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Medical Policy

Subject:	Transendoscopic Therapy for Gastroesophageal Reflux Disease, ~~and~~ Dysphagia and Gastroparesis		
Document #:	SURG.00047	**Publish Date:**	12/18/2019~~02/27/2019~~
Status:	~~Reviewed~~Revised	**Last Review Date:**	1~~0~~1/07~~24~~/2019

Description/Scope

This document addresses selected transendoscopic therapies for the treatment of gastroesophageal reflux disease (GERD), ~~and~~ dysphagia and 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-SURG-101 Ablative Techniques as a Treatment for Barrett's Esophagus
- SURG.00131 Lower Esophageal Sphincter Augmentation Devices for the Treatment of Gastroesophageal Reflux Disease (GERD)

Position Statement

Investigational and Not Medically Necessary:

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

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

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

~~6.~~7. Gastric peroral endoscopic myotomy or peroral pyloromyotomy.

Rationale

Transendoscopic Therapy for GERD

~~*General Considerations*~~

Randomized placebo-controlled trials with self-reported outcomes are ideally required to validate the safety and effectiveness 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 placebo or sham-controlled randomized trials. The durability of treatment response is another important outcome that has been reported in case series. It is important to note that since proton pump inhibitor (PPI) therapy is an 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 effectiveness of transendoscopic procedures, ultimately these techniques would ideally be compared to other surgical therapies.

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." Their 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 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 questionnaires, medication usage, and esophageal acid exposure. At 6 months, active treatment participants had improvement in heartburn scores and both GERD-related and general quality of life 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 are equivocal. The large proportion of sham-treated participants who successfully reduced medication use points to possible placebo effect of the procedure. An accompanying editorial also notes the discrepancies between the objective and subjective findings and hypothesizes that the possible mechanism of action of the Stretta procedure is neurolysis resulting in decreased esophageal sensitivity to acid exposure, rather than any reduction in acid exposure itself (Kahrilas, 2003).

Richards and colleagues (2003) reported on their findings from a nonrandomized controlled trial of subjects 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 subjects discontinued PPI treatment, and an additional 31% had reduced their dose significantly. They also reported that 97% of fundoplication subjects discontinued PPIs. No statistical data was provided for this comparison. At a mean of 7.2 ± 0.5 months, 22 Stretta subjects (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 since insufficient statistical analysis is provided, no real conclusions can be made based on this data.

Coron and colleagues (2008) reported the results of a small RCT that involved 20 subjects 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 subjects 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, lower esophageal sphincter (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 subjects who received treatment with either the Stretta device (n=11) or sham treatment (n=11) (Arts, 2012). Subjects 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 quality of life as measured by GERD HRQOL scale (p=0.001), and improved quality of life 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). While the findings of this study are interesting, this does not overcome the fact that the data used were exposed to significant bias. Of the 20 studies included in the author's 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. In summary, the available literature does not demonstrate improvement in net health outcomes with the use of the radiofrequency ablation techniques.

A trial was reported by Liang and colleagues in 2014. This study involved 215 subjects who underwent either laparoscopic Nissen fundoplication (n=102) or Stretta (n=113). At the 5 year follow-up point, 197 evaluable subjects were available (87 Nissen group and 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 the abdominal distention. The authors concluded that even though laparoscopic Nissen fundoplication and the Stretta procedure are capable of controlling GERD symptoms effectively and safely 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 subjects, of which 149 (68.7%) reached the 10 year follow-up time point. An additional 50 subjects were lost to follow-up, leaving 99 evaluable subjects 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 subjects which was achieved in 72% of subjects at 10 years. A 50% reduction in PPI use was reported in 64% of subjects 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 subjects. This new report includes data from 26 subjects (30.2%) who were followed for 8 years. Of those subjects 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 subjects (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. One severe adverse event was reported, with 1 subject experiencing transient severe gastric paresis requiring hospitalization. These studies indicate some significant benefits to the use of the Stretta device. However, 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; 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, safety, or longevity of the Stretta procedure.

A nonrandomized controlled trial involving 137 subjects with severe asthma and coexisting GERD, undergoing Stretta (n=82) or Nissen fundoplication (n=55), was reported by Hu and colleagues in 2015. All subjects were successfully followed for 5 years. At 1 and 5 years post-procedures, subjects 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.

Liang and colleagues (2015) reported on the results of a nonrandomized controlled study involving 165 subjects 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%) subjects were available, including 60 (70.6%) Stretta subjects and 65 (81.3%) fundoplication subjects. 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 subjects were free from PPI use, with no differences between groups. No serious adverse events were reported for either group, but 8 Stretta subjects 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 subjects. 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 subjects were using PPIs, and after the procedure 850 subjects resumed using PPIs (risk ratio [RR] 0.49, 0.40 to 0.60; p<0.001). Of the subjects 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 subjects with heartburn (n=637), the Stretta procedure improved the heartburn standardized score by –1.53 (–1.97, –1.09; p<0.001). For subjects 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 subjects 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 mmHg 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 subjects 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 safe and 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 subjects, but a significant number of serious complications, including gastric mucosal and esophageal tears requiring transfusions, were reported.

A case control study was reported involving three cohorts of 20 subjects each undergoing TIF with the EsophyX device, laparoscopic Nissen fundoplication or laparoscopic Toupet fundoplication (Toomey, 2014). The authors reported that TIF subjects 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 subjects 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 subjects 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 is the first study directly comparing TIF and fundoplication procedures. Although the sample sizes are small, and there was no randomization or blinding, these findings are promising and indicate further investigation with more rigorous methodology is warranted.

Wilson and colleagues (2014) published the results of a retrospective case series study of 100 subjects treated with the EsophyX$_2$ device with 12 month follow-up. Esophageal acid exposure was normalized in 52% (n=14) of the 27 subjects who underwent 12 month pH testing. A total of 74% of all subjects 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 subjects, respectively. Median RSI score was reduced from 20 (0 to 41) to 5 (0 to 44), ($p=0.001$). Only 2 subjects reported de novo dysphagia, and 1 reported bloating (scores 0 to 3). Revision surgery was done in 6 subjects. No major complications were reported. These results are promising, but as noted previously, longer-term results are needed.

Bell and colleagues (2014) reported the results of a case series study involving 127 subjects who underwent TIF 2.0 with the EsophyX$_2$ device and were followed for 2 years. Revision surgery occurred in 8 subjects who were considered treatment failures and 19 subjects 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 subjects with elevated cores at baseline. RSI scores normalized in 56% of subjects and daily PPI use decreased from 91% to 29%. In the subjects available for evaluation, esophageal acid exposure normalized in 57% of subjects (8/14). These results are good, but the lack of a comparison group weakens their value.

In a prospective single-center study by Testoni and colleagues (2015), 50 carefully selected subjects 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 subjects 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 cms, previous major thoracic or abdominal surgery and severe co-morbidities. Pre-operatively, the subjects 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. Fifty-one TIF 2.0 procedures were performed on 50 subjects, where in 49 subjects the procedure was successful. Two subjects experienced severe complications (pneumothorax) but both subjects 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 post TIF; 83.7, 79.6, 87.8, and 84.4% of the subjects 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 prove that TIF 2.0 is a safe, effective therapeutic option for prudently selected GERD subjects.

In 2015, Trad and colleagues published the results of the TEMPO trial, an RCT involving 63 subjects undergoing TIF 2.0 treatment with the EsophyX_2 device. Subjects were followed for 6 months following randomization to either TIF 2.0 (n=39) or optimum 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 subjects vs. 50% (9/18) of subjects 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 subjects vs. 5% (1/21) of control subjects ($p<0.001$). At 6 months follow-up, 90% of TIF 2.0 subjects had completely stopped taking PPIs, another 3% were taking PPIs on demand and the remaining 8% were back on daily PPIs. All subjects 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 subjects vs. 38% (5/13) of control subjects ($p=0.018$). 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 subjects vs. 13% (2/16) of controls ($p=0.003$). The median total Reflux Symptom Index (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 a double-blind, sham controlled randomized RESPECT trial in 2015. This study involved 87 subjects treated with the EsophyX_2 device followed by 6 months of sham medical therapy vs. 42 subjects treated with sham surgery and 6 months of PPI medical therapy. The per-protocol analysis included 81 TIF 2.0 and 38 control subjects. At 3 months follow-up, 36% (15/42) of control group subjects 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 subjects were considered early treatment failures and all were returned to PPI therapy. In total, 76 TIF 2.0 and 28 control subjects completed the 6-month study period. The intent-to-treat analysis resulted in 68% (58/87) TIF 2.0 group subjects reporting elimination of troublesome regurgitation vs. 45% (19/42) of the control subjects ($p=0.023$). 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 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 subjects with esophagitis at baseline, 13 (76%) underwent re-evaluation at 6 months, with 77% (10/13) having complete healing. An additional 2 subjects had improvement from grade B to grade A esophagitis. In the sham group, only 2 (33%) of the 6 subjects with esophagitis at baseline underwent 6 month re-evaluation, with healing reported in 1 subject. There was no difference between groups in regard to adverse events.

Witteman and colleagues (2015) described the interim results of a non-blinded RCT involving 60 subjects assigned to either TIF 2.0 treatment with the EsophyX_2 device (n=40) or continuation of PPI therapy (n=20). Control subjects were allowed to cross over to TIF 2.0 treatment at the end of the 6 month trial period, and all 20 subjects did undergo TIF 2.0. At the end of the initial 6 month follow-up point, 37 TIF 2.0 subjects and 20 control subjects 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 subjects and none of the controls. Serious adverse events 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 subjects following crossover treatment with TIF2.0. TIF 2.0-group subjects 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 subjects for an 80% power to detect a difference between groups.

Hakansson and colleagues (2015) reported the results of a RCT. This study involved 44 subjects 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 subjects 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 subjects and 18% (14/22) of controls. Ambulatory pH monitoring was done in 68% (15/22) of TIF 2.0 subjects 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 subjects 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% and 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 (TEMPO) randomized trial with a crossover arm. 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 subjects at 1 year, in 84% (43/51) of subjects 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 subjects who discontinued PPI therapy at 1 year was 78% (47/60), 76% (42/55) at 2 years and 71% (37/52) at 3 years. The authors' data revealed that TIF 2.0 performed with the EsophyX in well-chosen symptomatic GERD subjects provided sustained relief of symptoms at 3 years follow-up. They recommended that TIF 2.0 should be considered in the management of GERD due to its safety and efficacy.

Stefanidis and colleagues (2017) conducted a small, retrospective study to evaluate the long-term efficacy and safety of TIF 2.0. A total of 45 subjects (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 subjects; 86.7%) and pharynx irritation (22 subjects; 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 subjects (57.1%), and regurgitation was eliminated in 15 out of 17 subjects (88.2%). Of the 44 subjects that completed the study, 32 (72.7%) reported the elimination of their main symptom and could stop using PPIs. Three subjects chose to have a redo procedure: two Nissen fundoplication surgeries with excellent results and one redo TIF without favorable results.

Ebright and colleagues (2017) reported an intermediate follow-up study that examined TIF 2.0 using the EsophyX$_2$ device. All subjects (n=80) had a mean follow-up of 24 months, with a minimum of 6 months. Subjects 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 subjects 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 subjects who were using PPIs before the procedure, 56% of subjects were still using PPIs at follow-up. A total of 63% of subjects were off PPIs or were taking a reduced dosage. Of the subjects 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 subjects, 44 out of 63 (70%) completed the 5 year follow-up. A total of 37/43 subjects had elimination of troublesome regurgitation (95% confidence interval [CI], 72% to 94%). Troublesome atypical symptoms were eliminated in 31/39 subjects (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 ($p<.001$). Complete cessation of PPI therapy was achieved in 20/44 subjects (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 ($p<.001$ 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 done 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. Subjects 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 subjects (n=1407; 95 % CI, 82 to 95; p<0.001). In the subjects 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 subjects 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 subjects, including 12 subjects 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 subjects with intractable foregut symptoms after TIF who underwent surgical remediation between June 2011 and September 2016. A total of 5/11 subjects had a combined laparoscopic hiatal hernia repair in addition to TIF. All subjects had remedial surgery after a median of 35.8 months

(range 10-72 months). After remediation surgery, 8 subjects had incorporation of the left crural pillar with at least one fastener. A total of 6 subjects had very dense adhesions and 4 subjects 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 subjects, 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 a safe and effective 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.

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 subjects who were treated with the MUSE System and followed for 6 months. A total of 66 subjects completed the trial, at which time GERD-HRQOL scores improved by 50% in 73% of subjects ($p<0.001$). PPI use was discontinued in 64.6%, and a 50% reduction in dose was reported in 56.5% of subjects 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 subjects, 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 subjects recovered with treatment. An interim analysis of these events led to revisions to the protocol and device after the first 24 subjects.

Roy-Shapira (2015) reported a pilot case series study of 15 subjects. Clinical evaluation was conducted at 6 months post-treatment with the MUSE System and telephonic follow-up was done for 5 years. In 2 subjects, the MUSE procedure was abandoned, leaving 13 evaluable subjects. GERD HRQOL measures improved significantly with 92% of subjects 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 subjects and 69% were off PPIs completely. One case of benign pneumoperitoneum was reported.

Kim and colleagues (2016) performed a retrospective analysis of subjects who were included in the previous study on MUSE by Zacherl and colleagues (2014). Of the small sample of subjects (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.

The studies addressing the MUSE System are promising, but the incidence of serious adverse events, specifically pneumomediastinum, pneumoperitoneum, and pneumothorax, warrant additional research before this device becomes more widely utilized.

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 subjects, 9 of whom completed the 12 month follow-up. The authors report that 70% of subjects discontinued all antacid medications, and 90% reduced their PPI use by greater than 50%. Normal esophageal pH was detected in 4 subjects. These results are promising, but further data from large-scale trials is warranted before the safety and efficacy 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 supports 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 current 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 2016, the American Gastroenterological Association (AGA) issued a report entitled *Technology Coverage Statement on Minimally Invasive Surgical Options for Gastroesophageal Reflux Disease*. The document cited several recent studies illustrating the utility, benefits and effectiveness of transoral fundoplication and concluded:

> …the three year plus evidence is sufficient to demonstrate sustainable improvement in health outcomes, symptom relief, decrease in PPI utilization and improvement in esophageal pH with transoral fundoplication. The selection criteria for transoral fundoplication includes GERD patients with BMI ≤ 35, hiatal hernia ≤ 2 cm, esophagitis LA grade A or B, Barrett's esophagus ≤ 2 cm, and absence of achalasia and esophageal ulcer. This option should be considered in patients not responding to PPI therapy (symptoms of regurgitation) who have documented objective evidence of GERD (pathologic acid exposure on pH testing [both off and on medication]) or esophagitis. Transoral fundoplication should be covered and reimbursed for appropriate patients who meet the selection criteria as described.

In a 2017 spotlight review on endoluminal treatments for GERD, The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) made the following recommendations for EsophyX and TIF 2.0:

> Based on existing evidence, TIF can be performed with an acceptable safety risk in appropriately selected patients. The procedure leads to better control of GERD symptoms compared with PPI treatment in the short term (6 months), but appears to lose effectiveness during longer term follow-up and is associated with moderate patient satisfaction scores. Objective GERD measures improve similarly after TIF 2.0 compared with PPI. No comparative, controlled trials exist between TIF and surgical fundoplication, but preliminary evidence suggests that the latter can be used safely after TIF failure (Level of evidence +++, strong recommendation).

For the Stretta procedure, SAGES stated:

> Based on existing evidence, Stretta significantly improves health related quality of life score, heartburn scores, the incidence of esophagitis, and esophageal acid exposure in patients with GERD, but does not increase lower esophageal sphincter basal pressure. In addition, it decreases the use of PPI by approximately 50%. The effectiveness of the procedure diminishes some over time, but persistent effects have been described up to 10 years after the procedure in appropriately selected patients with GERD. Stretta is more effective than PPI, but less so than fundoplication.

Stretta is safe in adults and has a short learning curve. (Level of evidence +++, strong recommendation).

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.

Transendoscopic Therapy for Dysphagia and Related Conditions
~~*Per-Oral Endoscopic Myotomy (POEM) for Dysphagia-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 subjects 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 subjects with achalasia. They reported that at 3 months after POEM, 97% of subjects 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 subjects (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 months evaluations, the percentage of subjects 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 (Inoue, 2011; 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.

The largest controlled study published to date on the use of POEM for achalasia was reported by Bhayani and colleagues in 2014. This study involved 101 subjects, 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 mmHg vs. 7.1 mmHg, $p=0.006$). 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 subjects and 48% myotomy subjects and the authors reported that 39% of POEM subjects and 32% myotomy subjects had abnormal acid exposure ($p=0.7$). They concluded that POEM is comparable with LHM for safe and 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 subjects with achalasia and treated with POEM. Postoperatively, Eckardt scores declined to less than or equal to 3 in 97.7% of subjects, from a pre-operative mean of 7.1 to post-operative mean of 0.04 ($p=0.001$). Symptom relief and quality of life 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 mmHg to 3.8 mmHg ($p<0.001$). 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 subjects (10/87), mucosal injury was reported in 2.3% (2/87), and pneumothorax in 1.1% (1/87). At 3 months follow-up, 5 subjects 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 subjects 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 subjects who were treated with POEM for type III achalasia compared to 26 subjects who underwent LHM. POEM subjects 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 was 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 subjects 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 subjects 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 mmHg and 15.2 ± 6.3 mmHg, respectively ($p=0.001$). Erosive esophagitis was seen in 16% of subjects 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) subjects with esophageal motility disorders as defined by the Chicago classification were considered for POEM. Of the subjects 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 subjects, 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 subjects 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 subjects 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 subjects 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 subjects (60%) underwent pH testing 6 months after POEM. Eleven (42%) subjects had normal esophageal acid exposure, while 15 subjects (58%) demonstrated abnormal esophageal acid exposure. Seven subjects (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 subjects will continue to experience asymptomatic GERD symptoms post-operatively. They recommended that postoperative pH measurement and EGD be performed for subjects requiring long-term PPI therapy.

A systematic review and meta-analysis by Marano and colleagues (2016) was conducted to assess the effectiveness and safety 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 subjects (median age was 48.4, 41 males) All subjects had a confirmed diagnosis of achalasia and preoperatively experienced esophagogastrotroduoendosopy (EGD), esophageal manometry and timed barium esophagogram procedures. The 100 subjects were categorized under the Chicago classification: 42 subjects 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 subjects, 94 (94%) successfully completed the procedure with varying follow-up periods and in 6 subjects the procedure was terminated. Two subjects were lost to follow-up, 17 subjects completed a 24-month follow-up, 3 subjects completed an 18-month follow-up, 31 subjects completed a 12-month follow-up, 36 subjects completed a 6-month follow-up and 5 subjects completed follow-up at 3 months. Of the 92 subjects 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 subjects agreed to 24-hour pH monitoring to assess for postoperative GERD symptoms. Total reflux time > 5% was observed in 39/73 (53.4%) subjects who underwent esophageal pH monitoring; 17/73 (24.6%) subjects reported heartburn and used antacids every day; esophagitis was seen in 20 subjects (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 subjects 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 subjects 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 subjects. 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.

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 subjects, 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 1-3 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%) subjects. Of those who had technical success, clinical success was achieved in 90.8% of subjects, 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 subjects. There were 14 adverse events in 11 subjects (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 subjects 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 Heller myotomy 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 Heller myotomy 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 Heller myotomy, 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."

The available studies are all of relatively short duration, and the long-term impact of POEM is not well understood. This 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. Larger, longer-term, randomized and controlled trials are needed to fully evaluate the safety and efficacy of POEM.

Other Considerations for Per-Oral Endoscopic Myotomy

In a 2012 guideline on the surgical treatment of esophageal achalasia, SAGES stated that POEM "is in its infancy, and further experience is needed before recommendations can be provided."

In 2013, the ACG released a clinical guideline on the diagnosis and management of achalasia. This document stated the following about the POEM procedure:

> Overall, the success rate, defined by an improvement in symptoms and no requirement of additional medical or surgical treatment, in prospective cohorts have been > 90%, and this does appear to have promise as an alternative to the laparoscopic approach. Randomized prospective comparison trials with standard laparoscopic myotomy and / or PD are needed and POEM should only be performed in

> the context of clinical trials with the understanding that other effective well-studied alternatives are available.

In a 2014 guideline on the role of endoscopy in the evaluation and management of dysphagia, the ASGE made the following statement about POEM:

> Long-term data and randomized trials comparing this technique to conventional modalities of management are necessary before it can be adopted into clinical practice, but the procedure is becoming more widely used in expert centers.

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 done 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.

Transendoscopic Therapy for Gastroparesis

Recently, researchers started investigating gastric peroral endoscopic myotomy (G-POEM) or peroral pyloromyotomy (POP) for the treatment of gastroparesis. The published, peer-reviewed literature consists of small feasibility and observational studies with promising short-term outcomes (Gonzalez, 2017 [n=29]; Khashab, 2017 [n=30]; Rodriguez, 2017 [n=47]). 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 subjects. 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.

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. When functioning normally, the muscle that separates these two structures, 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. In cases of achalasia this does not occur, and the LES does not relax properly during swallowing.

The goal of treatment of achalasia 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

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.

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.

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.

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 cms) 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

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

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

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

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.

Treatments for GERD
When services are Investigational and Not Medically Necessary:
For the following procedure codes, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

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

ICD-10 Diagnosis

All diagnoses

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

CPT

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]
43499	Unlisted procedure, esophagus [when specified as endoscopic gastroplasty, endoluminal plication or transesophageal injection therapy for treatment of GERD]

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

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K21.0-K21.9	Gastro-esophageal reflux disease
R12	Heartburn

Treatment for Dysphagia
When services are Investigational and Not Medically Necessary:

CPT

43499	Unlisted procedure, esophagus [when specified as transendoscopic (per oral) esophageal 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
R13.10-R13.19	Dysphagia

Treatment for Gastroparesis
When services are 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

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

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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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Index

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	11/07/2019	Medical Policy & Technology Assessment Committee (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	~~Medical Policy & Technology Assessment Committee (~~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.

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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