. The authors reported a technical success rate at 1 year of 92%. Mean Eckardt score was 7.2 ± 1.55 prior to POEM and 1.18 ± 0.74 after POEM (p=0.001). There was significant improvement of esophageal emptying on timed barium esophagogram (38.4 ± 14.0% vs. 71.5 ± 16.1%; p=0.001). Pre-procedure and post-procedure mean lower esophageal sphincter pressure was 37.5 ± 14.5 mm Hg and 15.2 ± 6.3 mm Hg, respectively (p=0.001). Erosive esophagitis was seen in 16% of participants who underwent POEM. No major adverse events were reported.

A retrospective, cross-sectional study conducted by Hoppo and colleagues (2015) involving 33 (achalasia n=25 and non-achalasia n=8; mean age 56.9 years; mean BMI 30.9) participants with esophageal motility disorders as defined by the Chicago classification were considered for POEM. Of the participants with achalasia preoperatively, 1 subject was classified as Type I (4%, 1/25), 19 were classified as Type II (76%, 19/25) and 5 were classified as Type III (20%, 5/25). Of the non-achalasia participants, 5 (62.5%, 5/8) had Jackhammer esophagus, 2 (25%, 2/8) had Nutcracker esophagus and 1 (12.5%, 1/8) had Diffuse Esophageal Spasm (DES). The chief symptoms experienced by the participants included dysphagia, regurgitation, heartburn, chest pain, cough, and nausea. The study utilized GERD HRQOL questionnaires, RSI and achalasia disease specific HRQOL where results were obtained preoperatively and postoperatively over a 23-month period. The authors hypothesized that POEM could achieve therapeutic success with rare adverse occurrences such as mediastinitis and abscess formation. An initial concern for the frequency of postoperative GERD symptoms (i.e., esophagitis; abnormal pH testing) was recognized; however, a previous 2014 study revealed that this prevalence was similar to participants who had the LHM with partial fundoplication. A limitation of this study was that postoperative pH testing or endoscopy data was insufficient although there was meaningful improvement in the GERD HRQOL and RSI scores, implying POEM does not exacerbate GERD symptoms. The authors determined that POEM can be used in conjunction with laparoscopic procedure and as salvage for esophageal dysmotility noting that further long-term investigative evaluation is needed.

Jones and colleagues (2015) led a prospective study with 43 participants undergoing POEM (mean age 53.5; BMI 29.6) over a 23-month period. The authors utilized unbiased testing (48-hour pH probe, manometry, endoscopy), the GERD HRQOL assessment, the GERD Symptom Score (GERSS) and antacid use to investigate their hypothesis that reflux symptoms and HRQOL scores were not associated with esophageal acid exposure. Dysphagia scores improved from 4 (0-5) at baseline to 0 (0-3) following POEM (p<0.0001), GERSS scores improved from 33 (1-64) to 9 (0-47; p<0.0001) and GERD HRQOL scores improved from 22 (3-43) to 8 (0-30; p<0.0001) Twenty-six participants (60%) underwent pH testing 6 months after POEM. Eleven (42%) participants had normal esophageal acid exposure, while 15 participants (58%) demonstrated abnormal esophageal acid exposure. Seven participants (28%) had significant reflux symptoms that were managed with PPI therapy. The authors established that POEM is a successful therapeutic option to treat esophageal achalasia although some participants will continue to experience asymptomatic GERD symptoms post-operatively. They recommended that postoperative pH measurement and EGD be performed for participants requiring long-term PPI therapy.

A systematic review and meta-analysis by Marano and colleagues (2016) were conducted to assess the durable effectiveness between POEM and LHM surgical interventions for treating achalasia. The results revealed that both procedures were similar in reducing Eckardt scores, complication rates, the necessity for post-operative analgesia, operative duration, and hospital length of stay. However, POEM had inferior short-term outcomes for post procedure

GERD symptoms as compared to LHM. Based on the authors' observations and conclusions, the recommendation for randomized clinical trials comparing POEM with other standard procedures is warranted.

Familiari and colleagues (2016) reported on a retrospective study with a goal to present the outcomes from their institution's first 100 POEM participants (median age was 48.4, 41 males) All participants had a confirmed diagnosis of achalasia and preoperatively experienced esophagogastroduodenoscopy (EGD), esophageal manometry and timed barium esophagogram procedures. The 100 participants were categorized under the Chicago classification: 42 participants were classified as Type I, 41 classified as Type II, 1 classified as Type III, 15 were unclassified, and classification of 1 subject was silent. The mean Eckardt score was 8.1 at baseline and the mean preoperative basal LES pressure was 41.4 mm Hg (± 19.3). Of the 100 POEM participants, 94 (94%) successfully completed the procedure with varying follow-up periods and in 6 participants the procedure was terminated. Two participants were lost to follow-up, 17 participants completed a 24-month follow-up, 3 participants completed an 18-month follow-up, 31 participants completed a 12-month follow-up, 36 participants completed a 6-month follow-up and 5 participants completed follow-up at 3 months. Of the 92 participants who completed the procedure and some length of follow-up, 87 (94.5%) achieved clinically effective results with no complications. The mean Eckardt score decreased from 8.1 at baseline to 1.1 at the last follow-up visit. The postoperative "mean basal LES pressure significantly decreased from 40.2 mm Hg at baseline to 19 mm Hg at the 12-month follow-up and 20 mm Hg at the 24-month follow-up." During follow-up, 73 participants agreed to 24-hour pH monitoring to assess for postoperative GERD symptoms. Total reflux time > 5% was observed in 39/73 (53.4%) participants who underwent esophageal pH monitoring; 17/73 (24.6%) participants reported heartburn and used antacids every day; esophagitis was seen in 20 participants (Los Angeles classification: Grade A=9, Grade B=5, Grade C=3, Grade D=2 and 1 subject with esophagitis but no GERD symptoms). Limitations identified in the study included inadequate evidence of the efficacy of the procedure, even though 51 participants had follow-ups for 12-months, and the lack of pre and post GERD HRQOL assessments. The authors concluded that their results would potentially be confirmed if long-term randomized trials were conducted to substantiate POEM as a first-line therapeutic option for the treatment of achalasia.

Werner and colleagues (2016) published a retrospective analysis to determine the short-term and long-term outcomes of POEM. The primary outcome was POEM failure (defined as an Eckardt score > 3) at 2 years or longer. A total of 80 participants were initially included. At the end of the study period there were 17 POEM failures: 3 within 3 months and 14 within a mean of 20.1 months. There were 16 cases that had minor adverse events during the procedure including small perforations, bleeds, and a single case of deep ulceration of the mucosa. The overall success of the treatment was 77.5%; however, reflux was found in 37.5% of participants. The authors stated that PPIs may need to be given routinely after POEM procedures. Limitations included a small sample size, the subjective nature of the Eckardt score, and differences in follow-up protocols between centers. The authors recommend large, prospective, comparative studies.

A retrospective cohort study enrolled 180 individuals with achalasia who underwent POEM. The cohort was divided into two groups, those with a history of HM (n=90) and those with no history of HM (n=90). Technical success, clinical success (defined by a decrease in Eckardt scores to < 3), and rates of adverse events were compared between the two groups at the median follow-up of 8.5 months. Technical success was achieved in 98% of the HM group and 100% of non-HM group (p=0.49). A significantly lower proportion of the HM group achieved clinical success with POEM (81%) than in the non-HM group (94%; p=0.01). Rates of adverse events between the groups were not significantly different (p=0.23). Symptomatic reflux and reflux esophagitis were comparable between the two groups after POEM (Ngamruengphong, 2017).

In a systematic review and meta-analysis, Schlottmann and colleagues (2017) compared outcomes of POEM (n=1958) to LHM (n=5834). Improvement of achalasia symptoms, as reported by the participants, was 93.2% in the POEM group and 87.7% in the LHM group. The predicted probability for improvement at 12 months for POEM and LHM was 93.5% and 91%, respectively (p=0.01), and at 24 months was 92.7% and 90%, respectively (p=0.01). The researchers estimated that the odds ratio of having GERD symptoms after POEM was 1.69 (95% CI, 1.33 to 2.14; p<0.0001). In studies that included post-procedure EGD, GERD was found in 22.4% of the POEM group and 11.5% of the LHM group (OR 9.31; 95% CI, 4.71 to 18.85; p<0.0001). Comparatively, in studies that included post-procedure pH monitoring, pathologic reflux was found in 47.5% of the POEM group and in 11.1% of the LHM group (OR 4.30; 95% CI, 2.96 to 6.27; p<0.0001). Hospital length-of-stay was 1.03 days longer for the POEM group (p=0.04). The researchers concluded that POEM and LHM were both effective for esophageal achalasia, with POEM showing statistical superiority. They pointed out, however, that the absolute difference between the procedures was small (5.5%), and to "be slow to draw conclusions as to superiority." The researchers also concluded that POEM has a much higher risk of pathologic GERD that is not completely understood. The LHM procedure, on the other hand, has evolved to include a fundoplication that reduces chances of GERD. Limitations of the study included a lack of prospective trials, short follow-up times, and a lack of heterogeneity in reporting outcomes. The researchers state that long-term follow-up and RCTs comparing POEM and LHM are needed.

In an international, multicenter, retrospective study, Chen and colleagues (2018) evaluated the clinical efficacy and safety of POEM in octogenarians. The researchers included 76 individuals with achalasia (Type I-III and unspecified), aged 80 and older, who had the POEM procedure between January 2010 and January 2016. The follow-up was a median of 256 days. The primary endpoint was clinical success defined as Eckardt scores ≤ 3 at follow-up. Secondary endpoints included technical success defined as completion of esophageal and gastric myotomy, length of post-procedure hospitalization, and rate and severity of adverse events. The researchers found that technical success was achieved in 71/76 (93.4%) participants. Of those who had technical success, clinical success was achieved in 90.8% of participants, with a significant difference between baseline and post-procedure Eckardt scores (7.0 ± 2.3 vs. 0.8 ± 1.0; p<0.001). In those who had high-resolution manometry (n=21), integrated relaxation pressure decreased from 24.4 ± 15.0 to 11.6 ± 8.9 mm Hg (p<0.001). Symptomatic reflux was reported by 16.1% of participants. There were 14 adverse events in 11 participants (rate of 14.5%), which included inadvertent mucosotomy (n=3), capnoperitoneum and/or capnothorax and/or capnomediastinum needing drainage (n=6), esophageal leaks (n=2), inadvertent entry of the endoscope into the mediastinum needing closure with endoscopic suturing (n=2), and cardiac arrhythmia (n=1). The researchers concluded that "POEM appears to be technically feasible and clinically effective in octogenarians with achalasia." They recommended further studies on this population that directly compare POEM to LHM or pneumatic dilation. The study was limited by a retrospective design, short follow-up duration, and the inclusion of only expert tertiary-care centers that perform a high number of POEM procedures.

Repici and colleagues (2018) conducted a systematic review and meta-analysis on the incidence of GERD after POEM compared to LHM with fundoplication. The researchers included prospective studies that included 10 or more adult participants with a diagnosis of achalasia (or other spastic esophageal disorder) and that provided the incidence of GERD after at least 2 months post-procedure. A total of 17 studies (n=1542) were included in the POEM group, and 28 studies (n=2581) were included in the LHM group. The primary outcome was the incidence of GERD based on symptoms, esophageal pH monitoring, and endoscopic findings. In the POEM group, the rate of reflux disease was 18.1% (symptoms), 39.3% (esophageal pH monitoring), and 30.7% (endoscopic findings). In the LHM group, the rate of reflux disease was 8.6 % (symptoms), 14.9% (esophageal pH monitoring), and 8.3% (endoscopic findings). The rate of esophagitis after POEM was 29.4% (95% CI, 18.5% to 43.3%) compared to 7.6% (95% CI, 4.1% to 13.7%) after LHM. The researchers found that POEM is associated with a 2- to 3-fold increased risk of reflux compared to

LHM. They concluded that "pH monitoring and appropriate treatment after POEM should be considered in order to prevent serious long-term reflux-related adverse events."

Park and colleagues (2019) published a meta-analysis on the comparison between POEM and LHM for individuals with achalasia. They searched for studies between January 2000 and September 2018 and included 15 studies (n=1213) in their analysis. They found that the Eckardt scores were better in the POEM group (pooled standardized mean difference [SMD], –0.58; 95% CI, –1.03 to –0.13), the length of myotomy was greater in the POEM group, and there was no difference in reflux between the groups. However, they found that erosive esophagitis was less in the LHM group (pooled RR, 1.88; 95% CI, 0.98 to 3.62). Overall, the researchers found that the short-term efficacy of POEM was superior to LHM, but long-term follow-up data is needed. The study was limited by the heterogeneity and observational nature of the studies, and the researchers stated that a "well-designed randomized controlled trial is warranted to reach a definitive conclusion."

A 2019 multicenter, open-label, randomized clinical trial sought to establish the safety and efficacy of POEM compared to LHM. 'Clinical success' was the primary end point, defined as an Eckardt symptom score of 3 or less without the use of additional treatments. Secondary endpoints included adverse events, esophageal function, Gastrointestinal Quality of Life Index (GIQLI) score (range, 0 to 144, with higher scores indicating better function), and gastroesophageal reflux. Study inclusion criteria included the following: at least 18 years of age, diagnosis of symptomatic, primary achalasia, a medical indication for surgical myotomy or pneumatic dilation, a baseline Eckardt symptom score greater than 3, and no history of prior surgery of the stomach or esophagus. A total of 221 individuals were randomly assigned to undergo either POEM (n=112) or LHM plus Dor's fundoplication (n=109); 4 in the POEM group and 5 in the LHM group were either lost to follow-up or had a major protocol deviation. Clinical success at the 24-month follow-up was achieved in 83.0% of the POEM group and 81.7% of the LHM group (95% CI, -8.7 to 11.4; p=0.007 for noninferiority). Serious adverse events occurred in 2.7% of the POEM group and 7.3% of the LHM group. At 24 months, study end, improvement in esophageal function from baseline (as assessed by measurement of the integrated relaxation pressure of the lower esophageal sphincter) did not differ significantly between the treatment groups (difference, -0.75 mm Hg; 95% CI, -2.26 to 0.76), nor did improvement in the score on the GIQLI (difference, 0.14 points; 95% CI, -4.01 to 4.28). At 24 months, 44% of the POEM group and 29% of the LHM group had reflux esophagitis, as assessed by endoscopy. A post hoc analysis of the use of PPIs showed that a higher percentage of participants in the POEM group than in the LHM group were receiving low-dose PPIs across all measured time points; at study end, 52.8% and 27.2%, respectively. Authors conclude that POEM was noninferior to LHM in controlling symptoms of symptomatic primary achalasia, though it was associated with increased incidence of GERD (Werner, 2019).

Another multicenter, open-label, randomized clinical trial sought to establish the safety and efficacy of POEM compared to pneumatic dilation with a 30-mm and a 35-mm balloon, among treatment-naive individuals diagnosed with achalasia (Eckardt score > 3). The primary outcome was treatment success, defined as an Eckardt score $\leq$ 3, in addition to the absence of severe complications or re-treatment. A total of 130 participants, 18 and older, were randomized at enrollment and underwent treatment (n=64, POEM group; n=66, pneumatic dilation group); 126 (95%) completed the 2-year study. At study-end, the primary outcome was achieved in 58 of 63 participants (92%) in the POEM group compared to 34 of 63 (54%) in the pneumatic dilation group, a difference of 38% (95% CI, 22%-52%; p<0.001). Newly diagnosed GERD occurred more often in the POEM group than in the pneumatic dilation group (22 of 54 [41%] vs 2 of 29 [7%]; difference, 34% [95% CI, 12%-49%]; p=0.002). A total of 2 serious adverse events, including 1 perforation, occurred after pneumatic dilation, while no serious adverse events occurred in the POEM group (Ponds, 2019).

In a continuation of the study by Ponds and colleagues (2019), Kuipers and colleagues (2022) published an analysis of 5-year follow-up data of the randomized, controlled trial. At 5 years, data were available for 62 participants in the POEM group and 63 participants in the pneumatic dilation group. Treatment success was achieved in 50 participants (81%) in the POEM group compared with 25 (40%) in the pneumatic dilation group, a 41% difference (95% CI, 25–57; p<0.0001). PPI use was significantly higher after POEM than after pneumatic dilation among participants still in clinical remission (23/50 participants [46%] vs 3/24 participants [13%]; p=0.008). The authors recommended that although PPI use remains high 5 years after POEM, this procedure should be proposed as an initial treatment for individuals with achalasia rather than pneumatic dilation based on the significantly greater long-term treatment success.

A retrospective cohort study compared the long-term efficacy of POEM with HM as a treatment for achalasia. Clinical failure was defined as: (1) Eckardt Score of > 3 for at least 4 weeks, (2) achalasia-related hospitalization, (3) or repeat intervention. A total of 98 study participants were enrolled, n=55 for the POEM group and n=43 for the HM group, and followed for an average of 4 years and 5.4 years, respectively. Overall, there was statistical difference in success (POEM 72.2%, HM 65.1%; p=0.417), with the exception of stratification by Type III achalasia, which favored POEM over HM for efficacy (53.3% vs 44.4%, p<0.05). There was no statistical difference in GERD, esophagitis or major complications reported (Podboy, 2020).

A prospective case-control study enrolled 280 individuals who had primary achalasia and planned treatment with either POEM (n=140) or HM + Dor's fundoplication (n=140). Clinical success was defined as an Eckardt score ≤ 3; endoscopic and pH-manometry evaluations were also included for analysis. POEM was associated with a significantly shorter operative time and postoperative stay compared to HM (p<0.001). There were no mortalities associated with either procedure and no significant difference in severe procedure-related complications (p=0.33). At a median follow-up of 24 months for POEM and 31 HM, there was no significant difference in clinical success (99.3% of the POEM group and 97.7% of the HM group; p<0.12). The probability of having symptoms adequately controlled 4 years post-procedure, was > 90% for both groups (p=0.2). HR-Manometry showed a similar reduction in the LES pressure whereas 24-h pH-monitoring showed an abnormal acid exposure in 38.4% of the POEM group compared to 17.1% of the HM group (p<0.01) and esophagitis was found in 37.4% of the POEM group and 15.2% of HM group (p<0.05) (Costantini, 2020). At 4 years, POEM shows similar clinical efficacy as HM + Dor's fundoplication for the treatment of achalasia, and potentially improved efficacy for Type III achalasia. However, the elevated of incidence of GERD and esophagitis was sustained at year 4 and the clinical implications of this warrants continued investigation.

A systematic review and meta-analysis sought to compare the effect of achalasia subtype on clinical outcomes after treatment with POEM versus LHM. A total of 20 studies were chosen for inclusion comprised of 1575 study participants. The overall success rate for POEM was 95%, 97% and 93% for Type I, II and III achalasia, respectively. For LHM, the overall success rate was 81%, 92% and 71%, respectively. POEM was significantly more likely to be successful compared to LHM for Type I and III achalasia (p=0.032 and p=0.007, respectively), whereas the success rates were similar for Type II achalasia (Andolfi, 2019).

A systematic review and meta-analysis by Chandan and colleagues (2020) published pooled available data from published trials on the safety and efficacy of POEM as a treatment for spastic esophageal disorders (SEDs), which included diffuse esophageal spasm, jackhammer esophagus and Type III achalasia. The final analysis included nine studies comprised of 210 enrolled participants. The overall pooled rate of success for POEM was 89.6% (95% CI,

93.5 to 92.1%). The overall pooled rate of clinical success in Type III achalasia alone was 92.2% (95% CI, 85.6 to 95.9; I^2=0%). Due to insufficient sample sizes, authors were unable to calculate a separate pooled success rate for jackhammer esophagus (n=28) and diffuse esophageal spasm (n=26).

A short-term, retrospective study (6 month follow-up) sought to determine the efficacy of POEM for non-achalasia esophageal motility disorders (NAEMDs [esophagogastric junction outflow obstruction n=7, nutcracker n=4, distal esophageal spasm n=6, and jackhammer esophagus n=13]) relative to match-controls treated with POEM for achalasia (Type I n=7, Type II n=23, Type III n=30). Interim response rates at 3 months were 80% (24/30), 90% (27/30), and 100% (30/30) in NAEMD, Type I–II achalasia and Type III achalasia, respectively (p<0.01). Eckardt scores improved from preoperative baseline in all groups. In the NAEMD group, there was a significant improvement of dysphagia, regurgitation, and chest pain scores. The 6-month response rates were 63.2% (12/19), 95.5% (21/22), and 87.0% (20/23) in NAEMD, Type I–II achalasia and Type III achalasia, respectively (p=0.03). Based on the short-term results of this small, retrospective matched-analysis, authors conclude that POEM is an effective treatment of NAEMD, albeit less than the efficacy achieved in the treatment of achalasia. Studies comparing established treatments (LHM, PD and botulinum injection) to POEM for the treatment of NAEMDs are warranted to further establish their clinical utility relative to the current standard of care (Bernardot, 2020).

In 2021, Xu and colleagues published a systematic review and meta-analysis evaluating the efficacy and safety of POEM for sigmoid-type achalasia. A total of eight studies were included (n=248) that were published up to September 2020. Clinical success was achieved in 90.4% of participants (95% CI, 85.5%-93.8%). The Eckardt scores, angle of esophageal tortuosity, diameter of esophageal, lower esophageal sphincter pressure, and integrated relaxation pressure were all significantly improved post-POEM (p<0.05). The rate of adverse events was 13.0% (95% CI, 3.6%-37.4%). The authors concluded that POEM is an effective and safe therapy for the treatment of sigmoid-type achalasia. However, all of the studies that were included were retrospective or cohort studies. The authors also stated that "a series of large-scale randomized controlled trials are still needed to prove the superiority of this technique."

Two systematic reviews and meta-analyses seeking to evaluate the effectiveness of POEM vs. other procedural interventions for the treatment of achalasia were published in 2021. Dirks and colleagues (2021) included 28 studies comparing POEM and LHM (21 studies) or PD (8 studies), with only 1 RCT addressing each. As measured by dysphagia, Eckardt scores, and need for reintervention due to treatment failure, POEM had similar efficacy to that of LHM but greater than that of PD. The authors acknowledged that the studies included in the analysis had predominantly low-quality observational evidence with limited randomized data. By contrast, Facciorusso and colleagues (2021) studied 6 RCTs in adults with achalasia that compared the efficacy of POEM (n=176), LHM (n=309) and PD (n=260). Primary outcome was 1-year treatment success based on decrease in Eckardt score. The conclusion, in agreement with Dirks and colleagues, was that POEM and LHM have similar efficacy and may be more effective than PD in treating adults with achalasia. While this study included only RCTs, there were still limitations. The studies had only a short term of follow up (1 year) which does not facilitate understanding of the long-term comparative efficacy of interventions. Understanding the durability of interventions is especially important in the setting of a chronic disease. The authors concluded that prospective studies comparing long-term efficacy and safety of POEM, LHM, and PD are needed.

In 2022, de Moura and colleagues reported the results of a single-center RCT of POEM vs. laparoscopic myotomy and partial fundoplication (LM-PF) for achalasia. A total of 40 adults with achalasia were randomized to undergo POEM or LM-PF. Anesthesia time and procedure time were significantly shorter in the POEM group than in the LM-PF group (p<0.001). At 1, 6, and 12 months of follow-up, there was no difference between the groups regarding

symptom improvement. However, rates of reflux esophagitis were significantly higher in the POEM group at all follow-up points (p=0.014, p<0.001, and p=0.002, respectively). QOL was measured using the SF-36 inventory. In the POEM group, there were improvements in all QOL domains at 12 months post-procedure but only 3 domains were improved in the LM-PF group. It was concluded that POEM and LM-PF are equally effective in controlling symptoms of achalasia, but this study is limited by short duration of follow-up. The authors recommended that "future research should focus on long-term follow-up and outcomes."

In 2023, Nabi and colleagues published a systematic review and meta-analysis of long-term outcomes of POEM in adults. Seventeen studies involving 3591 participants were included. Participants had either type I (27%), type II (54.5%) or type III (10.7%) motility disorders. Pooled mean follow-up duration was 48.9 months. The primary objective of the study was the clinical success (Eckardt score ≤ 3 or < 4) after POEM at mid-term (30 to < 60 months) and long-term (≥ 60 months) follow-up. Pooled rate of clinical success at mid-term follow-up was 87% (95% CI, 81-91) and long-term was 84% (95% CI, 76-89). However, there was a significant increase in the mean Eckardt scores during long-term follow-up suggesting deterioration of symptoms. There was considerable heterogeneity between the studies (I^2 of 85% for the pooled rate of clinical success from all 17 studies) which may be due to variable study population and different subtypes of motility disorders. Only 5 studies contained data on complications of gastroesophageal reflux beyond 2 years of follow-up, so the authors concluded that further long-term follow-up studies are needed.

Vespa and colleagues (2023) conducted a similar systematic review and meta-analysis of long-term outcomes of POEM for achalasia and obtained results that were much the same. Eleven studies were included involving 2342 participants with a median follow-up of 48 months. All but one of these studies were also included in the analysis by Nabi (2023). Clinical success was defined as having a post-procedure Eckardt score ≤ 3. The pooled clinical success rate was 87.3% (95% CI, 83.6-91.0). Heterogeneity was substantial with I^2 =73.1%. The conclusion was that POEM is effective as a long-term treatment of achalasia. However, the "results should be interpreted with caution due to heterogeneity and the retrospective nature of the studies included." The researchers also concluded that prospective, comparative studies investigating long-term outcomes of POEM are needed.

Available studies of POEM are of relatively short duration, and the long-term impact as a treatment of achalasia remains poorly understood. Elucidating long-term impacts of POEM is especially important when taking into consideration the high rate of GERD and esophagitis, which may lead to more serious conditions including Barrett's esophagus and esophageal cancer. The clinical utility of POEM has rarely been studied in individuals 18 and younger. Given the high-rate of GERD post-procedure, the risk-benefit in this age group is particularly unclear.

Other Considerations for PerOral Endoscopic Myotomy

In 2017, the AGA published a clinical practice update on the use of POEM in achalasia that, due to complexity, emphasizes the need for the procedure to be performed by experienced physicians in high-volume centers. They further stated that POEM "should be considered as a treatment option of comparable efficacy to LHM, albeit with no long-term outcomes data and minimal controlled outcomes data currently available." They also noted that individuals undergoing POEM are at high-risk for developing reflux and may need to start medical management post-procedure.

In 2020, an updated SAGES guideline entitled 'Endoscopic Myotomy (POEM) for the Treatment of Achalasia' was published with the following recommendations:

- The Guideline panel suggests that adult and pediatric patients with type I and II achalasia may be treated with either POEM or laparoscopic Heller myotomy based on surgeon and patient's shared decision-making (conditional recommendation, very low certainty evidence).
- Based on their collective experience, the panel suggests POEM over laparoscopic Heller myotomy for type III adult or pediatric achalasia (expert opinion).
- The Guideline panel recommends peroral endoscopic myotomy over pneumatic dilatation in patients with achalasia (strong recommendation, moderate certainty evidence).
- For the subgroup of patients who are particularly concerned about the continued use of PPI post-operatively, the panel suggests that either POEM or pneumatic dilatation can be used based on joint patient and surgeon decision-making (conditional recommendation, very low certainty evidence) (Kohn, 2020).

In 2020, ASGE published guidelines on the management of achalasia including recommendations on four well-recognized therapies for treatment; botulinum toxin injection, pneumatic dilation, laparoscopic Heller myotomy and POEM. With respect to POEM, the following recommendations were made:

- Laparoscopic Heller myotomy, pneumatic dilation, and POEM are effective therapeutic modalities for patients with achalasia. Decision between these treatment options should depend on achalasia type, local expertise, and patient preference [Evidence rating: "High-quality"].
- We suggest POEM as the preferred treatment for management of patients with type III achalasia [Evidence rating: "Very low-quality"].
- In patients with failed initial myotomy (POEM or laparoscopic Heller myotomy), we suggest pneumatic dilation or redo myotomy using either the same or an alternative myotomy technique (POEM or laparoscopic Heller myotomy) [Evidence rating: "Very low-quality"].
- We suggest that patients undergoing POEM are counseled regarding the increased risk of postprocedure reflux compared with pneumatic dilation and laparoscopic Heller myotomy. Based on patient preferences and physician expertise, postprocedure management options include objective testing for esophageal acid exposure, long-term acid suppressive therapy, and surveillance upper endoscopy [Evidence rating: "Low-quality"].
- We suggest that POEM and laparoscopic Heller myotomy are comparable treatment options for management of patients with achalasia types I and II, and the treatment option should be based on shared decision-making between the patient and provider [Evidence rating: "Low-quality"].

ASGE's recommendations were based on a meta-analysis of the literature through 2017, at that time, no RCTs investigating POEM as a treatment for achalasia had been published (Khashab, 2020).

In 2020, the ACG published updated clinical guidelines on the 'Diagnosis and Management of Achalasia.' The following graded recommendations were made related to POEM as a therapeutic option for achalasia:

- We suggest that POEM or PD result in comparable symptomatic improvement in patients with types I or II achalasia [Conditional recommendation; low quality evidence rating].
- We recommend that POEM and LHM result in comparable symptomatic improvement in patients with achalasia [Strong recommendation; moderate quality evidence rating].

- We recommend tailored POEM or LHM for type III achalasia as a more efficacious alternative disruptive therapy at the LES compared to PD [Strong recommendation; moderate quality evidence rating].
- We suggest that POEM is a safe option in patients with achalasia who have previously undergone PD or LHM [Strong recommendation; low quality evidence rating] (Vaezi, 2020).

Transendoscopic Therapy for Gastroparesis

The published, peer-reviewed literature on gastric peroral endoscopic myotomy (G-POEM) or peroral pyloromyotomy (POP) for the treatment of gastroparesis consists of small feasibility and observational studies with promising short-term outcomes (Gonzalez, 2017 [n=29]; Ichkhanian, 2022 [n=20]; Khashab, 2017 [n=30]; Rodriguez, 2017 [n=47]; Rappaport, 2022 [n=52]; Rodriguez, 2018 [n=100]). In 2018, Mekaroonkamol and colleagues evaluated the efficacy and outcomes of G-POEM in individuals with gastroparesis. They retrospectively reviewed 30 individuals with refractory gastroparesis who had undergone G-POEM between June 2015 and July 2017. They also evaluated a control group of 7 individuals who had refractory gastroparesis but did not undergo G-POEM. The primary outcome was symptomatic improvement measured by the Gastroparesis Cardinal Symptom Index (GCSI) and the SF-36 inventory. Baseline scores were collected on the day of the procedure, and follow-ups were obtained at 1, 6, 12 and 18 months. In the G-POEM group, 21 individuals were available for a 12-month post-procedure evaluation and 7 were available at 18 months. The researchers found that G-POEM was technically successful in all cases and significantly reduced GCSI scores ($p<0.0005$). Compared to the control group, the G-POEM group had significant reductions in GCSI after controlling for baseline scores and disease duration ($p=0.005$). They concluded that G-POEM may be a viable therapeutic option for refractory gastroparesis but note there are currently no reliable ways to predict which individuals have pylorospasm and would respond to G-POEM. In addition, they noted that G-POEM is technically difficult and would require a structured training program. The study was limited by a single-center and restrospective design, small sample size, significant loss to follow-up and subjective metrics.

In 2019, Meybodi and colleagues published a systematic review and meta-analysis on the efficacy and feasibility of G-POEM for individuals with refractory gastroparesis. They performed a literature search up to May 2018 and included studies with 5 or more participants. A total of 7 studies (n=196; 2 prospective and 5 retrospective) met inclusion criteria. In the study population, the etiology of gastroparesis included 83 (42.3%) idiopathic cases, 51 (26%) postsurgical cases, 56 (28.5%) diabetic cases, and 6 (3%) cases due to other etiologies such as infection or scleroderma. The follow-up duration ranged from 1 to 18 months. The weighted pooled rate of clinical success was 82% (95% CI, 74% to 87%; $p=0.82$). The GCSI values were significantly reduced at 5 days post-procedure and mean gastic emptying was significantly decreased 2-3 months post-procedure. A total of 12 adverse events were reported in the included studies, including capnoperitoneum (n=7), peptic ulcer and bleeding (n=2), pulmonary emboli (n=1), abscess (n=1), and stricture (n=1). The study was limited by a small number of studies and short follow-up duration. The authors noted the procedure in the included studies was perfomed by experienced endoscopists and may not be generalizable to the general population. They concluded that G-POEM is an effective therapeutic intervention but large, controlled trials are needed to identify the individuals most suited for the procedure.

Three additional meta-analyses and systematic reviews have been published on the feasiblity, and clinical utility of G-POEM. They included a total of 9 (n=235), 10 (n=292), and 11 (n=375) studies, with signficant overlap in the studies chosen for inclusion of analysis and all 7 studies in Meybodi's (2019) published analysis were included; every study had limited enrollment and most were retrospective in nature. Like Meybodi's (2019) analysis, the studies' authors

conluded that G-POEM holds promise as a treatment for gastroparesis, but RCTs with robust enrollment and long-term outcomes are warranted (Mohan, 2019; Spadaccini, 2020; Yan, 2020).

Pioppo and colleagues performed a study in 2021 comparing the efficacy and safety of G-POEM versus laparoscopic pyloromyotomy for refractory gastroparesis. A total of 102 participants were included; 39 had the G-POEM procedure while 63 underwent surgical pyloromyotomy. Participants were treated at 4 centers across the USA and Latin America. Among the G-POEM group, there was a significantly higher post-op GSCI score reduction by 1.3 units ($p<0.00001$) and procedure time was 20 min. less as compared with surgery. Participants in the G-POEM group also had a lower hospital length of stay by 2.8 days ($p<0.00001$). The G-POEM group had significantly fewer adverse events (13%) compared with the surgery group (33.3%; $p=0.021$). The authors concluded that their data suggest that G-POEM may be a less invasive and more efficacious treatment for refractory gastroparesis as compared with surgical pyloromyotomy. However, they also concluded that "further large, multicenter prospective studies are needed to validate these findings."

In 2021, Li and colleagues published a meta-analysis evaluating the feasibility and efficacy of G-POEM for refractory gastroparesis. They included a total of eight (n=272) studies that were published before April 2019, the majority of which were retrospective and single-center. None of the studies were RCTs. The authors concluded that G-POEM was feasible to use as a treatment for gastroparesis with various etiologies but future studies are needed to determine the patient group(s) that would benefit most from this treatment.

In 2022, Kamal and colleagues performed a systematic review with meta-analysis of 1-year outcomes of G-POEM for refractory gastroparesis. A total of 10 studies were included (n=482), published before June 2021. The majority of studies were retrospective, involving a low number of participants; no RCTs. The main outcomes of interest were clinical success at 1 year, adverse events, and difference in mean pre- and 1-year post-procedure GCSI score. Conclusions were that modest clinical success was associated with G-POEM at 1 year, however "additional studies with longer follow-up are required to evaluate its longer-term efficacy."

Peppas and colleagues (2023) published results of a systematic review and meta-analysis of the efficacy and safety of G-POEM in lung transplant patients with refractory gastroparesis. Four observational studies (one conference abstract) with 104 participants were included; no RCTs. Studies were selected for having GCSI scores before and after the procedure to evaluate effectiveness. The pooled mean reduction in GCSI following the procedure was -2.01 (95% CI, -2.35 to -1.65; $p=0.014$). However, mean follow-up periods were short, between 6 – 20 months (the latter being one study with 5 participants), therefore the benefit of G-POEM in offering long-term symptom relief or improving allograft function could not be assessed. The authors acknowledged that incomplete and relatively short post-procedure follow-up and the uncontrolled design of the studies might overestimate the true efficacy and benefit of G-POEM. Further research is needed to examine quantitative gastric emptying scan data before and after GPOEM and to assess the long-term benefit of the procedure.

Martinek and colleagues (2022) conducted a randomized, sham-controlled trial of G-POEM for the treatment of severe and refractory gastroparesis. A total of 41 participants were randomized. The primary outcome was the proportion of participants with treatment success (defined as a decrease in GCSI score by at least 50%) at 6 months. Treatment success rate was 71% (95% CI, 50-86) after G-POEM versus 22% (95% CI, 8-47) after sham ($p=0.005$). Participants randomized to the sham group with persistent symptoms were offered crossover to G-POEM. A total of 12 participants crossed over to G-POEM with 75% achieving treatment success. Although the study demonstrated benefit from G-POEM to the majority of participants, these results were short-term as follow-up was only for 6

months. Continued follow-up of the sham group was compromised by 60% of the participants crossing over to the treatment group. The authors concluded that "an emphasis on long-term results should be the focus of future research."

Hernández Mondragón and colleagues (2022) analyzed G-POEM outcomes after 4 years in a cohort of participants with refractory gastroparesis. A total of 102 individuals completed 48 months of follow-up at which time clinical success was 77.5%. The GCSI score improved from 3.84 ± 0.53 to 2.70 ± 0.70 at 48 months after G-POEM, and the mean half-emptying time decreased from 246 minutes to 135 minutes. G-POEM was concluded to be an effective 4-year treatment for individuals with refractory gastroparesis but the authors stressed the need for RCTs to confirm the results. This study was limited by the lack of an objective assessment of pyloric function and a sham or other comparative control group.

The ACG published a clinical guideline regarding the diagnosis and management of gastroparesis in adults (Camilleri, 2022). The guideline addressed the efficacy of G-POEM for gastroparesis based on open-label studies. It was determined that although G-POEM provides some benefit in terms of improved symptoms and gastric emptying, most studies were of short duration (3-6 months). One study with 12 months of follow-up showed only slightly more than half (56%) of the participants improved at 1 year. On balance, pyloromyotomy was suggested over no treatment in individuals with gastroparesis with symptoms refractory to medical therapy. However, this recommendation was conditional with a low quality of evidence. The AGA was similarly concerned about the available data supporting G-POEM in their clinical practice update on management of medically refractory gastroparesis (Lacy, 2022). They stated that "Although technically feasible, randomized, sham-controlled studies do not exist, and long-term follow-up data are not available." The AGA recommended that G-POEM not be considered first-line therapy and should only be performed at tertiary care centers using a team of experts.

In 2023, the AGA published a clinical practice update and expert commentary on G-POEM for gastroparesis (Khashab, 2023). G-POEM was recommended as a safe and clinically effective procedure, despite durable clinical response rates of only 50-60%. A sham-controlled clinical trial is being conducted now in the United States (NCT04869670) to assess physiological mechanisms and efficacy of G-POEM in individuals with diabetic or idiopathic gastroparesis. Future studies are needed to better understand which individuals might benefit the most from G-POEM as well as to analyze factors that may predict procedural success.

While G-POEM is promising, the evidence consists of small studies with short follow-up durations. Because not all individuals have gastroparesis due to pyloric dysfunction, studies need to be done to identify the subgroup that will benefit from the procedure. Large, prospective studies that incorporate objective testing to determine gastric emptying are needed. In addition, large studies are need to assess long-term outcomes.

Background/Overview

Gastroesophageal Reflux Disease (GERD)

GERD is related to inadequate functioning of the lower esophageal sphincter (LES), the muscle separating the esophagus from the stomach, which allows the reverse flow of stomach acid into the esophagus resulting in the symptoms of heartburn. While some degree of heartburn is normal, frequent heartburn occurring more than 2-3 times a week typically requires treatment. Frequent heartburn, which may be accompanied by other symptoms such as

regurgitation of stomach acid, chest or stomach pain, difficulty or pain when swallowing, the feeling of a lump in the throat, or recurrent pneumonia, are factors that distinguish GERD from normal heartburn. If left untreated, GERD may lead to esophageal ulcers, narrowing of the esophagus, problems swallowing, lung and throat inflammation, and a condition called Barrett's esophagus. Barrett's esophagus increases the risk of developing esophageal cancer.

Initial treatment of GERD usually includes weight loss, changes in eating habits, and a review of medications that may cause GERD. Additionally, over-the-counter medications like antacids and histamine H2 receptor blockers may be recommended. If further therapy is needed, proton pump inhibitor (PPI) medications are the strongest inhibitors of acid secretion. For severe cases resistant to PPIs, surgery may be indicated. Currently, a widely accepted gold-standard surgical treatment for GERD is Nissen fundoplication (usually done as a laparoscopic surgery) in which the junction of the esophagus and stomach is rearranged to create a "valve" that acts like the LES, thus preventing stomach acid from refluxing into the esophagus. Like any major surgical procedure, all accepted conservative therapies should be attempted prior to consideration of this procedure due to the risks involved. Due to the 360 degree wrap of the fundus around the esophagus, the Nissen fundoplication can cause unpleasant symptoms referred to as "gas bloat syndrome." Alternative forms of fundoplication which use a less restrictive wrap are being investigated, including the Toupet fundoplication surgery.

Several minimally invasive alternatives have been developed to alter either the lower esophagus or upper stomach to create a barrier from reflux of stomach contents into the esophagus. Endoscopic suturing (for example, EsophyX Z System, MUSE) uses sutures or staples in either the esophagus or the stomach in an attempt to create a barrier. The EsophyX Z system is used during transoral incisionless fundoplication (TIF 2.0), which has evolved to include partially wrapping the fundus around the esophagus in a manner similar to fundoplication surgery. MUSE is also performed using an incisionless procedure that creates a partial fundoplication. Transesophageal radiofrequency therapy (the Stretta procedure) uses high frequency radio waves to heat the lower esophageal lining, causing the tissue in the area to constrict, thereby lengthening and supporting the lower esophageal sphincter (LES). Endoscopic injection procedures involve the injection of various substances into the lower esophageal lining to cause constriction and lengthening of the LES.

Dysphagia

Dysphagia is a condition characterized by an impaired ability to swallow. In some cases this problem may be accompanied by pain. Individuals with dysphagia may have difficulty swallowing just solid foods, both solids and liquids, or may be completely unable to swallow anything. Accordingly, dysphagia can be a painful and life-threatening condition. The cause of dysphagia may be related to either impairment of the nervous system responsible for swallowing, or it may be related to structural problems with parts of the body involved in swallowing. This may include the tongue, jaw or other parts of the mouth and upper throat. However, this document addresses the esophagus and stomach, which may have impaired function due to muscle spasm or neurological conditions. The predominant condition that causes dysphagia due to esophageal problems is achalasia, which is described as a dysfunction of the esophagus where it meets the stomach.

Achalasia

In cases of achalasia, the LES does not relax properly during swallowing. When functioning normally, the muscle that separates the esophagus and stomach, the LES, is held closed to keep gastric juices from flowing into the esophagus. The LES relaxes during swallowing to allow the passage of food into the stomach. The cause of achalasia is unknown

(idiopathic) and it largely affects adults between the ages of 25 and 60 years of age. It is theorized that the condition may be caused by the degeneration of a group of nerves located in the chest (Auerbach's plexus). Spastic esophageal disorders (SEDs) include Type III achalasia, nutcracker esophagus, and jackhammer esophagus. Despite differences in pathophysiology, the clinical presentation of these disorders is similar and include dysphagia, chest pain, regurgitation, and heartburn. The National Organization of Rare Disorders (NORD) recognizes achalasia and jackhammer esophagus as rare disorders (NORD, 2017).

The goal of treatment for achalasia and SEDs is to relax the LES enough to allow proper swallowing. This can be done with the injection of botulinum toxin, mechanical dilation, or by surgery. The gold standard surgical procedure is the laparoscopic Heller myotomy (LHM), which involves disruption of the muscle structures at the lower esophagus. This weakens the muscles of the lower esophagus and the LES, allowing less effort to open the end of the esophagus. A fundoplication procedure is usually performed along with LHM to prevent gastric reflux. A new approach, POEM, has been proposed that allows the surgeon to conduct this procedure endoscopically. However, fundoplication is not performed with POEM, and the lower sphincter is left open.

Gastroparesis

Gastroparesis, also called delayed gastric emptying, is an uncommon disorder characterized by poorly working stomach muscles and the slowed or blocked movement of food from the stomach to the small intestine. Risk factors include diabetes, injury after surgery, radiation treatment, and neurologic diseases. Gastroparesis may cause nausea, vomiting, bloating, belching, abdominal pain, heartburn, and weight loss. Treatment options include diet/lifestyle changes, blood glucose control in diabetics, medications, and surgery. In severe cases, a feeding tube or gastrostomy may be required. Gastric peroral endoscopic myotomy (G-POEM) (also called peroral pyloromyotomy [POP]) has been proposed as a minimally invasive endoscopic treatment for gastroparesis. This procedure relaxes the muscles of the pyloric sphincter to allow gastric emptying.

Definitions

Achalasia subtypes:

- Type I (classic) with minimal contractility in the esophageal body
- Type II with intermittent periods of panesophageal pressurization
- Type III (spastic) with premature or spastic distal esophageal contractions

Chicago classification: An algorithmic system for the diagnosis of esophageal motility and the interpretation of clinical high resolution esophageal pressure topography (EPT) classified as Type I, achalasia with minimal esophageal pressurization; type II, achalasia with esophageal compression; and Type III, achalasia with spasm.

Diffuse esophageal spasm (DES): Uncoordinated esophageal contractions or spasms causing dysphagia, regurgitation and chest pain.

Eckardt symptom score: A 4-item self-report scale measuring weight loss in kilograms (kg), chest pain, regurgitation, and dysphagia. Each item is graded on a score of 0 to 3, with a maximum score of 12. Scores greater than or equal to 3 are considered suggestive of active achalasia.

Score	Dysphagia	Regurgitation	Retrosternal pain	Weight loss (kg)
0	None	None	None	None
1	Occasional	Occasional	Occasional	<5
2	Daily	Daily	Daily	5-10
3	Each meal	Each meal	Each meal	>10

Endoluminal gastric plication (ELGP): A surgical procedure where stitches are sewn into the esophagus where it connects to the stomach to create a barrier to reverse the flow of stomach acid; this procedure is conducted through an endoscope inserted into the esophagus. Procedures in this category include endoluminal gastroplasty, gastroplication, endoscopic suturing, the Bard Endocinch procedure, the Plicator procedure or the EsophyX System.

Endoscopic submucosal implantation of polymethylmethacrylate (PMMA) beads: A surgical procedure where Plexiglas beads are injected underneath the surface of the lower esophagus to create a barrier to the backflow of stomach acid; this procedure is conducted from inside of the esophagus.

Fundoplication: A surgical procedure designed to restore the barrier function of the LES. The most common type of fundoplication procedure is referred to as Nissen fundoplication, which is typically performed laparoscopically.

Gas-bloat syndrome: A recognized complication of a "too-tight" fundoplication procedure that inhibits the ability to belch or vomit, with accumulation of gas in the stomach.

Gastroesophageal reflux disease (GERD): A disease caused by chronic back-flow of acid from the stomach into the esophagus, causing heartburn and leading to irritation and possible damage to the lining of the esophagus.

Gastroesophageal Reflux Disease-Health Related Quality of Life (GERD-HRQL): Total scores range from 0 to 50, with higher scores indicating worse symptoms.

Hill's grade classification: Endoscopic assessment of the axial length of hiatus hernia and the gastroesophageal flap
- Hill Grade I: a prominent fold of tissue along the lesser curvature next to the endoscope.
- Hill Grade II: the fold is less prominent and there are periods of opening and rapid closing around the endoscope.
- Hill Grade III: the fold is not prominent and the endoscope is not tightly gripped by the tissue.
- Hill Grade IV: there is no fold, and the lumen of the esophagus is open, often allowing the squamous epithelium to be viewed from below. A hiatal hernia is always present.

Jackhammer esophagus: Hypercontractile peristalsis of high amplitude of a prolonged duration.

Jobe's length of the gastro-esophageal valve: The distance from (in cm) the apex of the fundus to the valve lip using biopsy forceps with valves opening at 7 mm wide and Hill's grade.

Los Angeles Classification system: A system used to describe the appearance of reflux esophagitis and grade its severity by endoscopy.

Type	Description

A	One (or more) mucosal break 5 mm or less that does not extend between the tops of two mucosal folds
B	One (or more) mucosal break more than 5 mm-long that does not extend between the tops of two mucosal folds
C	One (or more) mucosal break that is continuous between the tops of two or more mucosal folds but that involves less than 75% of the circumference
D	One (or more) mucosal break that involves at least 75% of the esophageal circumference

Lower esophageal sphincter (LES): The sphincter muscle separating the esophagus and the stomach. This muscle serves as a barrier to prevent the reflux of acid into the esophagus. GERD is the result of an incompetent lower esophageal sphincter.

Nutcracker esophagus: Hypertensive peristalsis causing dysphagia, chest pain or may be asymptomatic.

Proton pump inhibitors (PPIs): Group of pharmacological therapies indicated to reduce the production of gastric acid to treat GERD and peptic ulcers.

Spastic esophageal disorders (SEDs): Characterized by hyperactive esophageal contractions of either premature contraction or extreme vigorous contraction, for example Type III achalasia, jackhammer esophagus or nutcracker esophagus.

Transesophageal radiofrequency therapy (the Stretta procedure): A procedure using high frequency radio waves to heat the lining of the lower esophagus; this is proposed to cause stiffening of the area to resist stretching when the stomach is full, creating a barrier to the reverse flow of stomach acid. The procedure is performed from the inside of the esophagus.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

CPT

43497	Lower esophageal myotomy, transoral (ie, peroral endoscopic myotomy [POEM])

ICD-10 Procedure

0D848ZZ	Division of esophagogastric junction, via natural or artificial opening endoscopic

ICD-10 Diagnosis

K22.0	Achalasia of cardia
K22.4	Dyskinesia of esophagus
Q39.5	Congenital dilatation of esophagus
R13.10-R13.19	Dysphagia

When services are Not Medically Necessary:
For the procedure codes listed above when criteria are not met or for all other diagnoses, or when the code describes a procedure indicated in the Position Statement section as not medically necessary.

When services are Investigational and Not Medically Necessary:
When the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

43210	Esophagogastroduodenoscopy, flexible, transoral; with esophagogastric fundoplasty, partial or complete, includes duodenoscopy when performed
43257	Esophagogastroduodenoscopy, flexible, transoral; with delivery of thermal energy to the muscle of lower esophageal sphincter and/or gastric cardia, for treatment of gastroesophageal reflux disease
43499	Unlisted procedure, esophagus [when specified as endoscopic gastroplasty, endoluminal plication or transesophageal injection therapy for treatment of GERD]
	For the following CPT codes **when specified as injection of a bulking agent for GERD**:
43192	Esophagoscopy, rigid, transoral; with directed submucosal injection(s), any substance [*when specified as injection of bulking agent*]
43201	Esophagoscopy, flexible, transoral; with directed submucosal injection(s), any substance [*when specified as injection of bulking agent*]
43236	Esophagogastroduodenoscopy, flexible, transoral; with directed submucosal injection(s), any substance [*when specified as injection of bulking agent*]

ICD-10 Procedure

0D548ZZ	Destruction of esophagogastric junction, via natural or artificial opening endoscopic
0DQ48ZZ	Repair esophagogastric junction, via natural or artificial opening endoscopic
0DU48JZ	Supplement esophagogastric junction with synthetic substitute, via natural or artificial opening endoscopic
0DV48DZ	Restriction of esophagogastric junction with intraluminal device, via natural or artificial opening endoscopic
0DV48ZZ	Restriction of esophagogastric junction, via natural or artificial opening endoscopic

ICD-10 Diagnosis

	All diagnoses, including, but not limited to the following:
K21.00-K21.9	Gastro-esophageal reflux disease
R12	Heartburn

When services are also Investigational and Not Medically Necessary:

CPT	
43999	Unlisted procedure, stomach [when specified as transendoscopic (peroral) gastric myotomy G-POEM]
ICD-10 Procedure	
0D878ZZ	Division of stomach, pylorus, via natural or artificial opening endoscopic
ICD-10 Diagnosis	
	All diagnoses, including but not limited to the following:
E08.43	Diabetes mellitus due to underlying condition with diabetic autonomic (poly)neuropathy
E09.43	Drug or chemical induced diabetes mellitus with neurological complications with diabetic autonomic (poly)neuropathy
E10.43	Type 1 diabetes mellitus with diabetic autonomic (poly)neuropathy
E11.43	Type 2 diabetes mellitus with diabetic autonomic (poly)neuropathy
E13.43	Other specified diabetes mellitus with diabetic autonomic (poly)neuropathy
K31.84	Gastroparesis
M34.0-M34.9	Systemic sclerosis (scleroderma)

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Durasphere
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EsophyX Z System
Gastric Per-Oral Endoscopic Myotomy
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Radiofrequency Ablation
Stretta Procedure

TIF
Transendoscopic Gastroplasty
Transendoscopic Therapies for Gastroesophageal Reflux Disease
Transoral Incisionless Fundoplication

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Revised	08/08/2024	Medical Policy & Technology Assessment Committee (MPTAC) review. Changed the word 'and' to 'or' in the title and INV&NMN statement. Revised Description, Rationale and References sections. Revised Coding section, added ICD-10-CM Q39.5.
Reviewed	08/10/2023	MPTAC review. Updated References section.
Reviewed	05/11/2023	MPTAC review. Updated Rationale, References and Index sections.
Reviewed	05/12/2022	MPTAC review. Updated Rationale and References sections.
	12/29/2021	Updated Coding section with 01/01/2022 CPT changes; added 43497 effective 01/01/2022 replacing NOC code for POEM.
Reviewed	05/13/2021	MPTAC review. Updated Rationale and References sections.
	10/01/2020	Updated Coding section with 10/01/2020 ICD-10-CM changes; added K21.00 replacing K21.0 deleted 09/30/2020.
Revised	05/14/2020	MPTAC review. Added MN criteria for peroral endoscopic myotomy (POEM). Updated Rationale, Background/Overview, Definitions, Coding, and References sections.
Revised	11/07/2019	MPTAC review. Title change and scope expansion to include Gastroparesis. Rationale, Background, Index and References sections updated. Updated Coding section; added 43999, 0D878ZZ.
Reviewed	01/24/2019	MPTAC review. Rationale, Background, and References sections updated.
Reviewed	01/25/2018	MPTAC review. The document header wording updated from "Current Effective Date" to "Publish Date." Rationale, Background, Index, and References sections updated.
Revised	02/02/2017	MPTAC review. Removed acronyms from the Position Statement section. Updated the Rationale, Definitions, Index and References sections
Reviewed	02/04/2016	MPTAC review. Updated Rationale and Reference sections.
	01/01/2016	Updated Coding section with 01/01/2016 CPT and HCPCS changes, removed C9724 deleted 12/31/2015; also removed ICD-9 codes.
Reviewed	08/06/2015	MPTAC review. Revised Rationale, Reference, and Index sections.
Reviewed	08/14/2014	MPTAC review. Revised Rationale and Reference sections.
	01/01/2014	Updated Coding section with 01/01/2014 CPT changes.
Reviewed	08/08/2013	MPTAC review. Revised Rationale and Reference sections.

Revised	05/09/2013	MPTAC review. Added dysphagia to title. Added per-oral endoscopic myotomy (POEM) to investigational and not medically necessary position statement. Revised Rationale, Background, Coding, Reference, and Index sections.
Revised	05/10/2012	MPTAC review. Removed product names from the position statement and clarified criteria. Revised Rationale, Reference, and Index sections.
Reviewed	05/19/2011	MPTAC review.
Reviewed	05/13/2010	MPTAC review.
Reviewed	05/21/2009	MPTAC review. Updated Rationale and Reference sections
Reviewed	05/15/2008	MPTAC review. Updated Rationale and Reference sections.
	02/21/2008	The phrase "investigational/not medically necessary" was clarified to read "investigational and not medically necessary." This change was approved at the November 29, MPTAC meeting.
Reviewed	05/17/2007	MPTAC review. Updated Rationale and Reference sections. Coding updated; removed CPT codes 0133T deleted 06/30/2007, and 0008T deleted 12/31/2006.
Revised	06/08/2006	MPTAC revision. Added the use of the Plicator procedure and Gatekeeper procedure as investigational. Updated Rationale, Definitions and References.
	01/01/2006	Updated Coding section with 01/01/2006 CPT/HCPCS changes
	11/18/2005	Added reference for Centers for Medicare and Medicaid Services (CMS) – National Coverage Determination (NCD).
Revised	07/14/2005	MPTAC review. Revision based on Pre- merger Anthem and Pre-merger WellPoint Harmonization.

Pre-Merger Organizations	**Last Review Date**	**Document Number**	**Title**
Anthem, Inc.	10/28/2004	SURG.00047	Transendoscopic Therapy for Gastroesophageal Reflux Disease
WellPoint Health Networks, Inc.	12/02/2004	2.06.11	Transendoscopic Therapies for Gastroesophageal Reflux Disease