Medical Policy

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Title: Transesophageal Endoscopic Therapies for Gastroesophageal Reflux Disease

Professional
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Populations	Interventions	Comparators	Outcomes
Individuals: • With gastroesophageal reflux disease and hiatal hernia ≤2 cm that is not controlled by proton pump inhibitors	Interventions of interest are: • Transoral incisionless fundoplication (eg, EsophyX)	Comparators of interest are: • Laparoscopic fundoplication	Relevant outcomes include: • Symptoms • Change in disease status • Quality of life • Medication use • Treatment-related morbidity
Individuals: • With gastroesophageal reflux disease and hiatal hernia ≤2 cm that is controlled by proton pump inhibitors	Interventions of interest are: • Transoral incisionless fundoplication (eg, EsophyX)	Comparators of interest are: • Proton pump inhibitor therapy	Relevant outcomes include: • Symptoms • Change in disease status • Quality of life • Medication use • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: • With gastroesophageal reflux disease	Interventions of interest are: • Endoscopic radiofrequency energy (eg, Stretta)	Comparators of interest are: • Proton pump inhibitor therapy • Laparoscopic fundoplication	Relevant outcomes include: • Symptoms • Change in disease status • Quality of life • Medication use • Treatment-related morbidity
Individuals: • With gastroesophageal reflux disease	Interventions of interest are: • Esophageal bulking agents	Comparators of interest are: • Proton pump inhibitor therapy • Laparoscopic fundoplication	Relevant outcomes include: • Symptoms • Change in disease status • Quality of life • Medication use • Treatment-related morbidity

DESCRIPTION

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.

Objective

The objective of this evidence review is to determine whether transoral incisionless fundoplication using the EsophyX System, application of radiofrequency energy, or injection or implantation of prosthetic devices or bulking agents is an effective treatment for gastroesophageal reflux disease.

Background

GASTROESOPHAEAL REFLUX DISEASE

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.[1]

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 or incompetence of the diaphragm. Another mechanism is abnormally slow clearance of stomach acid. 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.[1] Proton pump inhibitors (PPIs) have been shown to be the most effective medical treatment. In a Cochrane systematic review, van Pinxteren et al (2010) reported that proton pump inhibitors demonstrated superiority to H_2-receptor agonists and prokinetics in both network meta-analyses and direct comparisons.[2]

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 lower esophageal sphincter (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 gastroesophageal reflux disease (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. Three types of procedures have been investigated:

1. Transesophageal endoscopic gastroplasty (gastroplication, transoral incisionless fundoplication) can be performed as an outpatient procedure. During this 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, RF energy is applied through 4 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) 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. U.S. Food and Drug Administration product code: DQX

Endoscopic submucosal implantation of polymethylmethacrylate beads into the lower esophageal folds has also been investigated.

The Agency for Healthcare Research and Quality published a systematic review of management strategies for GERD in 2005, which was updated by Ip et al (2011).[3,4,] The 2005 comparative effectiveness review evaluated studies on the EndoCinch Suturing System, Stretta, Enteryx, and the NDO Plicator.[3,] The 2011 update 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.[4,] The 2011 report concluded that, for the 3 available endoscopic procedures (EndoCinch, Stretta, EsophyX), effectiveness remained substantially uncertain for the long-term management of GERD. All procedures have been associated with complications, including dysphagia, infection/fever, and bloating, although bloating and dsyphagia are also adverse events of laparoscopic fundoplication.[5,] A review of endoscopic treatment of GERD by Hummel and Richards (2015) noted that EndoCinch is no longer manufactured.[6,]

Regulatory Status

In 2007, EsophyX® (EndoGastric Solutions) was cleared for marketing by 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 (K160960) for use in transoral tissue approximation, full-thickness plication, ligation in the gastrointestinal tract, narrowing the gastroesophageal junction, and reduction of hiatal hernias of 2 cm or less in patients with symptomatic chronic GERD.[7,] 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 patients with hiatal hernias larger than 2 cm when a laparoscopic hiatal hernia repair reduces a hernia to 2 cm or less.[8,] FDA product code: ODE.

The Medigus SRS Endoscopic Stapling System (MUSE, Medigus) 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. FDA product code: ODE.

In 2000, the CSM Stretta® System was cleared for marketing by FDA through the 510(k) process for general use in the electrosurgical coagulation of tissue and was specifically intended for use in the treatment of GERD. Stretta® is currently manufactured by Mederi Therapeutics. FDA product code: GEI.

Durasphere is a bulking agent approved for 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 the Durasphere® GR product is intended to treat problems associated with GERD but is considered an investigational device in the United States.

POLICY

1. Transoral incisionless fundoplication (TIF) (ie, Esophyx) is considered **experimental / investigational** as a treatment of gastroesophageal reflux disease.

2. Transesophageal radiofrequency to create submucosal thermal lesions of the gastroesophageal junction (ie, Stretta procedure) is considered **experimental / investigational** as a treatment of gastroesophageal reflux disease.

3. Endoscopic submucosal implantation of a prosthesis or injection of a bulking agent (eg, polymethylmethacrylate beads, zirconium oxide spheres) is considered **experimental / investigational** as a treatment of gastroesophageal reflux disease.

RATIONALE

This evidence review has been updated with searches of the MEDLINE database. The most recent literature update was performed through September 25, 2018.

This evidence review was informed, in part, by a TEC Assessment (2003) of transesophageal endoscopic treatments for gastroesophageal reflux disease (GERD) and an Evidence Street Assessment (2016) on transoral incisionless fundoplication (TIF).[9,] This review addresses procedures currently available for use in the United States.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function¾including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Transoral Incisionless Fundoplication for symptoms uncontrolled by proton pump inhibitors

Clinical Context and Test Purpose
The purpose of TIF (eg, EsophyX) is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with GERD and hiatal hernias of 2 cm or less not controlled by proton pump inhibitors (PPIs).

The question addressed in this evidence review is: Does TIF using the EsophyX System improve the net health outcomes in individuals with GERD?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with GERD and a hiatal hernia of 2 cm or less uncontrolled by PPIs.

Interventions
The therapy being considered is TIF (eg, EsophyX).

Comparators
The following practice is currently being used to treat GERD: laparoscopic fundoplication.

Outcomes
The general outcomes of interest are symptoms, change in disease status, quality of life, mediation use, and treatment-related morbidity.

Timing
Follow-up at 3 years is of interest to monitor outcomes.

Setting
Patients with GERD and a hiatal hernia of 2 cm or less uncontrolled by PPIs are actively managed by gastroenterologists and primary care providers in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews
McCarty et al (2018) published a systematic review of RCTs and nonrandomized studies that showed significant improvement in a number of clinical outcomes for patients treated with TIF.[10,] For example, 89% of TIF patients discontinued PPI therapy after the procedure, and the Gastroesophageal Reflux Disease Health-Related Quality of Life (GERD-HRQL) questionnaire, Gastroesophageal Reflux Symptom Score, and Reflux Symptom Index (RSI) measures showed significant improvement. The review had several limitations, including the risk of heterogeneity bias, due to the inclusion of studies of first- and second-generation TIF devices and protocols.

Richter et al (2018) published a network meta-analysis of RCTs comparing TIF or laparoscopic Nissen fundoplication(LNF) with sham or PPIs.[11,] The meta-analysis was limited by low-quality studies (one did not report randomization method, others lacked data on allocation concealment, blinding of outcome assessors, or other aspects of study protocol). It should be noted that a reason behind for scarcity of direct comparisons between TIF and LNF is the discrepancy in populations requiring the respective treatments: consequently, TIF studies included patients with mild esophagitis and small hiatal hernias (<2 cm), while LNF studies included patients with Los Angeles grade A, B, C, or D esophagitis and all sizes of hiatal hernias.

Tables 1 and 2 summarize the characteristics and results of selected systematic reviews.

Table 1. Characteristics of Systematic Reviews

Study	Dates	Trials	Participants	N (Range)	Design	Duration
McCarty et al (2018)[10,]	2008-2016	32	Patients met standard criteria for the TIF procedure[a]	1475 (10-124)	5 RCTs, 21 prospective and 6 retrospective studies	NR
Richter et al (2018)[11,]	NR	7	Patients had GERD, established by endoscopic results indicating erosive esophagitis and/or abnormal ambulatory esophageal pH monitoring[b]		2 RCTs (TIF vs PPI); 2 RCTs (TIF vs sham); 3 RCTs (LNF vs PPIs)	• TIF: 6-12 mo • LNF vs PPI: 1-5 y

GERD: gastroesophageal reflux disease; LNF: laparoscopic Nissen fundoplication; NR: not reported; PPI: proton pump inhibitor; RCT: randomized controlled trial; TIF: transoral incisionless fundoplication.
[a] Body mass index <35 kg/m^2; hiatal hernia size ≤2 cm; grade A, B, or C esophagitis using the Los Angeles classification; no underlying esophageal motility disorder.
[b] DeMeester score >14.7 and/or percentage total time at a pH <4 of ≥4.0%.

Table 2. Results of Systematic Reviews

Study	Complete PPI Cessation	GERD-HRQL Score	GERSS	RSI Score	Other Objective Measures
					Esophageal Acid Exposure (% time with pH <4)
McCarty et al (2018)[10,]					
N	1407 (28 studies)	1236 (25 studies)	NR (6 studies)	NR (8 studies)	722 (15 studies)
% (95% CI)	89 (82 to 95)				
MD (95% CI)		17.72 (17.31 to 18.14)	23.78 (22.96 to 24.60)	14.28 (13.56 to 15.01)	3.43 (2.98 to 3.88)
p	<0.001	<0.001	<0.001	<0.001	<0.001
I^2 (p)	93.6 (0.00)	94 (<0.001)	98 (<0.001)	95 (<0.001)	86 (<0.001)
Mean follow-up (SD), mo	15.5 (14.6)				
		TIF-2 Subgroup			TIF-2 Subgroup
N		997 (15 studies)			
MD (95% CI)		17.62 (17.19 to 18.05)			53.18 (49.49 to 56.87)
p		<0.001			<0.001
Richter et al (2018)[11,]					
N		•TIF=293 (4 studies) •LNF=875 (3 studies)			
OR (95% CrI)		TIF vs LNF: 2.08 (0.71 to 6.09)			LNF vs TIF: 0.08 (0.02 to 0.36)
Ranking probability (SUCRA)		•TIF=0.96 •LNF=0.66 •Sham=0.35 •PPI=0.042			• LNF=0.99 • PPI=0.64 • TIF=0.32 • Sham=0.05

CI: confidence interval; CrI: credible interval; GERD-HRQL: Gastroesophageal Reflux Disease Health-Related Quality of Life questionnaire; GERSS: Gastroesophageal Reflux Symptom Score; LNF: laparoscopic Nissen fundoplication; MD: mean difference; NR: not reported; OR: odds ratio; PPI: proton pump inhibitor; RSI: Reflux Symptom Index; TIF: transoral incisionless fundoplication.

Randomized Controlled Trials

Two RCTs have evaluated TIF using ExophyX2 in patients with troublesome symptoms despite daily PPI therapy (see Table 3). Hunter et al (2015) compared treatment using TIF plus placebo pills (n=87) with treatment using sham TIF plus PPIs (n=42) in the RESPECT trial.[12,] 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.[13,] The primary outcome in both trials was the elimination of symptoms, measured in slightly different ways (see Table 3).

In both trials, the primary outcome was achieved by a higher percentage of patients treated with TIF than with PPIs (see Table 4). 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 (p=0.023). 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 for the RESPECT trial showed no significant differences between treatments, except for Reflux Disease Questionnaire scores, which showed significant improvement in the TIF group compared with baseline. Physiologic measurements such as the number of reflux episodes, percentage of total time pH less than 4, and DeMeester score (a composite score of acid exposure based on esophageal monitoring) showed statistically significant differences 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 3. Characteristics of Randomized Controlled Trials Comparing TIF with Medical Management in Patients Whose Symptoms Were Not Controlled on PPIs

Study; Trial	TIF/CTL, n	Patient Symptoms or Other Characteristics	Comparator	FU, mo	Principal Clinical Outcome
Hunter et al(2015)[12,]; RESPECT	87/42	• Hiatal hernia ≤2 cm • Troublesome regurgitation[a] not controlled on PPI	Sham + PPI	6	Relief of regurgitation without PPI in TIF group vs PPI escalation in control group
Trad et al (2015)[13,]; TEMPO	40/23	• Hiatal hernia ≤2 cm • 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 4. Results for RCTs Comparing TIF with Medical Management in Patients Whose Symptoms Were Not Controlled on PPIs

Trial	Symptoms[a]	Regurgitation	Heartburn	Reflux	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)[12,]					
TIF + placebo, % (n/N)	67% (58/87)	-3	-2.1	-2.5	
Sham + PPI, % (n/N)	45% (19/42)	-3	-2.2	-2.4	
p	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)[13,]					
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	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 a composite of 3 GERD symptom scales: the GERD-HRQL, RSI, and RDQ.

Trad et al (2017) reported 3-year follow-up for patients treated with TIF in the TEMPO trial (see Table 5).[14,] 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 77% of patients. pH normalization was available for 40% of available patients following TIF, whereas 90% reported elimination of troublesome regurgitation.

Trad et al (2018) also reported 5-year follow-up for the TEMPO trial (see Table 5).[15,] Data were available for 44 patients, of whom 37 (86%) showed elimination of troublesome regurgitation at 5 years. Twenty (43%) patients were completely off PPIs at the 5-year follow-up, and 31 (70%) patients expressed satisfaction with the procedure, as assessed by the GERD-HRQL scores. While data on pH normalization were available for 24 patients at the 3-year follow-up, at 5 years, 22% (n=5) of these patients could not be assessed for pH normalization.

Table 5. Follow-Up of Patients Treated with EsophyX2 in the TEMPO Trial

Outcome Measure	Baseline	1 Year	2 Years	3 Years	5 Years
Sample size (% of 63)		60 (95%)	55 (87%)	52 (83%)	44 (98%)
Elimination of troublesome regurgitation (RDQ)[a]		88% (42/48)	90% (41/44)	90% (37/41)	86% (37/43)
Elimination of atypical symptoms (RSI ≤13)[a]		82% (45/55)	84% (43/51)	88% (42/48)	80% (31/39)
GERD-HRQL score	32.8 (/60)	7.1 (/58)	7.3 (/52)	5.0 (/43)	6.8 (/31)
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)	46% (20/44)
pH normalization[b]		41% (24/59)	37% (18/49)	40% (16/40)	

Adapted from Trad et al (2017) and Trad et al (2018).[14,15,]
Values are % (n/N) unless otherwise noted.
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 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 <4 of ≥5.3%.

The purpose of the gaps tables (see Tables 6 and 7) is to display notable gaps identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 6. Relevance Gaps

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Hunter et al (2015)[12,]			2. Not compared to fundoplication 3. Measurement off PPIs group		
Trad et al (2015)[13,]			2. Not compared to fundoplication 3. No sham surgery		
Hakansson et al (2015)[16,]			2. Sham only (no active treatment)		
Witteman et al (2015)[17,]			3. Continued PPI only (no sham surgery)		

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
FU: follow-up; PPI: proton pump inhibitor; RCT: randomized controlled trial.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms

Table 7. Study Design and Conduct Gaps

Study	Allocation[a]	Blinding[b]	Selective Reporting[d]	Data Completeness[e]	Power[d]	Statistical[f]
Hunter et al (2015)[12]						
Trad et al(2015)[13,]		1, 2. No blinding				1. Within-group analysis only
Hakansson et al(2015)[16,]				1. Unequal dropout rates in both treatment groups	1. Power calculations not reported	2. Adjusted for baseline values but not for repeated measures
Witteman et al(2015)[17,]		1, 2. No blinding		1. Study stopped following unplanned interim analysis	1. Power calculations not reported	

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Nonrandomized Studies

Two nonrandomized comparative studies have compared TIF with laparoscopic fundoplication in patients whose symptoms were not controlled on PPIs.[18,19,]

A nonrandomized study by Toomey et al (2014) compared 20 patients undergoing TIF, 20 patients undergoing Nissen fundoplication, and 20 patients undergoing Toupet fundoplication.[18,] 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, and only patients who had a hiatal hernia of 2 cm or less were offered TIF. As a result, only 15% of the TIF group had a hiatal hernia vs 65% and 55% of the 2 fundoplication groups, limiting comparison of both treatments. Adverse events were not reported.

Frazzoni et al (2011) compared 10 patients undergoing TIF with 10 patients undergoing laparoscopic fundoplication with the first-generation EsophyX procedure.[19,] The patients selected which treatment they wanted, but the groups were comparable to a baseline. Regarding clinical outcomes assessed at 3 months, 7 patients undergoing TIF reported only partial/no symptom remission vs 0 patients undergoing fundoplication. 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 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.

Tables 8 and 9 summarize the characteristics and results of selected nonrandomized studies.

Table 8. Nonrandomized Study Characteristics

Study	Study Type	Country	Dates	Participants	Treatment	Treatment	Follow-Up
Toomey et al (2014)[18,]	Case control	U.S.	2010-2013	Patients with GERD undergoing TIF, LNF, or LTF	20 patients underwent TIF	20 patients each had LTF or LNF	NR
Frazzoni et al (2011)[19,]	Prospective open-label	Italy	2000-2008	Patients had heartburn and/or regurgitation despite high-dose PPIs	10 patients chose first-generation EsophyX fundoplication	10 patients chose laparoscopic fundoplication	3 mo

GERD: gastroesophageal reflux disease; LNF: laparoscopic Nissen fundoplication; LTF: laparoscopic Toupet fundoplication; NR: not reported; PPI: proton pump inhibitor; TIF: transoral incisionless fundoplication.

Table 9. Nonrandomized Study Results in Patients Whose Symptoms Were Not Controlled by PPIs

Study	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)[19],						
TIF, %	70	50	20	40	10	0
Fundoplication, %	0	100	90	100	20	20
p	0.003	0.03	0.005	0.011	NR	NR

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

Section Summary: Transoral Incisionless Fundoplication for Symptoms Uncontrolled by Proton Pump Inhibitors

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 for 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 the 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 did not differ between the TIF and sham-PPI groups. 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 significant improvements in subjective measures with TIF compared with 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 would suggest the most appropriate comparator for patients whose symptoms are not controlled on PPIs is laparoscopic fundoplication. However, 5-year follow-up of the TEMPO trial found sustained cessation of PPI therapy in most patients with data available, as well as the resolution of several types of trouble symptoms. These results may suggest long-term safety and durability of TIF 2.0 as an alternative to LNF.

Studies Comparing TIF with Laparoscopic Fundoplication

Each study comparing TIF with laparoscopic fundoplication has methodologic problems that do not permit conclusions on the comparative efficacy of the 2 procedures. The Frazzoni nonrandomized study showed that TIF is less effective than fundoplication. However, this study was conducted with an earlier device. In the Toomey study, 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 a lack of statistically significant differences across symptom outcomes. However, because of the small sizes of these samples, the 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 (eg, 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 for SYMPTOMS CONTROLLED BY PPIS

Clinical Context and Test Purpose
The purpose of TIF (eg, EsophyX) is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with GERD and hiatal hernias of 2 cm or less controlled by PPIs.

The question addressed in this evidence review is: Does TIF using the EsophyX System improve the net health outcomes in individuals with GERD?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with GERD and hiatal hernias of 2 cm or less controlled by PPIs.

Interventions
The therapy being considered is TIF (eg, EsophyX).

Comparators
The following therapy is currently being used to treat GERD: PPI therapy.

Outcomes
The general outcomes of interest are symptoms, change in disease status, quality of life, medication use, and treatment-related morbidity.

Timing
Follow-up at 2, 3, and 6 years is of interest to monitor outcomes.

Setting
Patients with GERD and hiatal hernias of 2 cm or less controlled by PPIs are actively managed by gastroenterologists and primary care providers in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected using the principles outlined in indication 1.

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 10). Hakansson et al (2015) compared TIF (n=22) with sham only

(n=22).[16,] The expected outcome in the sham group was that, without PPIs, GERD symptoms would eventually recur. Witteman et al (2015) compared TIF (n=40) with continued PPI therapy (n=20) without a sham procedure (see Table 10).[17,] 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 to resume PPIs. The primary outcome of the Witteman trial was treatment success, defined by an improvement of 50% or more on the GERD-HQRL score.

In Hakansson et al (2015), 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 (2015), PPI therapy was stepped up or down as necessary during follow-up. At 6 months, 55% of TIF patients had more than a 50% improvement in subjective GERD symptoms vs 5% of patients on continued PPI therapy (see Table 11). 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 the Hakansson trial 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 were reported in twice as many patients undergoing TIF (4, 4, and 2, respectively) compared with sham (2, 2, and 1, 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 10. Characteristics of Randomized Trials Assessing TIF in Patients Whose Symptoms Were Controlled by PPIs

Study	TIF/CTL, n	Patient Symptoms or Other Characteristics	Comparator	FU, mo	Principal Clinical Outcome
Hakansson et al(2015)[16,]	22/22	Controlled on PPI, run-in to confirm PPI dependence	Sham only	³6	Time to resumption of PPI, percent needing PPI at 6 mo
Witteman et al(2015)[17,]	40/20	Controlled on PPI; those who received TIF had GERD with hiatal hernias ≤2 cm	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 11. Results of RCTs Comparing TIF with Nonsurgical Treatment in Patients Whose Symptoms Were Controlled on PPIs

Study	Days to PPI Resumption	Change in PPI Therapy	Change in Symptoms	Change in QOL	Change in Esophagitis	Esophageal pH
		Remission at 6 Months	Median GSRS Score	Median QOLRAD Score		Percent Time pH <4
Hakansson et al (2015)[16,]						
TIF	197	13 (59%)	4	1.5		3.6%
Sham only	107	4 (18%)	1.4	0.4		9.8%
p	0.001	0.01	NR	NR		NR
			Percent >50% Improvement in GERD-HRQL Score	Mean GERD-HRQL Score	Percentage With Esophagitis	Percent Patients With Normalized pH[a]
Witteman et al (2015)[17,]						
TIF			55%	-14.1	-19%	50%
Continued PPI			5%	-3.1	-20%	63%
p			<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% of recording time.

In the trial by Witteman et al (2015), 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 lower esophageal sphincter resting pressure, 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. Sixty patients eventually underwent TIF. 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%. 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 a hiatal hernia. Although this RCT met its principal end point at 6 months and improvements in GERD symptoms appeared to be maintained for 12 months, long-term reflux control was not achieved, and the trialists 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 dual-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 were included if they provided additional information on treatment durability or addressed treatment safety.

A case series and a cohort study have evaluated outcomes to 6 years after TIF 2 (see Tables 12 and 13). Both 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. Stefanidis et al (2017) reported on a retrospective series that about 75% of patients had the elimination of esophagitis and had discontinued PPI use at 5 years, while 62% of the 13 patients with hiatal hernias had a reduction in hernia size at follow-up.[20,]

In a prospective cohort by Testoni et al (2015), 72% of the patients were completely responsive to PPIs at baseline, and24% were partially responsive.[21,] 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, the presence of esophagitis at baseline, and use of fewer fasteners. About half the patients with a complete response initially resumed PPI use, although this finding is limited by the low number of patients followed to six years. The number of fasteners used in this study might also be lower than current procedures.

Table 12. Characteristics of Observational Studies with Long-Term Outcomes in Patients Whose Symptoms Were Controlled by PPIs

Study	Country	Participants	Treatment Delivery	Mean FU, mo
Stefanidis et al(2017)[20,]	Greece	PPI-controlled, hiatal hernia ≤2 cm	EsophyX2	59
Testoni et al (2015)[21,]	Prospective study from 1 center in Italy	Daily PPI, esophagitis or abnormal pH, hiatal hernias ≤2 cm	ExophyX2	53

FU: follow-up; PPI: proton pump inhibitor.

Table 13. Long-Term Durability of TIF in Patients Whose Symptoms Were Controlled by PPIs

Outcomes	Mean Baseline	6 Months	1 Year	2 Years	3 Years	6 Years
Stefanidis et al (2017)[20,]						
Sample size	45					44
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%
Testoni et al (2015)[21,]						
Sample size	50	49[a]	49	45[b]	32	14

Outcomes	Mean Baseline	6 Months	1 Year	2 Years	3 Years	6 Years
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%		

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

Huang et al (2017) conducted a systematic review with meta-analysis of TIF for the treatment of GERD.[22,] 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. The 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 for Symptoms 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 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 trial by Witteman et al (2015) 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

Clinical Context and Test Purpose
The purpose of endoscopic radiofrequency energy (eg, Stretta) is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with GERD.

The question addressed in this evidence review is: Does the use of endoscopic radiofrequency energy improve the net health outcomes in individuals with GERD?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with GERD.

Interventions
The therapy being considered is endoscopic radiofrequency energy (eg, Stretta).

Comparators
The following therapies and practices are currently being used to treat GERD: PPI therapy and laparoscopic fundoplication.

Outcomes
The general outcomes of interest are symptoms, change in disease status, quality of life, medication use, and treatment-related morbidity.

Timing
Follow-up at 3, 5, and 6 years is of interest to monitor outcomes.

Setting
Patients with GERD are actively managed by gastroenterologists and primary care providers in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected using the principles outlined in indication 1.

Systematic Reviews
Fass et al (2017) published a meta-analysis of cohort studies and RCTs evaluating the Stretta procedure for patients with GERD.[23,] When RCT and cohort results were pooled, there were clinically significant treatment effects for several of end points; however, the analysis was limited by the lack of control groups in many studies. Also, only 1 end point was shared between the four included RCTs.

A meta-analysis of 4 RCTs (total N=165 patients) was published by Lipka et al (2015) (see Table 14).[24,] Three trials compared Stretta with sham, and one compared Stretta with PPI therapy (see Table 15). 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 improvements 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 or esophageal acid exposure.[25,] Aziz et al (2010) found statistically significant improvements in GERD-HRQL scores in all treatment

groups.[26,] 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.[27,] Pooled results of the meta-analysis showed no significant differences between Stretta and either sham treatment or PPI management for the measured outcomes, including the ability to stop PPI therapy (see Table 16). 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 times.

A meta-analysis by Perry et al (2012) included 20 studies.[28,] This review analyzed 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 was limited by the inclusion of lower quality studies and by its analysis of within-subject differences and not between-subject differences, as reported in the RCTs.

Table 14. Meta-Analytic Characteristics of RCTs Assessing TERF

Study	Dates	Trials	Participants	N (Range)	Design	Duration, mo
Fass et al (2017)[23,]	2002-2012	28	Patients with GERD undergoing endoscopic radiofrequency (Stretta)	2468 (9-558)	Meta-analysis of 4 RCTs, 23 cohort studies, and 1 registry	3-120
Lipka et al(2015)[24,]	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
Perry et al(2012)[28,]	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

GERD: gastroesophageal reflux disease; PPI: proton pump inhibitor; RCT: randomized controlled trial; TERF:transesophageal radiofrequency.

Table 15. Characteristics of RCTs Assessing TERF

Study	TERF/CTL, n	Patient Symptoms or Other Characteristics	Comparator	FU, mo	Principal Clinical Outcome
Arts et al (2012)[27,]	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
Aziz et al (2010)[26,]	12/12	GERD controlled by PPIs; patients randomized to single or double TERF or sham	Sham	12	GERD-HRQL score
Coron et al(2008)[29,]	20/16	GERD symptoms controlled by PPIs and abnormal EAE	Continued PPI	6	Stopping or decreasing PPI use
Corley et al (2003)[25,]	35/29	Abnormal EAE, symptoms at least partially controlled by PPIs, hiatal hernia ≤2 cm	Sham	6	Heartburn, QOL, PPI use, pH

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

Table 16. Meta-Analytic Results

Study	Heartburn	GERD-HRQL Score	SF-36 PCS Score	Acid Exposure Time (pH <4)	Other Objective Outcome Measures
	Heartburn Score				**DeMeester score**
Fass et al (2017)[23,]					
Patients (studies), n	637 (12)	507 (11)		364 (11)	407 (8)
Pooled RR (95% CI)	-0.53 (-1.97 to -1.09)	RCT: -14.56 (-16.63 to-12.48) Cohort: -14.69 (-16.90 to-12.47)		-3.01 (-3.72 to -2.30)	-13.79 (-20.01 to -7.58)
MD (95% CI)		-14.60 (-16.48 to -12.73)			
p	<0.001	<0.001		<0.001	<0.001
I^2 (p)	Significant in all subgroups (p<0.001)	RCTs: *NS* Cohort: 85% (<0.001)		Not significant in any subgroup	77%
	Use of PPI Therapy				**LES Basal Pressure**
Patients (studies), n	1795 (23)				269 (9)
Baseline, n (%)	1743 (97.1)				+1.73 (-0.29 to 3.74)
Posttreatment, n (%)	850 (49)				
Pooled RR (95% CI)	0.49 (0.40 to 0.60)				
p	<0.001				0.09
I^2 (p)	RCTs: *NS* Cohort: 95% (<0.001)				
	Ability to Stop PPI Therapy				**Mean LES Pressure**
Lipka et al (2015)[24,]					
Patients (studies), n	118 (3)	88 (2)		153 (4)	110 (3)
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% (<0.001)		99% (<0.001)	96% (<0.001)
Range of N	24-51	22-64		22-64	
	Heartburn Score				**Johnson-DeMeester Score**
Perry et al (2012)[28,]					
Patients (studies), n	525 (9)	433 (9)	299 (6)	364 (11)	267 (7)

Study	Heartburn	GERD-HRQL Score	SF-36 PCS Score	Acid Exposure Time (pH <4)	Other Objective Outcome Measures
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

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

Randomized Controlled Trials

Although not included in the meta-analyses tabulated in Table 14, Kalapala et al (2017) published interim results from a small RCT of 20 patients randomized to PPI plus Stretta or PPI alone, with 3 months of follow-up.[30,] While short-term outcomes such as GERD symptoms and cessation of PPIs appeared improved for the Stretta group, the study sample was small and power calculations were not conducted.

Controlled Trials Comparing TERF with Laparoscopic Fundoplication

Liang et al (2015) reported on a prospective comparison of laparoscopic Toupet fundoplication with the Stretta procedure (see Table 17).[31,] Of 165 patients treated, 125 (76%) completed the 3-year follow-up (65 fundoplications, 60 Stretta) and were included in the analysis. Although the 2 groups were comparable in symptoms at baseline, 9 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 2 groups achieved complete PPI independence and had similar improvements in belching, hiccup, cough, and asthma. The Stretta procedure was less effective than laparoscopic fundoplication in reducing symptoms of heartburn, regurgitation, and chest pain (see Table 18). Significantly more patients in the Stretta group underwent reoperation, while more patients in the fundoplication group complained of bloating, but this difference was not statistically significant. This study lacked randomization and, along with not reporting the TERF failures, had a high loss to follow-up. Also, while symptom scores were comparable at baseline, the study might have been subject to selection bias related to treatment choice, which affected baseline differences for other variables.

Table 17. Characteristics of Studies Comparing TERF with Laparoscopic Fundoplication

Study	Study Type	Country	Dates	Participants	Treatment 1	Treatment 2	FU, y
Liang et al(2015)[31,]	Comparative cohort	China	2011	165	TERF	Laparoscopic fundoplication	3

FU: follow-up; TERF: transesophageal radiofrequency.

Table 18. Results Comparing TERF with Laparoscopic Fundoplication

Study	PPI Independence	Improvement in Heartburn Score	Improvement in Regurgitation Score	Improvement in Chest Pain Score	Re-operation	Bloating
Liang et al (2015)[31,]						

Study	PPI Independence	Improvement in Heartburn Score	Improvement in Regurgitation Score	Improvement in Chest Pain Score	Re-operation	Bloating
TERF	68.3%	2.53	2.41	2.96	11.8%	0%
LF	72.3%	4.05	4.03	5.50	0%	6.2%
p	0.627	0.01	0.004	0.005	0.006	0.120

LF: laparoscopic fundoplication; 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-ups after TERF were reported in 2014 (see Table 19).[32,33,] Elimination of PPI use was similar for both studies at around 42% (see Table 20). Liang et al (2014) 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 19. Cohort Study and Case Series Characteristics

Study	Country/Institution	Participants	Follow-Up, y	Loss to Follow-Up
Liang et al (2014)[32,]	China	152 who failed PPI therapy	5	9%
Noar et al (2014)[33,]	University of Pittsburgh	149 who failed PPI therapy	10	34% (7% deceased)

PPI: proton pump inhibitor.

Table 20. Cohort Study and Case Series Results at Follow-Up

Study	Elimination of PPI Use	Symptom Improvement	Elimination of Dysplasia	Bloating
Liang et al (2014)[32,]	42.8%	p<0.001 vs pretreatment		8.7%
Noar et al (2014)[33,]	41%	72%	85%	

PPI: proton pump inhibitor.

Section Summary: Transesophageal Radiofrequency (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 define the risks and benefits of this procedure better.

Esophageal Bulking Agents

Clinical Context and Test Purpose

The purpose of esophageal bulking agents is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with GERD.

The question addressed in this evidence review is: Does the use of esophageal bulking agents improve the net health outcomes in individuals with?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with GERD.

Interventions
The therapy being considered is esophageal bulking agents.

Comparators
The following therapies and practices are currently being used to treat GERD: PPI therapy and laparoscopic fundoplication.

Outcomes
The general outcomes of interest are symptoms, change in disease status, quality of life, medication use, and treatment-related morbidity.

Timing
Though not completely standardized, follow-up for GERD symptoms would typically occur in the months to years after starting treatment.

Setting
Patients with GERD are actively managed by gastroenterologists and primary care providers in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected using the principles outlined in indication 1.

Durasphere
The available evidence for Durasphere consists of a single case series. One open-label pilot study by Ganz et al (2009) assessed 10 GERD patients injected Durasphere (Carbon Medical Technologies), a bulking agent approved for treatment of urinary and fecal incontinence, at the gastroesophageal junction.[34,] At 12 months, 7 (70%) patients 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 Gatekeeper Reflux Repair System consists of a single RCT reported by Fockens et al (2010).[35,] In this 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 4 Gatekeeper prostheses. At 3 months, 44% of implanted patients received retreatment with up to 4 additional prostheses due to unsatisfactory symptom control. The primary safety endpoint was a reduction in serious device- and procedure-related adverse events, compared with a surgical procedure composite complication rate of 15%. Four serious adverse events were reported (2 perforations, 1 pulmonary infiltrate related to a perforation, 1 severe chest pain). The primary efficacy end

point was a reduction in heartburn symptoms using the GERD-HRQL 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 6 months, but there was no significant difference between groups. The trial was terminated early due to a lack of efficacy.

Polymethylmethacrylate Beads

The available evidence for polymethylmethacrylate beads consists of a single case series. A case series by Feretis et al (2001) evaluated on transesophageal submucosal implantation of polymethylmethacrylate beads in 10 patients with GERD who were either refractory to or dependent on PPIs.[36,] While a significant decrease in symptom scores was noted at post treatment follow-up (time not specified), the small number of patients and lack of long-term follow-up precluded scientific analysis. No additional studies have been identified evaluating this treatment option.

Section Summary: Esophageal Bulking Agents

The evidence on injection of bulking agents includes an RCT 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 (ie, drug therapy, laparoscopic fundoplication). Well-designed trials should use standardized outcome measures to examine both subjective (eg, GERD-HRQL scores) and objective (eg, esophageal acid exposure) effects on health outcomes.

Summary of Evidence

For individuals who have GERD and a hiatal hernia of 2 cm or less that is not controlled by PPIs who receive TIF (eg, 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 sham-controlled that compared TIF 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. The sham-controlled trial reported 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 compared with PPI therapy. Together, these trial results would suggest a strong placebo effect of the surgery and a modest benefit of TIF in patients whose symptoms were not controlled by PPIs. For these patients, the most appropriate comparator would be laparoscopic fundoplication. Studies comparing TIF with fundoplication have limitations that include earlier TIF procedures and unbalanced 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 a 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 (eg, Stretta), the evidence includes 4 small RCTs, a nonrandomized comparative study, 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. The RCTs reported some improvements in symptoms and quality of life following treatment with radiofrequency 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 define the risks and benefits of this procedure better. 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 an RCT and case series. Relevant outcomes are symptoms, change in disease status, quality of life, medication use, and treatment-related morbidity. The RCT for a single product was terminated early due to lack of efficacy, while other products have only case series to support use. High-quality data from large RCTs are needed to compare bulking procedures with both sham controls and with the currently accepted treatments for GERD (ie, drug therapy, laparoscopic fundoplication). Well-designed trials should use standardized outcome measures to examine whether subjective improvement (eg, discontinuation of medication therapy, GERD-HRQL scores) is supported by objective improvement (eg, esophageal acid exposure). The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical Input From Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2015 Input
In response to requests for clinical input on transesophageal radiofrequency (Stretta) as a treatment of gastroesophageal reflux disease (GERD), input was received from 1 physician specialty society (2 reviewers) and 3 academic medical centers while this policy was under review in 2015. Input was mixed on the treatment of GERD with transesophageal radiofrequency to create submucosal thermal lesions of the gastroesophageal junction (ie, Stretta). Potential conflicts of interest were noted by 2 reviewers.

2011 Input
In response to requests for clinical input on transoral incisionless fundoplication (TIF) using EsophyX, input was received from 2 physician specialty societies and 4 academic medical centers while this policy was under review in 2011. Reviewers agreed that TIF differed sufficiently

different from laparoscopic Nissen fundoplication to warrant evaluation as a separate procedure. Reviewers considered TIF (ie, EsophyX) to be investigational for the treatment of GERD.

Practice Guidelines and Position Statements

American Society for Gastrointestinal Endoscopy

The American Society for Gastrointestinal Endoscopy (2015) published guidelines on endoscopic procedures for GERD.[37,] In its 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 from the American College of Gastroenterology (2013) indicated the use of current endoscopic therapy or transoral incisionless fundoplication (TIF) could not be recommended as an alternative to medical or traditional surgical therapy (conditional recommendation, moderate level of evidence).[1,] The guidelines also cited limited data on small numbers of subjects and short duration of follow-up.

Society of American Gastrointestinal and Endoscopic Surgeons

The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES; 2017) updated its evidence-based guidelines on endoluminal treatments for GERD.[38,] SAGES gave a strong recommendation based on moderate quality evidence that TIF using 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 improvements 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 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; 2011) issued a position statement on transoral fundoplication stating that "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."[39,]

American Gastroenterological Association

The American Gastroenterological Association (2016) issued a technology coverage statement on minimally invasive surgical options for GERD.[40,]{American Gastroenterological Association, 2016

#99} Based on a literature review of 4 randomized controlled trials, a multicenter registry, and case series with longer term follow-up, the Association stated:
"…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 [body mass index] ≤ 35, hiatal hernia ≤ 2 cm, esophagitis LA [Los Angeles classification] 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."

National Institute for Health and Care Excellence
The National Institute for Health and Care Excellence (NICE; 2013) updated its guidance on endoscopic radiofrequency treatment for GERD, concluding: "The evidence on the safety of endoscopic radiofrequency ablation for gastro-esophageal 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…."[41] NICE 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 (2011) issued guidance on endoluminal gastroplication for GERD, concluding that "The evidence on endoluminal gastroplication for gastroesophageal reflux disease raises no major safety concerns. Evidence from a number of RCTs [randomized controlled trials] 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 esophageal pH measurements…."[42,]

NICE (2004) issued 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…."[43,] NICE (2016) 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.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 21.

Table 21. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01118585[a]	Prospective Outcome Evaluation of Transoral Incisionless Fundoplication (TIF) for the Treatment of Gastroesophageal Reflux Disease (GERD): The TIF Registry Study	500	Dec 2017 (ongoing)

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT01682265	Stretta in Reflux Uncontrolled by Intake of Inhibitors of Protons Pump (IPP)-The SIRUP Trial-Multicentric, Randomized, Double Blind, Prospective Study	60	May 2019
NCT02366169[a]	A Worldwide Post-Market Surveillance Registry to Assess the Medigus Ultrasonic Surgical Endostapler (MUSE™) System for the Treatment of GERD	200	Dec 2019
Unpublished			
NCT02211105	Laparoscopic Nissen Fundoplication (LNF) Surgery Versus TransoralIncisionless Fundoplication (TIF): Anti-Reflux Treatment Registry	46	Apr 2017 (terminated)
NCT01110811[a]	A Randomized Controlled Trial Comparing Transoral Incisionless Fundoplication (TIF) Using EsophyX With Sham Procedure for the Treatment of PPI Dependent GERD: the TIF vs. Sham Study	60	Mar 2017 (unknown)

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

CODING

The following codes for treatment and procedures applicable to this policy 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. 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.

CPT/HCPCS

43201	Esophagoscopy, flexible, transoral; with directed submucosal injection(s), any substance
43210	Esophagogastroduodenoscopy, flexible, transoral; with esophagogastric fundoplasty, partial or complete, includes duodenoscopy when performed.
43212	Esophagoscopy, flexible, transoral; with placement of endoscopic stent (includes pre- and post-dilatation and guide wire passage, when performed)
43236	Esophagogastroduodenoscopy, flexible, transoral; with directed submucosal injection(s), any substance
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
43266	Esophagogastroduodenoscopy, flexible, transoral; with placement of endoscopic stent (includes pre- and post-dilation and guide wire passage, when performed)
43499	Unlisted procedure, esophagus
43659	Unlisted laparoscopy procedure, stomach

- There are specific CPT codes for transoral incisionless fundoplication and the radiofrequency procedure: 43210, 43257.
- Endoscopic submucosal injection of a bulking agent would most likely be coded using 43201 or 43236.

- Endoscopic implantation of a prosthesis would most likely be coded using code 43212, 43266, or 43499.

Diagnoses

Experimental / Investigational for all diagnoses related to this medical policy.

REVISIONS	
12-15-2009	In Header Section: ▪ Changed title From: Endoscopic gastroplasty for gastroesophageal reflux disease (GERD) and weight reduction To: Transesophageal Endoscopic Therapies for Gastroesophageal Reflux Disease
	Updated Description Section.
	In Policy Section: ▪ No change in policy intent was made, however, wording was updated to current version From: "The following transesophageal endoscopic therapies are considered experimental/investigational for all indications, including but not limited to gastroesophageal reflux disease and weight reduction due to the lack of long-term studies: 1. Transesophageal endoscopic gastroplasty (i.e., the Endocinch procedure) 2. Transesophageal radiofrequency energy to create submucosal thermal lesions of the gastroesophageal junction (i.e., the Stretta® procedure) 3. Endoscopic submucosal implantation of a biocompatible polymer (i.e., Enteryx) 4. Endoscopic submucosal implantation of polymethylmethacrylate beads into the lower esophageal folds"
	Added Rationale Section.
	In Coding Section: ▪ Removed CPT codes: 0008T, 0133T.
	Updated Revision and References Sections.
01-03-2012	Updated Description Section
	Updated Rationale Section
	In Policy Section: ▪ Combined Items #3 and #4 of "3. Endoscopic submucosal implantation of a biocompatible polymer (e.g., Enteryx) is considered experimental / investigational as a treatment of gastroesophageal reflux disease. 4. Endoscopic submucosal implantation of polymethylmethacrylate beads into the lower esophageal folds is considered experimental / investigational as a treatment of gastroesophageal reflux disease." to read: "3. Endoscopic submucosal implantation of a prosthesis or injection of a bulking agent (e.g., biocompatible liquid polymer, polymethylmethacrylate beads, zirconium oxide spheres) is considered experimental / investigational as a treatment of gastroesophageal reflux disease." This update does include the addition of "Endoscopic submucosal implantation of a prosthesis" to the policy language as experimental / investigational.
	In Coding Section: ▪ Added CPT code: 43219
	Updated References section
06-05-2012	Updated Description section

REVISIONS	
	Updated References
03-12-2013	Description section updated
	Rationale section updated
	In Coding section: ▪ Coding notations added.
	References updated
01-01-2014	Description section updated
	Rationale section updated
	In Coding section: ▪ Added CPT code: 43212, 43236, 43266 (Eff 01-01-2014) ▪ Revised nomenclature on CPT codes: 43201, 43257 (Eff 01-01-2014) ▪ Terminated CPT code: 43219 (Eff 12-31-2013) ▪ Removed the Diagnosis section as the policy is experimental / investigational for all diagnoses related to this policy.
	References updated
07-21-2015	Description section updated
	In Policy section: ▪ In Item 1 removed "Transesophageal endoscopic gastroplasty" and "(e.g., the EndoCinch ™, NDO Plicator™, or EsophyX™ procedures)" to read, "Transoral incisionless fundoplication (TIF) (ie, Esophyx®) is considered experimental / investigational as a treatment of gastroesophageal reflux disease." ▪ In Item 3 removed "biocompatible liquid polymer" as a bulking agent example.
	Rationale section updated
	In Coding section: ▪ Removed CPT Code 43219 as the code terminated 12-31-2013. ▪ Coding notations updated.
	In Revision section: ▪ Corrected a code effective date in 01-01-2014 Revision.
	References updated
01-01-2016	In Coding section: ▪ Added CPT code: 43210
02-09-2016	In Title section: ▪ Added "See Also: Injectable Bulking Agents for the Treatment of Urinary and Fecal Incontinence" ▪ Corrected Professional and Institutional Current Effective Date from January 1, 2016 back to July 21, 2015.
	Description section updated
	Rationale section updated
	In Coding section: ▪ Coding notations updated ▪ Added "Experimental / Investigational for all diagnoses related to this medical policy." as this was erroneously left off of prior versions.
	References updated
03-10-2017	Description section updated
	Rationale section updated
	In Coding section: ▪ Coding notations updated
	References updated
03-01-2018	Description section updated
	Rationale section updated
	References updated

REVISIONS	
04-24-2019	Description section updated
	Rationale section updated
	References updated

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