Policy Replaced with
LCDs L34434, L34553 & 36954
Effective February 26, 2018

BlueCross BlueShield of Alabama

For Transoral Incisionless Fundoplication (TIF), refer to LCD L34298

Name of Blue Advantage Policy:

Transesophageal Endoscopic Therapies for Gastroesophageal Reflux Disease-GERD

Policy #: 023
Category: Surgery

Latest Review Date: January 2018
Policy Grade: B

Background:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*

    - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
    - *Furnished in a setting appropriate to the patient's medical needs and condition;*
    - *Ordered and furnished by qualified personnel;*
    - *One that meets, but does not exceed, the patient's medical need; and*
    - *At least as beneficial as an existing and available medically appropriate alternative*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Description of Procedure or Service:

Transesophageal endoscopic therapies are being developed for the treatment of gastroesophageal reflux disease (GERD). A variety of procedures are being evaluated, including transesophageal (or transoral) incisionless fundoplication (TIF), application of radiofrequency (RF) energy, and injection/implantation of prosthetic devices or bulking agents.

Gastroesophageal Reflux Disease

GERD is a common disorder characterized by heartburn and other symptoms related to reflux of stomach acid into the esophagus. Nearly all individuals experience such symptoms at some point in their lives; a smaller number have chronic symptoms and are at risk for complications of GERD. The prevalence of GERD has been estimated to be 10% to 20% in the Western world, with a lower prevalence in Asia.

Pathophysiology

The pathophysiology of GERD involves excessive exposure to stomach acid, which occurs for several reasons. There can be an incompetent barrier between the esophagus and stomach, either due to dysfunction of the lower esophageal sphincter (LES) or incompetence of the diaphragm. Another mechanism is abnormally slow clearance of stomach acid by the esophagus. A third mechanism is abnormally slow clearance of acid by the stomach. In this situation, delayed clearance leads to an increased reservoir of stomach acid and a greater tendency to reflux.

In addition to troubling symptoms, some patients will have more serious disease, which results in complications such as erosive esophagitis, dysphagia, Barrett esophagus, and esophageal carcinoma. Pulmonary complications may result from aspiration of stomach acid into the lungs and can include asthma, pulmonary fibrosis and bronchitis, or symptoms of chronic hoarseness, cough, and sore throat.

Treatment

Guidelines on the management of GERD emphasize initial medical management. Weight loss, smoking cessation, head of bed elevation, and elimination of food triggers are all recommended in recent practice guidelines. PPIs have been shown to be the most effective medical treatment. In a Cochrane systematic review, PPIs demonstrated superiority to H2-receptor agonists and prokinetics in both network meta-analyses and direct comparisons.

Surgical Treatment

The most common surgical procedure used for GERD is laparoscopic Nissen fundoplication. Fundoplication involves wrapping a portion of the gastric fundus around the distal esophagus to increase LES pressure. If a hiatal hernia is present, the procedure also restores the position of the LES to the correct location. Laparoscopic fundoplication was introduced in 1991 and has been rapidly adopted because it avoids complications associated with an open procedure.

Although fundoplication results in a high proportion of patients reporting symptom relief, complications can occur, and sometimes require conversion to an open procedure. Patients who have relief of symptoms of GERD after fundoplication may have dysphagia or gas-bloat syndrome (excessive gastrointestinal gas).

Other Treatment Options
Due in part to the high prevalence of GERD, there has been interest in creating a minimally invasive transesophageal therapeutic alternative to open or laparoscopic fundoplication or chronic medical therapy. This type of procedure may be considered natural orifice transluminal surgery (NOTES). Three types of procedures have been investigated.

1. The transesophageal endoscopic gastroplasty is also referred to as gastroplication, fundoplication or transoral incisionless fundoplication (TIF). During the procedure, the fundus of the stomach is folded, and then held in place with staples or fasteners that are deployed by the device. The endoscopic procedure is designed to recreate a valve and barrier to reflux.

2. Radiofrequency (RF) energy has been used to produce submucosal thermal lesions at the gastroesophageal junction. (This technique has also been referred to as the Stretta procedure). Specifically, radiofrequency energy is applied through four electrodes inserted into the esophageal wall at multiple sites both above and below the squamocolumnar junction. The mechanism of action of the thermal lesions is not precisely known but may be related to ablation of the nerve pathways responsible for sphincter relaxation or may induce a tissue-tightening effect related to heat-induced collagen contraction and fibrosis.

3. Submucosal injection or implantation of a prosthetic or bulking agent to enhance the volume of the lower esophageal sphincter has also been investigated.

One bulking agent, pyrolytic carbon-coated zirconium oxide spheres (Durasphere®), is being evaluated.

The Gatekeeper Reflux Repair System (Medtronic, Shoreview, MN) utilizes a soft, pliable, expandable prosthesis made of a polyacrylonitrile-based hydrogel. The prosthesis is implanted into the esophageal submucosa and with time the prosthesis absorbs water and expands, creating bulk in the region of implantation.

In addition, the endoscopic submucosal implantation of polymethylmethacrylate beads into the lower esophageal folds has also been investigated.

Policy:

Effective February 26, 2018: Refer to LCDs L34434, L34553 & 36954 for Transesophageal Endoscopic Therapies for Gastroesophageal Reflux Disease-GERD

Effective December 1, 2012; Refer to LCD L32826/L34298 for Transoral Incisionless Fundoplication (TIF)

Effective for dates of service on or after October 17, 2011 and prior to February 26, 2018:
Blue Advantage will treat the **implantation of a prosthesis or hydrogel** as a **non-covered** benefit and as **investigational**.

Effective for dates of service on or after July 18, 2005:
Blue Advantage will treat the **Stretta procedure or radiofrequency to create submucosal thermal lesions of the lower esophageal sphincter** as a **non-covered** benefit and as **investigational** when used as a treatment for gastroesophageal reflux disease.

Blue Advantage will treat **implantation of polymers, spheres, or injection of beads into the lower esophageal sphincter** as a **non-covered** benefit and as **investigational**.

Blue Advantage will treat the **fixation of a transmural suture-pledget (Plicator procedure) for the treatment of gastroesophageal reflux diseases** as a **non-covered** benefit and as **investigational**.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The most recent literature review was performed through October 31, 2017. This policy will address procedures which are currently available for use in the U.S.

The Agency for Healthcare Research and Quality (AHRQ) published a systematic review on management strategies for gastroesophageal reflux disease in 2005, which was updated in 2011. The 2005 comparative effectiveness review evaluated studies on the EndoCinch Suturing System, Stretta, Enteryx, and the NDO Plicator. The 2011 update of the AHRQ report excluded Enteryx and the NDO Plicator, because they were no longer available in the United States, and added the EsophyX procedure (endoscopic fundoplication), which was commercialized after the 2005 review. The 2011 AHRQ report concluded that for the 3 available endoscopic procedures (EndoCinch, Stretta, EsophyX), effectiveness remains substantially uncertain for the long-term

management of GERD. All of these procedures have been associated with complications, including dysphagia, infection/fever, and bloating, although bloating and dsyphagia are also adverse effects of laparoscopic fundoplication. A 2015 review of endoscopic treatment of GERD noted that EndoCinch is no longer manufactured.

Transoral Incisionless Fundoplication (Esophyx®)

The following discussion examines separately studies for patients whose symptoms are not controlled by proton pump inhibitors (PPIs; see Tables 1 to 4) and those whose symptoms are controlled by PPIs (see Tables 5 and 6). For patients whose symptoms are not controlled by PPIs, the optimal comparator would be fundoplication, while the optimal comparator in patients whose symptoms are controlled by PPIs would be continued PPI therapy.

TIF in Patients whose Symptoms are not Controlled by PPIs

Randomized Trials

Two RCTs have evaluated TIF using ExophyX2 in patients with troublesome symptoms despite daily PPI therapy (see Table 1). Hunter et al (2015) compared TIF plus placebo pills (n=87) with treatment using sham TIF plus PPI (n=42) in the RESPECT trial. Increases in medication (placebo or PPI depending on treatment group) were allowed at 2 weeks. At 3 months, patients with continued troublesome symptoms were declared early treatment failures, and failed TIF patients were given PPI and failed sham patients were offered TIF. Trad et al (2015) compared TIF (n=40) with maximum PPI therapy (n=23) without a sham procedure in the TEMPO trial. The primary outcome in both trials was the elimination of symptoms, measured in slightly different ways (see Table 1).

In both trials, the primary outcome was achieved by a higher percentage of patients treated with TIF than with PPIs (see Table 2). Elimination of symptoms was reported by 62% to 67% of patients treated by TIF compared with 5% of patients treated with maximum PPIs and 45% of patients who had a sham procedure plus PPIs. In TEMPO, the relative risk of achieving the primary outcome was 12.9 (95% confidence interval [CI], 1.9 to 88.9; $p<0.001$).

Secondary outcomes (e.g., RDQ regurgitation score, RDQ heartburn score) showed no significant differences between treatments. Physiologic measurements such as number of reflux episodes, percent total time pH less than 4, and DeMeester score (a composite score of acid exposure based on esophageal monitoring) showed differences that were statistically significant between groups, but these measurements were performed when off PPIs for 7 days, and the difference in pH between TIF and continued PPI therapy cannot be determined from this trial.

In TEMPO, self-reported troublesome regurgitation was eliminated in 97% (29/30) of TIF patients who were off PPIs. However, the objective measure of esophageal acid exposure did not differ significantly between groups.

Table 1: Characteristics of Randomized Controlled Trials Comparing TIF with Medical Management in Patients whose Symptoms were not Controlled on PPIs

Study	TIF:CTRL	Patient Symptoms or other Characteristics	Comparator	Follow-up, mos	Principal Clinical Outcome
Hunter et al (2015) (RESPECT)	87:42	• Hiatal hernia ≤2cm • Troublesome regurgitation[a], not controlled on PPI	Sham + PPI	6	Relief of regurgitation without PPI in TIF group vs with PPI escalation in control group
Trad et al (2015) (TEMPO)	40:23	• Hiatal hernia ≤2cm • Troublesome symptoms, not controlled on PPI[b]	Maximum dose PPI	6	Elimination of daily symptoms other than heartburn

CTL: control; FU: follow-up; PPI: proton pump inhibitor; TIF: transoral incisionless fundoplication. a Troublesome regurgitation was defined as mild symptoms for ≥2 days a week or moderate-to-severe symptoms >1 day a week. b Gastroesophageal reflux disease for >1 year and a history of daily PPI use for >6 months.

Table 2. Summary of Key Results for RCTs Comparing TIF With Medical Management in Patients Whose Symptoms Were Not Controlled on PPIs

Trial (Year)	Elimination of Symptoms	Change in Regurgitation	Change in Heartburn	Reflux Symptoms	Esophageal pH
	Elimination of Troublesome Regurgitation	**Change in RDQ Regurgitation Score**	**Change in RDQ Heartburn Score**	**Change in RDQ Heartburn Plus Regurgitation Score**	
RESPECT (2015)					
TIF + placebo	67% (58/87)	-3	-2.1	-2.5	
Sham + PPI	45%	-3	-2.2	-2.4	
p value	0.023	0.072	0.936	0.313	
	Elimination of Symptoms other than heartburn[b]	**Change in GERD-HRQL Score**	**Change in GERD-HRQL Heartburn Score**	**RSI Score**	**Percent Time with pH >4**
TEMPO (2015)					
TIF	62%	-21.1	-14	-17.4	54%
Maximum-dose PPI	5%	-7.6	-5.2	-3.0	52%
RR (95% CI)	-12.9 (1.9-88.9)				
p value	0.001	NR	NR	NR	0.914
Summary					
TIF	62%-67%				

CI: confidence interval; GERD-HRQL: Gastroesophageal Reflux Disease Health-Related Quality of Life; NR: not reported; PPI: proton pump inhibitor; RCT: randomized controlled trial; RDQ: Reflux Disease Questionnaire; RR: relative risk; RSI: Reflux Symptom Index; TIF: transoral incisionless fundoplication. a Primary outcome measure. b Primary outcome measure – composite of 3 gastroesophageal reflux disease symptom scales: the GERD-HRQL, RSI, and RDQ.

In 2017, Trad et al reported 3-year follow-up for patients treated with TIF in the TEMPO trial (see Table 3). All patients in the control group (maximum PPIs) had crossed over to TIF and were included in the follow-up. Symptom scores, esophagastroduodenoscopy, and 48-hour pH

monitoring were conducted off PPIs, and the 2 TIF failures who had undergone fundoplication were assigned the worst scores. Of 63 patients treated with TIF, data on PPI use was available for 52 (83%), with 71% of patients reporting a cessation of PPI use. However, completion of the Reflux Disease Questionnaire and assessment of pH normalization were available for less than 65% of patients. pH normalization was available for 40% of available patients following TIF, whereas 90% reported elimination of troublesome regurgitation.

Table 3. Follow-Up of Patients Treated With EsophyX2 in the TEMPO Trial

Outcome Measure	Baseline	1 Year	2 Years	3 Years
Sample size (% of 63)		60(95%)	55 (87%)	52 (83%)
Elimination of troublesome regurgitation (RDQ)[a]		88% (42/48)	90% (41/44)	90% (37/41)
Elimination of atypical symptoms (RSI ≤13)[a]		82% (45/55)	84% (43/51)	88% (42/48)
GERD-HRQL score	32.8 (/60)	7.1 (/58)	7.3 (/52)	5.0 (/43)
Esophagitis	55% (33/60)	5% (3/59)	10% (5/50)	12% (5/41)
Cessation of PPI use		78% (47/60)	76% (42/55)	71% (37/52)
pH normalization[b]		41% (24/59)	37% (18/49)	40% (16/40)

Adapted from Trad et al (2017). GERD-HRQL: Gastroesophageal Reflux Disease Health-Related Quality of Life; PPI: proton pump inhibitor; RDQ: Reflux Disease Questionnaire; RSI: Reflux Symptom Index.

[a] Primary outcome: elimination of daily troublesome regurgitation and atypical symptoms as measured with the RDQ and the RSI. Troublesome symptoms are defined as mild symptoms, occurring ≥2 days a week, or moderate-to severe symptoms, occurring >1 day a week.

[b] Normality was defined as percent of total recorded time pH

Studies Comparing TIF to Laparoscopic Fundoplication

Svoboda et al compared 34 patients receiving TIF to 18 patients receiving fundoplication, but more than half of the patients who had TIF did so with a discontinued device, so that the trial results may not generalize to EsophyX. There was no separate analysis of patients undergoing TIF with the EsophyX device, and the results of this trial are not discussed further.

Nonrandomized Studies

Two nonrandomized comparative studies have compared TIF with laparoscopic fundoplication in patients whose symptoms were not controlled on PPIs.

Frazzoni et al (2011) compared 10 patients undergoing TIF to 10 patients undergoing laparoscopic fundoplication with the first-generation EsophyX procedure (see Table 4). Patients selected which treatment they wanted, but the groups were comparable to a baseline. In terms of clinical outcomes assessed at 3 months, 7 patients undergoing TIF reported only partial/no symptom remission versus 0 patients undergoing fundoplication (see Table 4). Mild dysphagia was reported by 2 patients after fundoplication and 1 patient after TIF. Two patients reported epigastric bloating after fundoplication. Several measures of GERD as assessed by manometry and impedance pH monitoring showed greater improvement in the fundoplication group than in the TIF group. This study reported that TIF with the first-generation EsophyX device is less effective than fundoplication in improving symptoms of GERD. Adverse perioperative events were not described.

Table 4. Summary of Key Results in Patients Whose Symptoms Were Not Controlled by PPIs

Study (Year)	Percent Partial or no Symptom Remission	Normalization Esophageal Acid Exposure Time	Normalization of Distal Refluxes	Normalization of Proximal Refluxes	Mild Dysphagia	Bloating
Frazzoni et al (2011)						
TIF, %	70	50	20	40	10	0
Fundoplication, %	0	100	90	100	20	20
p value	0.003	0.03	0.005	0.011	NR	NR

NR: not reported; PPI: proton pump inhibitor; TIF: transoral incisionless fundoplication

A nonrandomized study by Toomey et al compared 20 patients undergoing TIF, 20 patients undergoing Nissen fundoplication, and 20 patients undergoing Toupet fundoplication. The trialists stated that age, body mass index, and preoperative DeMeester score were controlled; however, the indications for each procedure differed. Patients with abnormal esophageal motility underwent Toupet fundoplication. Only patients who had a hiatal hernia of 2 cm or less were offered TIF. Due to these selection criteria, at baseline, 15% of the TIF group had a hiatal hernia versus 65% and 55% of the 2 fundoplication groups, limiting comparison of both treatments Adverse events were not reported.

Section Summary: Patients whose Symptoms Are Not Controlled by PPIs

Studies Comparing TIF with Continued PPIs

The evidence on TIF in patients whose symptoms are not controlled by PPIs includes 2 RCTs, one of which followed TIF patients out to 3 years. The highest quality study is the sham-controlled RESPECT trial by Hunter et al (2015). RESPECT found a significantly greater proportion of patients who reported elimination of troublesome regurgitation compared with sham plus PPIs, however, elimination of regurgitation was achieved in only 67% of patients treated with TIF. Also, other symptom measures were no different between the TIF and sham-PPI group. A strong placebo effect of the procedure is suggested by the subjective outcome measures in the sham group, in which 45% of patients whose symptoms were not previously controlled on PPIs reported elimination of troublesome regurgitation. The strong placebo effect suggested by the RESPECT trial raises questions about the validity of the nonblinded TEMPO trial. TEMPO reported a significant improvement in subjective measures with TIF compared to maximum PPI treatment, but there was no significant difference in the objective measure of esophageal acid exposure. At a 3-year follow-up, about twice as many patients reported symptom improvement compared with improvement in the objective measure. It is not clear whether the discrepancy is due to a general lack of correlation between pH and symptoms, or to a placebo effect on the subjective assessment. Together, these data suggest that the most appropriate comparator for patients whose symptoms are not controlled on PPIs is laparoscopic fundoplication.

Studies Comparing TIF to Laparoscopic Fundoplication

Each study comparing TIF to laparoscopic fundoplication has methodologic problems that do not permit conclusions on the comparative efficacy of the 2 procedures. The nonrandomized study by Frazzoni et al showed that TIF is less effective than fundoplication. However, this study was

conducted with an earlier device. The RCT by Svoboda et al included in the TIF group patients who underwent the procedure using a different device. In the third study by Toomey et al, patients were assigned to different procedures based on specific baseline characteristics. Two of the studies concluded that TIF and fundoplication were similarly effective based on lack of statistically significant differences across symptom outcomes. However, because of the small sizes of these samples, lack of a statistically significant difference in outcomes cannot be interpreted as equivalent outcomes. For these studies, several outcomes favored fundoplication over TIF. The studies did not report adverse events or rates of postoperative symptoms associated with fundoplication (e.g., dysphagia, bloating). Thus it is not possible to evaluate whether a difference in effectiveness between procedures might be accompanied by a difference in adverse events. Limited data suggest that the first-generation TIF is considerably inferior to laparoscopic fundoplication in patients who have failed PPI therapy, and this treatment is no longer available. Current data are insufficient to determine the risks and benefits of the second-generation TIF procedure compared with laparoscopic fundoplication in patients whose symptoms are not controlled by PPIs.

TIF in Patients whose Symptoms Are Controlled by PPIs

Randomized Trials

Two published RCTs have evaluated the efficacy of TIF in patients whose symptoms were adequately controlled on PPIs, but who were considering an intervention over lifelong drug dependence (see Table 5). Hakansson et al (2015) compared TIF (n=22) to sham only (n=22). The expected outcome in the sham group was that, without PPI, GERD symptoms would eventually recur. Witteman et al compared TIF (n=40) to continued PPI therapy (n=20) without a sham procedure (see Table 5). The objective was to demonstrate that outcomes with TIF were not significantly worse than those with continued PPI therapy. The primary outcome of the Hakansson trial was treatment failure, defined as the need for resumption of PPIs (see Table 5). The primary outcome of the Witteman trial was treatment success, defined by an improvement of 50% or more on the GERD-HQRL.

In Hakansson et al, Kaplan-Meier curves showed a higher rate of treatment failure in the sham group than in the TIF group ($p<0.001$, time to treatment failure), with significantly more patients in the TIF group in remission at 6 months (59%) compared with the sham without PPI group (18%, $p=0.01$). In Witteman et al, PPI therapy was stepped up or down as necessary during follow-up. At 6 months, 55% of TIF patients had more than 50% improvement in subjective GERD symptoms vs 5% of patients on continued PPI therapy (see Table 6). Mean change in GERD symptoms from baseline was consistent with this result (TIF, -14.1; control, -3.1), however, it is uncertain whether the difference between groups was due to a combination of TIF plus PPI, or if the PPI therapy in the control group was at maximum following the step-up protocol.

Secondary outcomes measuring GERD symptoms in Hakansson et al showed results consistent with more favorable outcomes in the TIF group. However, no statistical between-group analysis was reported for these outcomes. Dysphagia, bloating, and flatulence was reported in twice as many patients undergoing TIF (four, four, and two, respectively) compared with sham (two, two, and one, respectively). These results were reported as not statistically different. However, it is unlikely that the trial was powered to detect differences in these outcomes.

Table 5. Characteristics of Randomized Trials of TIF in Patients Whose Symptoms Were Controlled by PPIs

Study (Year)	TIF:CTL, n	Patient Symptoms or other Characteristics	Comparator	FU, mo	Principal Clinical Outcome
Hakansson et al (2015)	22:22	Controlled on PPI, run-in to confirm PPI dependence	Sham only	≥6	Time to resumption of PPI, percent needing PPI at 6 mo
Witteman et al (2015)	40:20	Controlled on PPI	Continued PPI only	6	Mean GERD symptoms, percent with >50% improvement

CTL: control; FU: follow-up; GERD: gastroesophageal reflux disease; PPI: proton pump inhibitor; TIF: transoral incisionless fundoplication.

Table 6. Principal Clinical Outcomes of RCTs Comparing TIF With Nonsurgical Treatment in Patients Whose Symptoms Were Controlled on PPIs

Study (Year)	Days to PPI Resumption	Change in PPI Therapy	Change in Symptoms	Change in QOL	Change in QOL	Esophagitis	Esophageal pH
		Remission at 6 mos	Change in Median GSRS Score	Change in Median QOLRAD Score	Change in Median QOLRAD Score		% Time pH<4
Hakansson et al (2015)							
TID	197	13(59%)	4	1.5	1.5		3.6%
Sham only	107	4(18%)	1.4	0.4	0.4		9.8%
p value	0.001	0.01	NR	NR	NR		NR
			Percent >50% Improvement in GERDHRQL Score	Mean Change in GERD-HRQL Score		Change in% with Esophagitis	% Patients with Normalized pH[a]
Witteman et al (2015)							
TIF			55%	-14.1		-19%	50%
Continued PPI			5%	-3.1		-20%	63%
p value			<0.001	<0.001		>0.05	NR

GERD-HRQL: Gastroesophageal Reflux Disease Health-Related Quality of Life; GSRS: Gastrointestinal Symptom Rating Scale; NR: not reported; PPI: proton pump inhibitor; QOL: quality of life; QOLRAD: Quality of Life in Reflux and Dyspepsia; RCT: randomized controlled trial; TIF: transoral incisionless fundoplication. a Defined as <4% for ≤4.2

In Witteman et al, 26% of TIF patients resumed at least occasional PPI use by 6 months, and 100% of control patients remained on PPI therapy. With the exception of LES resting pressure, secondary physiologic and endoscopic outcome measures did not differ significantly between groups. No adverse events related to fundoplication were identified on the Symptom Rating Scale.

TIF patients were followed beyond 6 months, with additional control patients who crossed over to have TIF. A total of 60 patients eventually underwent TIF, but there were losses to follow-up at 6 (7 patients) and 12 months (additional 8 patients). Although GERD symptoms remained improved over baseline ($p<0.05$), esophageal acid exposure did not differ significantly from baseline. At least occasional use of PPI increased between 6 months and 12 months, from 34% to 61%. Three TIF patients underwent fundoplication during this follow-up period. Endoscopy findings at 6 months and 12 months showed several findings indicating possible worsening of GERD in terms of esophagitis rating, Hill grade rating of the gastroesophageal valve, and size of hiatal hernia, but no formal statistic analysis of these changes was reported. Although this RCT met its principal end point at 6 months, and improvements in GERD symptoms appeared to be maintained to 12 months, due to findings observed between 6 months and 12 months in TIF patients, the authors concluded that "TIF is no[t an] equivalent alternative for PPIs in GERD treatment, even in this highly selected population." The trial was originally designed as a 2-center study, but it was terminated following interim analysis showing loss of reflux control.

Observational Studies

Observational case series and prospective cohort studies can provide information on the durability of the TIF procedure. Studies are included if they provide additional information on treatment durability or address treatment safety.

A case series and a cohort study have evaluated outcomes to 6 years after TIF 2 (see Tables 7 and 8). Both of these studies were performed in patients with hiatal hernias of 2 cm or less in size whose symptoms were adequately controlled on PPIs but did not want to take medication indefinitely. In a prospective cohort by Testoni et al (2015), 72% of the patients were completely responsive to PPIs at baseline, and 24% were partially responsive. Hiatal hernias had recurred by 12 months in 46% of the patients who had hernias at baseline, and at the 24-month follow-up, 20% of TIF procedures were considered unsuccessful. Eight percent of patients had additional surgery for poor response by 2 years. The Johnson-DeMeester score was not significantly improved. A poor response to treatment was associated with a hiatal hernia of 2 cm, higher Hill grade, presence of esophagitis at baseline, and use of fewer fasteners. About half the patients with a complete response initially had gone back to PPI use, although this finding is limited by the low number of patients followed to 6 years. The number of fasteners used in this study might also be lower than current procedures.

Stefanidis et al (2017) reported in a retrospective series that about 75% of patients had elimination of esophagitis and had discontinued PPI use at 6 years, while 62% of the 13 patients with a hiatal hernia had a reduction in hernia size at follow-up.

Table 7. Summary of Characteristics of Observational Studies With Long-Term Outcomes in Patients Whose Symptoms Were Controlled by PPIs

Author (Year)	Country/Institution	Participants	Treatment Delivery	Mean FU, mo
Testoni et al (2015)	Prospective study from 2 centers in Italy	Daily PPI, esophagitis or abnormal pH, hiatal hernia ≤2cm	ExophyX2	53
Stefanidis et al (2017)	Greece	PPI-controlled, hiatal hernia ≤2cm	ExophyX2	59

FU: follow-up; PPI: proton pump inhibitor

Table 8. Long Term durability of TIF in Patients whose Symptoms were Controlled by PPIs

Outcomes by Study	Baseline	6 Months	1 Year	2 Years	3 Years	6 years
Testoni et al (2015)						
Sample size	50	49	49[a]	45[b]	32	14
GERD-HRQL score off PPI(SD)	46(19)			16(13)	17(14)	
GERD-QUAL score off PPI (SD)	114(20)			71(24)	80(21)	
Johnson-DeMeester score (SD)	22(12)	18(15)		19(20)		
PPI discontinuation		61.2%	51.0%	56.1%	53.1%	35.7%
Additional surgery for poor response				8.2%		
Stefanidis et al (2017)						
Sample size	45					44
Median GERD-HRQL score off PPI	27					4
PPI discontinuation						72.7%
Elimination of esophagitis	n=33		81.8%			72.7%
Reduction in hiatal hernia	n=13					61.5%

GERD-HRQL: Gastroesophageal Reflux Disease Health-related Quality of Life; GERD-QUAL: Gastroesophageal Reflux Disease Quality of Life; PPI: proton pump inhibitor; SD: standard deviation; TIF: transoral incisionless fundoplication.
[a] Excluding 1 failed procedure due to pneumothorax
[b] Excluding 4 patients who underwent Nissen fundoplication for failed procedure.

Adverse Events

In 2017, Huang et al conducted a systematic review with meta-analysis of TIF for the treatment of GERD. They included 5 RCTs and 13 prospective observational studies, of which 14 were performed with the TIF 2 procedure. Efficacy results from the RCTs were combined for patients whose symptoms were controlled by PPIs and for those whose symptoms were not controlled by PPIs, and are not further discussed here. Follow-up to 6 years in prospective observational studies indicated a decrease in efficacy over time. The reported incidence of severe adverse events, consisting of gastrointestinal perforation and bleeding, was 19 (2.4%) of 781 patients. This included 7 perforations, 5 cases of post-TIF bleeding, 4 cases of pneumothorax, 1 case requiring intravenous antibiotics, and 1 case of severe epigastric pain.

Section Summary: TIF in Patients Whose Symptoms Are Controlled by PPIs

The evidence on TIF in patients whose symptoms are controlled by PPIs includes 2 RCTs and observational studies with long-term follow-up. The sham-controlled trial by Hakansson et al (2015) found that the time to resume PPI therapy was longer following TIF and the remission rate was higher, indicating that TIF is more effective than no therapy. Statistical analysis was not reported for other subjective and objective outcome measures, and it is unclear whether the trial was adequately powered for these outcomes. The nonblinded trial by Witteman et al found a benefit of TIF compared with continued PPI therapy for subjective measures, but not for the objective measures of pH normalization and esophagitis, raising questions about a possible placebo effect. Extended follow-up of the TIF patients in the Witteman trial found the use of PPI increased over time, while endoscopy showed several findings indicating possible worsening of GERD. The limited evidence beyond 2 years is consistent with some loss of treatment effectiveness. Increased use of PPIs beyond 2 years occurred in Testoni et al (2015). Adverse events associated with the procedure may be severe. Current evidence is insufficient to determine the effect of this intervention on the net health outcome in patients whose symptoms are adequately controlled by PPIs.

Transesophageal Radiofrequency (i.e., Stretta Procedure)

The available evidence on the use of transesophageal radiofrequency (TERF) consists of a meta-analysis and four small RCTs, three of which include a sham control, along with numerous uncontrolled case series.

Systematic Reviews

A meta-analysis of 4 RCTs (total N=165 patients) was published by Lipka et al in 2015 (see Table 9). Three trials compared Stretta with sham, and one compared Stretta with PPI therapy (see Table 10). Results of the individual sham-controlled trials were inconsistent, generally supporting some improvement in symptoms, but not in objective measures of esophageal acid exposure. For example, Corley et al (2003) reported improvement in heartburn symptoms, quality of life, and general physical quality of life in the active treatment group compared with the sham group, but there were no significant differences in medication use and esophageal acid exposure. Aziz et al (2010) found statistically significant improvements in GERD-HRQL score in all treatment groups. Arts et al (2012) reported that the symptom score and quality-of-life score for bodily pain improved, but no changes were observed in PPI use, esophageal acid exposure or lower esophageal sphincter pressure after RF. Pooled results of the meta-analysis showed no significant difference between Stretta and either sham treatment or PPI management for the measured outcomes, including the ability to stop PPI therapy (see Table 11). The overall quality of evidence was considered to be very low with a high risk of bias, and the meta-analysis was limited by heterogeneity in the included studies, which might have been due to small sample sizes, differences in measures, and differences in follow-up time.

A 2012 meta-analysis by Perry et al included 20 studies (two RCTs and 18 case series) with a total of 1,441 patients in their meta-analysis. This review analyzed the within-subjects results following treatment only. The control groups of available clinical trials were not included for comparison. Significant improvements were reported for subjective heartburn scores, GERD-HRQL scores, and 36-Item Short-Form Health Survey Physical Component Summary scores. For the studies that measured esophageal pH, significant improvements were found in the

Johnson-DeMeester score, the esophageal acid exposure time, and lower esophageal sphincter pressure. This meta-analysis is limited by the inclusion of lower quality studies and by the analysis, which only examined within-subject differences and did not include between-subjects differences, as reported in the RCTs.

Table 9. Meta-Analytic Characteristics of RCTs of TERF

Study (Year)	Dates	Trials	Participants[a]	N (Range)	Design	Duration, mo
Perry et al, (2012)	1966-2010	20	Patients with GERD undergoing TERF	1441 (7-558)	Meta-analysis of single arm of 2 RCTs and 18 case series	4-48
Lipka et al (2015)	Inception to Feb 2014	4	Patients with physiologic evidence of GERD who were on PPI therapy	165 (22-64)	Meta-analysis of RCTs	6-12

GERD: gastroesophageal reflux disease; RCT: randomized controlled trial; TERF: transesophageal radiofrequency.
a Key eligibility criteria.

Table 10. Characteristics of RCTs of TERF

Study	TERF:CTL, n	Patient Symptoms or other Characteristics	Comparator	FU, mo	Principal Clinical Outcomes
Corley et al (2003)	35:29	Abnormal EAE, symptoms at least partially controlled by PPIs, hiatal hernia ≤2 cm	Sham	6	Heartburn, QOL, PPI use, pH
Aziz et al (2010)	12:12:12	GERD controlled by PPIs, patients were randomized to single or double TERF or sham	Sham	12	GERD-HRQL score
Arts et al (2012)	11:11	GERD at least partially controlled by PPIs and abnormal pH, hiatal hernia ≤3 cm	Sham with crossover at 3 mo	3	Composite reflux symptom score, esophageal pH, motility, and distensibility
Coron et al (2008)	20:16	GERD symptoms controlled by PPIs and abnormal EAAE	Continued PPI	6	Stopping or decreasing PPI use

CTL: control; EAE: esophageal acid exposure; FU: follow-up; GERD: gastroesophageal reflux disease; GERD-HRQL: Gastroesophageal Reflux Disease Health-related Quality of Life; pH: acid exposure; PPI: proton pump inhibitor; QOL: quality of life; RCT: randomized controlled trial; TERF: transesophageal radiofrequency.

Table 11. Meta-Analytic Results

Study (Year)	Heartburn	GERD-HRQL Score	SF-36 PCS Score	Acid Exposure Time (pH <4)	Other Objective Outcome Measures
	Heartburn Score				**Johnson-Demeester Score**
Perry et al (2012)					
N	525(9studies)	433 (9 studies)	299 (6 studies)	364 (11 studies)	267 (7 studies)
Mean follow-up, mo	24.1	19.8	9.5	11.9	13.1
Baseline (SE)	3.55 (3.9)	26.11 (27.2)	36.45 (51.6)	10.29% (17.8%)	44.37 (93)
Posttreatment (SE)	1.19 (3.4)	9.25 (23.7)	46.12 (61.9)	6.51% (12.5%)	28.54 (33.4)
p	0.001	0.001	0.001	0.003	0.007
	Ability to Stop PPI Therapy				**Mean LES Pressure**
Lipka et al (2015)					
N	118 (3 studies)	88 (2 studies)		153 (4 studies)	110 (3 studies)
MD (95% CI)	RR=0.87 (0.75 to 1.00)	-5.24 (-12.95 to 2.46)		1.56% (-2.56% to 5.69%)	0.32 mm Hg (-2.66 to 2.02 mm Hg)
p	0.06	0.18		0.46	0.79
I^2 (p)	0%	96% (p<0.001)		99% (<0.001)	96% (<0.001)
Range of N	24-51	22-64		22-64	

CI: confidence interval; GERD-HRQL: Gastroesophageal Reflux Disease Health-related Quality of Life; LES: lower esophageal sphincter; MD: mean difference; PCS: Physical Component Summary; RR; relative risk; SE: standard error; SF-36: 36-Item Short-Form Health Survey.

Controlled Trials Comparing TERF vs Laparoscopic Fundoplication

In 2015, Liang et al reported a prospective comparison of laparoscopic Toupet fundoplication (n=80) versus the Stretta procedure (See Table 12). Of the 165 patients treated, 125 (76%) completed the three year follow-up (65 fundoplication and 60 Stretta) and were included in the analysis. Although the two groups were comparable in symptoms at baseline, nine patients in the Stretta group had revised treatment and were not included in the final symptom scores. A similar percentage of remaining patients in the two groups achieved complete PPI independence (laparoscopic fundoplication: 72.3% versus Stretta: 68.3%, p =0.627) and had similar improvements in belching, hiccup, cough and asthma. The Stretta procedure was less effective than laparoscopic fundoplication in improving symptoms of heartburn, regurgitation, and chest pain (See Table 13). Significantly more patients in the Stretta group underwent re-operation (11.8% vs 0%, p = 0.006), while more patients in the fundoplication group complained of bloating (6.2% vs 0%, p = 0.120), but this differences was not statistically significant. This study is limited by the lack of randomization and, along with not reporting the TERF failures, had a high loss to followup. While symptom scores were comparable at baseline, it is possible that selection bias in choosing treatment may have resulted in baseline differences on other variables.

Table 12. Summary of Characteristics of Key Study Comparing TERF With Laparoscopic Fundoplication

Author (year)	Study Type	County	Dates	Participants	Treatment 1	Treatment 2	RU, y
Liang et al (2015)	Comparative cohort	China	2011	165	TERF	Laparoscopic fundoplication	3

FU: follow-up; TERF: transesophageal radiofrequency.

Table 13. Study Results Comparing TERF With Laparoscopic Fundoplication

Study (Year)	PPI Independence	Improvement in Heartburn Score	Improvement in Regurgitation Score	Improvement in Chest Pain Score	Reoperation	Bloating
Liang et al (2015)						
TERF	68.3%	2.53	2.41	2.96	11.8%	0%
Laparoscopic Fundoplication	72.3%	4.05	4.03	5.50	0%	6.2%
p	0.627	0.01	0.004	0.005	0.006	0.120

PPI: proton pump inhibitor; TERF: transesophageal radiofrequency

Prospective Cohort Studies

Long-term follow-up from case series and cohort studies can inform the durability of TERF. For example, 5- and 10-year follow-up after TERF were reported in 2014 (see Table 14). Elimination of PPI use was similar for both studies at around 42% (see Table 15). Liang et al reported that symptoms of heartburn, regurgitation, chest pain, cough, and asthma were all decreased compared with baseline. Noar et al reported symptom improvement in 72% of patients and elimination of dysplasia in 85% of patients, but the interpretation of these findings is limited due to the 34% loss to follow-up in this study.

Table 14. Summary of Key Prospective Cohort Study and Case Series Characteristics

Author (Year)	Country/Institution	Participants	Follow-Up, y	Loss to Follow-Up
Liang et al (2014)	China	152 who had failed PPI therapy	5	9%
Noar et al (2014)	University of Pittsburgh	149 who had failed PPI therapy	10	34% (7% deceased)

PPI: proton pump inhibitor.

Table 15. Summary of Key Prospective Cohort Study and Case Series Results at Follow-Up

Author (Year)	Elimination of PPI Use	Symptom Improvement	Elimination of Dysplasia	Bloating
Liang et al (2014)	42.8%	P<0.001 vs pretreatment		8.7%
Noar et al (2014)	41%	72%	85%	

PPI: proton pump inhibitor.

Section Summary: Transesophageal Radiofrequency (i.e. Stretta Procedure)

Four RCTs (N range, 22-64 patients), three of which were sham-controlled, reported some improvements in symptoms following treatment with TERF. However, measures of esophageal acid exposure were typically not improved. Also, meta-analyses of these same studies found no

significant improvements in outcomes. The findings of improvements in symptoms but not esophageal acid exposure have led to questions whether TERF is acting by reducing sensation in the esophagus. Although single-arm studies have shown maintenance of symptom relief at 5 to 10 years, interpretation depends on the efficacy of the procedure in the short term. A nonrandomized comparative study has suggested that symptom relief with TERF is lower than with fundoplication and there is a greater incidence of reoperations. Larger RCTs with longer follow-up are needed to better define the risks and benefits of this procedure.

Esophageal Bulking Agents

Durasphere

The available evidence for this device consists of one case series. One open-label pilot study of ten GERD patients injected Durasphere (Carbon Medical Technologies, St. Paul, MN), a bulking agent approved for treatment of urinary and fecal incontinence, at the gastroesophageal junction. At 12 months, seven patients (70%) discontinued all antacid medication completely. No erosion, ulceration, or sloughing of material was noted at any injection site.

Gatekeeper Reflux Repair System

The available evidence for this device consists of one randomized, controlled trial by Fockens et al (2010). An industry-funded sham-controlled single-blind multicenter study randomized 118 patients into Gatekeeper (n=75) or sham (n=43) treatment. An additional 25 patients were treated as lead-ins during the initial training of investigators and included only in the safety analysis. The patients were implanted initially with four Gatekeeper prostheses. At three months, 44% of implanted patients received retreatment with up to four additional prostheses due to unsatisfactory symptom control. The primary safety end point was reduction in serious device- and procedure-related adverse device effects compared with a surgical procedure composite complication rate of 15%. Four serious adverse events were reported (two perforations, one pulmonary infiltrate related to a perforation, and one severe chest pain). The primary efficacy end point was reduction in heartburn symptoms using the GERD-HRQL (health-related quality of life) questionnaire. Planned interim analysis after 143 patients were enrolled found that heartburn symptoms and esophageal acid exposure had improved significantly in both the Gatekeeper and sham groups at six months, but there was no significant difference between the two groups. The study was terminated early due to a lack of efficacy.

Polymethylmethacrylate Beads

The available evidence for this device consists of one case series. A 2001 publication on transesophageal submucosal implantation of polymethylmethacrylate beads consisted of a case series of ten patients with GERD who were either refractory to or dependent on PPIs. While a significant decrease in symptom scores was noted at posttreatment follow-up (time not specified), the small number of patients and lack of long-term follow-up preclude scientific analysis. No additional studies have been identified evaluating this treatment option.

Section Summary: Injection/Implantation of Prosthetics or Bulking Agents

The evidence on injection of bulking agents includes 1 RCT that was terminated early due to lack of efficacy and case series. High-quality data from large RCTs are needed to compare bulking procedures with both sham controls and with the currently accepted treatments for GERD (i.e., drug therapy, laparoscopic fundoplication). Well-designed trials should use

standardized outcome measures to examine both subjective (e.g. GERD–Health-Related Quality of Life scores) and objective (e.g., esophageal acid exposure) effects on health outcomes.

Summary

For individuals who have GERD and hiatal hernia of 2 cm or less that is not controlled by PPIs who receive TIF (e.g., EsophyX), the evidence includes 2 RCTs comparing TIF with PPI therapy, nonrandomized studies comparing TIF with fundoplication, and case series with longer term follow-up. Relevant outcomes are symptoms, change in disease status, quality of life, medication use, and treatment-related morbidity. The highest quality RCT (RESPECT) was a sham-controlled together with PPI therapy while the other RCT (TEMPO) compared TIF with maximum PPI therapy. Both trials found a significant benefit of TIF on the primary outcome measure in about 65% of patients, but the sham-controlled trial found improvement in 45% of the sham-controlled group and no benefit on secondary subjective outcome measures. The nonblinded RCT found significant improvements in subjective measures but no difference in objective outcome measures when compared with PPI therapy. Together, these trials suggest a strong placebo effect of the surgery and a modest benefit of TIF in patients whose symptoms are not controlled by PPIs. For these patients, the most appropriate comparator is laparoscopic fundoplication. Studies comparing TIF with fundoplication have limitations that include earlier TIF procedures and unequal groups at baseline and are inadequate to determine relative efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have GERD and hiatal hernia of 2 cm or less that is controlled by PPIs who receive TIF (eg, EsophyX), the evidence includes 2 RCTs and observational studies with longer term follow-up. Relevant outcomes are symptoms, change in disease status, quality of life, medication use, and treatment-related morbidity. A sham-controlled trial found that the time to resume PPI therapy was longer following TIF and the remission rate was higher, indicating that TIF is more effective than no therapy. The nonblinded RCT found a benefit of TIF compared with continued PPI therapy for subjective measures, but not for the objective measures of pH normalization and esophagitis. These results raise questions about a possible placebo effect for the procedure. Also, observational studies have indicated a loss of treatment effectiveness over time. Adverse events associated with the procedure (eg, perforation) may be severe. At present, the available evidence does not support the use of this intervention in patients whose symptoms are adequately controlled by medical therapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have GERD who receive endoscopic radiofrequency energy (e.g. Stretta) the evidence includes four small RCTs, a non-randomized comparative study and observational studies with longer-term follow-up. Relevant outcomes include symptoms, change in disease status, functional outcomes, quality of life, hospitalizations, medication use, resource utilization, treatment-related mortality, and treatment-related morbidity. The RCTs report some improvements in symptoms and quality of life following treatment with RF energy compared with sham controls, however, objective measures of GERD and a meta-analysis of these studies found no significant improvements in outcomes, raising questions about the mechanism of the symptom relief. Symptom relief is reported to be lower than after fundoplication, and reoperations greater. Larger RCTs with longer follow-up, preferably compared with

fundoplication, are needed to better define the risks and benefits of this procedure. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have GERD who receive esophageal bulking agents, the evidence includes 1 RCT and case series. Relevant outcomes include symptoms, change in disease status, quality of life, medication use, and treatment-related morbidity. The RCT for 1 product was terminated early due to lack of efficacy, while other products have only case series to support use. High-quality data from large randomized controlled trials are needed to compare bulking procedures with both sham controls and with the currently accepted treatments for GERD, i.e., drug therapy and laparoscopic fundoplication. Well-designed trials should use standardized outcome measures to examine whether subjective improvement, such as discontinuation of medication therapy and GERD–Health-Related Quality of Life scores, is supported by objective improvement, such as esophageal acid exposure. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

American Society for Gastrointestinal Endoscopy

In 2015, the American Society for Gastrointestinal Endoscopy (ASGE) published guidelines on endoscopic procedures for GERD. In their review of the EsophyX and Stretta procedures, the Society noted some positive findings but discrepancies between subjective and objective outcome measures or a lack of objective outcome measures in reported trials, concluding that these techniques represent "potentially new therapeutic indications for GI endoscopy", but that prospective trials using objective measures of GERD as the primary end point could be useful in defining the clinical role of these procedures.

American College of Gastroenterology

Updated guidelines released by the American College of Gastroenterology in 2013 state that the usage of current endoscopic therapy or transoral incisionless fundoplication cannot be recommended as an alternative to medical or traditional surgical therapy. (Conditional recommendation, moderate level of evidence). The guideline also cites limited data on small numbers of subjects and short duration of follow-up.

Society of American Gastrointestinal and Endoscopic Surgeons

In 2017, the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) updated its evidence-based guidelines on endoluminal treatments for GERD. SAGES gave a strong recommendation based on moderate quality evidence that TIF with EsophyX can be performed with an acceptable safety risk in selected patients. SAGES concluded that EsophyX results in better control of GERD symptoms than proton pump inhibitor (PPI) treatment in the short term (6 months), and leads to similar improvement in objective GERD measures compared with PPIs. TIF appears to lose effectiveness during longer term follow-up and is associated with moderate patient satisfaction scores. SAGES found no comparative, controlled trials between TIF and surgical fundoplication, but preliminary evidence suggested that the surgical fundoplication can be used safely after TIF failure.

SAGES gave a strong recommendation based on moderate quality evidence that Stretta is safe for adults and significantly improves health-related quality of life score, heartburn scores, the

incidence of esophagitis, and esophageal acid exposure in patients with GERD. Stretta was found more effective than PPI, but less so than fundoplication.

American Society of General Surgeons
The American Society of General Surgeons (ASGS) issued a position statement on transoral fundoplication in 2011 stating that "the ASGS supports the use of transoral fundoplication by trained General Surgeons for the treatment of symptomatic chronic gastroesophageal reflux disease (GERD) in patients who fail to achieve satisfactory response to a standard dose of Proton Pump Inhibitor (PPI) therapy or for those who wish to avoid the need for a lifetime of medication dependence."

American Gastroenterological Association
In 2016, the American Gastroenterological Association issued a technology coverage statement on minimally invasive surgical options for GERD. Based on a literature review of 4 randomized controlled trials, a multicenter registry, and case series with longer term follow-up, the Association stated:

> "…the 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 </= 2cm, esophagitis LA grade A or B, Barrett's esophagus </= 2cm, 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." Of note, the 2008 Medical Position Statement has not been updated and currently makes no recommendation for or against transoral fundoplication procedures.

National Institute for Health and Care Excellence
The National Institute for Health and Care Excellence (NICE) of the National Health Service of Great Britain issued updated interventional procedure guidance in 2013 on endoscopic radiofrequency treatment for GERD, concluding: "The evidence on the safety of endoscopic radiofrequency ablation for gastro-oesophageal reflux disease is adequate in the short and medium term but there is uncertainty about longer-term outcomes. With regard to efficacy, there is evidence of symptomatic relief but objective evidence on reduction of reflux is inconclusive. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research." The reviewing committee noted "concern on the part of some specialists about the possibility that symptoms may improve as a result of denervation caused by the procedure; if that were the case then failure to recognize and treat reflux might lead to complications in the long term."

NICE issued guidance in 2011 on endoluminal gastroplication for GERD, concluding that "The evidence on endoluminal gastroplication for gastro-oesophageal reflux disease raises no major safety concerns. Evidence from a number of randomized controlled trials (RCTs) shows a degree of efficacy in terms of reduced medication requirement in the short term, but changes in other efficacy outcomes are inconsistent and there is no good evidence of sustained improvement in

oesophageal pH measurements. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research."

In 2017, NICE updated its guidance on bulking agents for GERD found that "Current evidence on the safety and efficacy of endoscopic injection of bulking agents for gastro-esophageal reflux disease does not appear adequate for this procedure to be used without special arrangements…." In 2016, NICE removed guidance on endoscopic bulking agents/hydrogel implants from guidelines on treatment for "dyspepsia and gastro-esophageal reflux" because the product had been withdrawn by the manufacturer.

U.S. Preventive Services Task Force Recommendations
Not applicable

Key Words:

Stretta procedure, gastroplication, Endo Cinch, treatment for gastroesophageal reflux disease, endoscopic gastroplication or gastroplasty, endoscopic gastroplasty, radiofrequency of the lower esophageal sphincter (LES), Enteryx™, PMMA, Plicator™, EsophyX™ System with SerosaFuse™, EndoGastric StomaphyX™, Durasphere®, Gatekeeper Reflux Repair System, NDO plicator™, Transoral Incisionless Fundoplication, TIF, GERD, polymethylmethacrylate beads, bulking agent, hydrogel, sphere, polymer, transesophageal radiofrequency

Approved by Governing Bodies:

***Of Note: Two endoscopic suturing devices and a biocompatible polymer are no longer available in the United States.

- EndoCinch was discontinued by the manufacturer, Bard
- NDO Plicator was listed as terminated in October 2013
- Enteryx® was recalled by Boston Scientific Corporation

In 2007, EsophyX® (EndoGastric Solutions, Redmond, WA) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for full-thickness plication. In 2016, EsophyX® Z Device with SerosaFuse Fasteners was cleared for marketing by FDA through the 510(k) process for use in transoral tissue approximation, full thickness plication, ligation in the gastrointestinal tract, narrowing the gastroesophageal junction, and reduction of hiatal hernia of 2cm or less in patients with symptomatic chronic gastroesophageal reflux disease (GERD). In June 2017, EsophyX2 HD and the third-generation EsophyX Z Devices with SerosaFuse fasteners and accessories were cleared for marketing by FDA through the 510(k) process (K171307) for expanded indications, including patients who require and respond to pharmacologic therapy and in patients with hiatal hernias larger than 2 cm when a laparoscopic hiatal hernia repair reduces a hernia to 2 cm or less.

The Medigus SRS Endoscopic Stapling System (MUSE, Medigus Ltd) was cleared for marketing by FDA through the 510(k) process in 2012 (K120299) and 2014 (K132151). MUSE is intended for endoscopic placement of surgical staples in the soft tissue of the esophagus and

stomach to create anterior partial fundoplication for treatment of symptomatic chronic GERD in patients who require and respond to pharmacologic therapy.

In 2000, the CSM Stretta® System received 510(k) marketing clearance from FDA for general use in the electrosurgical coagulation of tissue and is specifically intended for use in the treatment of GERD. Stretta® is currently manufactured by Mederi Therapeutics, Greenwich, CT.

Durasphere® is a bulking agent approved for treatment of urinary and fecal incontinence (see MP# 455: *Injectable Bulking Agents for the Treatment of Urinary and Fecal Incontinence*). Use of this product for esophageal reflux would be considered off-label use. The website of Carbon Medical Technologies states that Durasphere GR "intended to treat problems associated with GERD" but is considered an investigational device in the United States.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Current Coding:

The following CPT codes are not specific to these procedures.

For transoral incisionless fundoplication **(TIF)**:

43210 ; with esophagogastric fundoplasty, partial or complete, includes duodenoscopy when performed. **(Effective 01/01/16)**

For radiofrequency procedure **(Stretta Procedure)**:

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

For Endoscopic submucosal injection of a bulking agent:

43201 Esophagoscopy, flexible, transoral; with directed submucosal injection(s), any substance

43236 Esophagogastroduodenoscopy, flexible, transoral; with directed submucosal injections(s), any substance

For endoscopic implantation of a prosthesis:

43212 Esophagoscopy, flexible, transoral; with placement of endoscopic stent (includes pre- and post-dilation and guide wire passage, when performed) **(Effective 01/01/2014)**

43266 Esophagogastroduodenoscopy, flexible, transoral; with placement of endoscopic stent (includes pre- and post-dilation and guide wire passage, when performed) **(Effective 01/01/2014)**

43499 unlisted procedure of esophagus.

For endoscopic suturing and Plicator Procedures:

Of note, the EndoCinch Suturing System and NDO Plicator are no longer available in the U.S.A.

43999 unlisted procedure, stomach

Previous Coding:

Prior to 12/31/15, there was **no** specific CPT code for **transoral incisionless fundoplication**. If it is performed endoscopically, it should be reported with CPT code **43499**.

43219 Esophagoscopy, rigid or flexible; with insertion of plastic tube or stent **(Deleted effective 01/01/2014)**

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