Title: Transesophageal Endoscopic Therapies for Gastroesophageal Reflux Disease

See Also: Injectable Bulking Agents for the Treatment of Urinary and Fecal Incontinence

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Contains Public Information
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
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

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. 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.

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. Proton pump inhibitors (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.

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).

Due in part to the high prevalence of gastroesophageal reflux disease, 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, 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. U.S. Food and Drug Administration product code: DQX

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

**Regulatory Status**

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 (K160960) 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 2 cm or less in patients with symptomatic chronic gastroesophageal reflux disease (GERD).³ 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 is specifically intended for use in the treatment of GERD. Stretta® is currently manufactured by Mederi Therapeutics (Greenwich, CT). FDA product code: GEI.

Durasphere® is a bulking agent approved for treatment of urinary and fecal incontinence (see the Injectable Bulking Agents for the Treatment of Urinary and Fecal Incontinence policy). Use of this product for esophageal reflux would be considered off-label use. The website of Carbon Medical Technologies states that Durasphere GR is an investigational device in the United States “intended to treat problems associated with GERD.”
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 was based, in part, on a 2003 TEC Assessment of transesophageal endoscopic treatments for gastroesophageal reflux disease (GERD) and a 2016 Evidence Street Assessment on transoral incisionless fundoplication (TIF). Since the 2003 Assessment, this review has been updated using the MEDLINE database. The most recent literature update was performed through August 31, 2016, which focused on TIF. This evidence review addresses procedures which are currently available for use in the United States.

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 dysphagia 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)

Patient Indications

The target population consisted of patients with chronic GERD eligible for TIF. This included patients with a hiatal hernia of 2 cm or less, and proven reflux either by endoscopy or ambulatory pH monitoring. Contraindications for TIF include a body mass index greater than 35 kg/m², Barrett esophagus greater than 2 cm, esophageal ulcer, fixed esophageal stricture, and other gastric disorders (eg, abnormal gastric motility). Patients may desire surgery if symptoms are not well controlled on medical therapy or, if controlled, they may desire to avoid chronic medical therapy.
In 2016, the Blue Cross and Blue Shield Center for Clinical Effectiveness published an Evidence Street Assessment on TIF for GERD using the EsophyX device.\(^9\) Included were 4 randomized controlled trials (RCTs) from 2015 (described below), 3 studies that compared TIF to laparoscopic fundoplication, a multicenter registry, and case series with longer term follow-up to evaluate the durability of TIF. The Assessment concluded that the RCTs show better patient-reported outcomes with TIF compared with medical therapy at 6 months, although a fair proportion of TIF patients required resumption of proton pump inhibitor (PPI) therapy. Evidence was insufficient to make conclusions about the comparative efficacy of TIF and laparoscopic fundoplication or about the durability of TIF.

**Randomized Trials Comparing TIF to Medical Therapy**

We identified 4 RCTs comparing TIF to medical therapy. Trials varied by types of patients enrolled (controlled vs not controlled by PPI), whether there was a sham control or not, and outcome measures employed (see Table 1). In general, patients included in these trials were eligible for surgery based on inadequate response to PPI therapy or desire to forgo long-term PPI therapy and a hiatal hernia of 2 cm or less. Patients were excluded if they had signs of severe GERD (eg, severe grade esophagitis, esophageal dysmotility, extra-esophageal manifestations of GERD, other complicating medical illnesses). The study by Hunter et al was rated as good quality; the other studies were fair to poor.\(^10\)

**Table 1. Randomized Trials of TIF Versus Medical Management, Selected Characteristics of Trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>TIF: CTL, n</th>
<th>Patient Symptoms or Other Characteristics</th>
<th>Comparator</th>
<th>Follow-Up, mo</th>
<th>Principal Clinical Outcome</th>
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<tr>
<td>Hunter et al (2015) (RESPECT)</td>
<td>87:42</td>
<td>Troublesome regurgitation, not controlled on PPI</td>
<td>Sham + PPI</td>
<td>6</td>
<td>Relief of regurgitation without PPI in TIF group vs with PPI escalation in control group</td>
</tr>
<tr>
<td>Hakansson et al (2015)</td>
<td>22:22</td>
<td>Controlled on PPI, run-in to confirm PPI dependence</td>
<td>Sham only</td>
<td>≥6</td>
<td>Time to resumption of PPI, percent needing PPI at 6 mo</td>
</tr>
<tr>
<td>Witteman et al (2015)</td>
<td>40:20</td>
<td>Controlled on PPI</td>
<td>Continued PPI</td>
<td>6</td>
<td>Mean GERD symptoms, percent with &gt;50% improvement</td>
</tr>
<tr>
<td>Trad et al (2015) (TEMPO)</td>
<td>40:23</td>
<td>Troublesome symptoms, not controlled on PPI</td>
<td>Maximum dose PPI</td>
<td>6</td>
<td>Elimination of daily symptoms other than heartburn</td>
</tr>
</tbody>
</table>

Ctl: control; GERD: gastroesophageal reflux disease; PPI: proton pump inhibitor; TIF: transoral incisionless fundoplication.

Hunter et al compared TIF plus placebo (n=87) to sham TIF plus PPI (n=42) in patients with troublesome regurgitation despite daily PPI therapy.\(^10\) Troublesome regurgitation was defined as mild symptoms for 2 or more days a week or moderate-to-severe symptoms more than 1 day a week. The primary outcome was elimination of troublesome regurgitation at 6 months. Secondary outcomes included percent early failure (continued troublesome regurgitation at 3 months after increased medication), symptom scores, acid exposure, healing of esophagitis, and common side effects of treatment. 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.

For the primary outcome of elimination of troublesome regurgitation, the intention-to-treat
analysis showed a higher success rate in the 67% (58/87) of TIF patients versus 45% (19/42) of
sham patients (p=0.023) (see Table 2). The per-protocol analysis excluding 10 randomized
patients not meeting original trial entry criteria showed similar findings. Other secondary
outcomes (eg, 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.

The RCT by Hakansson et al compared TIF (n=22) to sham only (n=22) in patients who were
well controlled by chronic PPI treatment.11 Although patients were controlled by chronic PPI
treatment, trial eligibility required a run-in phase that required persistent GERD symptoms off PPI
therapy and abnormal laboratory or endoscopic findings consistent with recurrence of GERD.
Thus the expected outcome in the sham group was that, without PPI, GERD symptoms would
eventually recur. The primary outcome was treatment failure, defined as the need for PPI
treatment to control reflux symptoms when assessed at posttreatment office visits. Secondary
outcomes included frequency and intensity of GERD symptoms, PPI usage, esophageal acid
exposure, and side effects of treatment.

Twenty-two patients were randomly assigned to each group. Kaplan-Meier curves of treatment
failure showed a higher rate of treatment failure in the sham group than in the TIF group
(p<0.001, time to treatment failure). The trial reported an average time in remission of 197 days
in the TIF group versus 107 in the sham group, but it is unclear at what point these values are
calculated (see Table 2). The follow-up time in the analysis must have been more than 6 months,
because the maximum possible remission time at 6 months was 182, assuming 0 failures. Fifty-
ine percent (13/22) of subjects in the TIF group were in remission at 6 months versus 18%
(4/22) in the sham group (p=0.01).

Several secondary outcomes showed results consistent with more favorable outcomes in the TIF
group. GERD symptoms, as assessed by the QOLRAD, only improved in the TIF group.
A similar pattern emerged for symptoms as assessed by the GSRS. However, no formal statistical analysis
was reported for between-group differences in these outcomes.

The RCT by Witteman et al compared TIF (n=40) to continued PPI therapy (n=20) without sham
controls in patients well-controlled with PPIs.12 The trial was described as an equivalence trial,
whose objective was to demonstrate that outcomes with TIF were not significantly worse than
those with continued PPI therapy. The declared equivalence delta was 2 points measured on the
GERD-HQRL. The trial population included patients well controlled with PPI therapy, but opting
for an intervention over lifelong drug dependence. The primary outcome was treatment success,
deefined by an improvement of 50% or more on the GERD-HQRL. Secondary outcome measures
included adverse events, esophageal acid exposure, number of reflux episodes, PPI usage,
appearance of gastroesophageal valve, and healing of esophagitis.

The trial was originally designed as a 2-center study, but this analysis was reported as an interim
before the second center enrolled patients. Based on these results, the trial was terminated.
Another critical aspect of the study is that baseline measurements of GERD symptoms were assessed after a 14-day cessation period of PPI therapy, thus allowing GERD symptoms to recur in many patients. Thus baseline GERD symptom levels do not represent patients’ steady-state levels of controlled symptoms. In the PPI therapy group, PPI therapy was stepped up or down as necessary during follow-up. In the TIF group, although patients did not initially start PPI therapy, they were allowed to use PPI in a similar step-up or step-down protocol as controls.

At 6 months, 55% of TIF patients had more than 50% improvement in GERD symptoms versus 5% of patients on continued PPI therapy (p<0.001) (see Table 2). Mean change in GERD symptoms from baseline was consistent with this result (TIF, -14.1; control, -3.1; p<0.001). For this primary outcome, the noninferiority aspect of the trial is irrelevant, because the superiority result means that the noninferiority criterion was also met. Twenty-six percent 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.

TIF patients were followed beyond 6 months as a nonrandomized case series, 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 statistical 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 not an equivalent alternative for PPIs in GERD treatment, even in this highly selected population.”

Trad et al evaluated TIF (n=40) and maximum PPI therapy (n=23) without sham controls in patients with daily symptoms of regurgitation while on daily PPI therapy.13 Eligible patients had had GERD for more than 1 year and a history of daily PPI use for more than 6 months. The control group was assigned to receive the maximum standard dose of PPI. The primary end point was elimination of daily troublesome GERD symptoms other than heartburn as assessed using a composite of 3 GERD symptom scales: the GERD-HRQL, RSI, and RDQ. It is unclear from the published article how the composite outcome was calculated, but it appears as if elimination of all symptoms except heartburn was required to achieve the end point. Another specific outcome mentioned was elimination of moderate-to-severe regurgitation with frequency reduced to 1 day a week or less, as assessed by the RDQ. Secondary end points included normalization of esophageal acid exposure, healing of esophagitis, PPI use, and serious adverse events. The trialists noted that some patients resumed PPI use after TIF, but did not describe any research protocol for this action.

At 6-month follow-up, 39 of 40 TIF and 21 of 23 control patients were available for follow-up. Complete elimination of all daily troublesome GERD symptoms other than heartburn was achieved in 62% of patients in the TIF group and 5% in the control group (relative risk, 12.9;
95% confidence interval [CI], 1.9 to 88.9; p<0.001) (see Table 2). Troublesome regurgitation was eliminated in 97% (29/30) of TIF patients who were off PPIs. This result appears to be misleadingly reported in the abstract of the article, where the denominator (patients off PPIs) is not mentioned. The trial reported that 90% (35/39) of patients in the TIF group had stopped taking PPIs, but the number of patients (n=35) is not the same as the previously reported denominator of 30 for patients off PPIs. However, esophageal acid exposure did not differ significantly between groups (TIF, 54%; PPI, 52%; p=0.914). At 6-month endoscopic assessment, healing or reduction in GERD symptoms was achieved in 90% of TIF patients and 38% in control patients (p=0.18), but not all patients were included in this comparison.

Table 2. Principal Clinical Outcomes of Randomized Trials Comparing TIF to Nonsurgical Treatment

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>TIF</th>
<th>Comparator</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hunter et al (2015)10</td>
<td>TIF + placebo</td>
<td>Sham + PPI</td>
<td></td>
</tr>
<tr>
<td>Elimination of troublesome regurgitation</td>
<td>67%</td>
<td>45%</td>
<td>0.023</td>
</tr>
<tr>
<td>Change in RDQ regurgitation score</td>
<td>-3</td>
<td>-3</td>
<td>0.072</td>
</tr>
<tr>
<td>Change in RDQ heartburn score</td>
<td>-2.1</td>
<td>-2.2</td>
<td>0.936</td>
</tr>
<tr>
<td>Change in RDQ heartburn plus regurgitation</td>
<td>-2.5</td>
<td>-2.4</td>
<td>0.313</td>
</tr>
<tr>
<td>Hakansson et al (2015)11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days to remission</td>
<td>197</td>
<td>107</td>
<td>0.001</td>
</tr>
<tr>
<td>Change in median QOLRAD score at 6 mo</td>
<td>1.5</td>
<td>0.4</td>
<td>NR</td>
</tr>
<tr>
<td>Change in median GSRs score at 6 mo</td>
<td>4</td>
<td>1.4</td>
<td>NR</td>
</tr>
<tr>
<td>Percent off daily PPI therapy at 6 mo</td>
<td>59%</td>
<td>18%</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean change in GERD-HRQL</td>
<td>-14.1</td>
<td>-3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percent &gt;50% improvement GERD-HRQL</td>
<td>55%</td>
<td>5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in percentage with esophagitis</td>
<td>-19%</td>
<td>-20%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Trad et al (2015)13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elimination of symptoms other than heartburn</td>
<td>62%</td>
<td>5%</td>
<td>0.001</td>
</tr>
<tr>
<td>Daily PPI use</td>
<td>8%</td>
<td>NR</td>
<td>–</td>
</tr>
<tr>
<td>Change in GERD-HRQL score</td>
<td>-21.1</td>
<td>-7.6</td>
<td>&lt;0.001, &lt;0.001^a</td>
</tr>
<tr>
<td>GERD-HRQL Heartburn score</td>
<td>-14</td>
<td>-5.2</td>
<td>&lt;0.001, &lt;0.001^a</td>
</tr>
<tr>
<td>RSI score</td>
<td>-17.4</td>
<td>-3.0</td>
<td>&lt;0.001, 0.205^a</td>
</tr>
</tbody>
</table>

GERD-HRQL: Gastroesophageal Reflux Disease Health-Related Quality of Life; GSRs: Gastrointestinal Symptom Rating Scale; NR: not reported; PPI: proton pump inhibitor; QOLRAD: Quality of Life in Reflux and Dyspepsia; RDQ: Reflux Disease Questionnaire; RSI: Reflux Symptom Index; TIF: Transoral Incisionless Fundoplication.

^a Within-group p values calculated separately for TIF and control, no between group analysis.

Safety and Adverse Event Reporting in the Randomized Trials

The RCT by Hunter et al reported that, with the exception of postoperative epigastric pain, complications and adverse effects did not differ between groups.\textsuperscript{10} One patient in the TIF group and 2 patients in the sham group developed de novo dysphagia.

The RCT by Hakansson reported rates of dysphagia, bloating, flatulence, and left shoulder pain that did not differ significantly different between groups.\textsuperscript{11} Postoperative epigastric pain was
much greater in the TIF group (45% vs 5%, p=NS). One TIF patient had dysphagia, which lasted for 3 months, but did not require intervention.

In the trial by Witteman et al, 1 TIF patient developed pneumoperitoneum perioperatively. Three TIF patients developed pneumonia, 1 of whom required hospital admission. Side effects of fundoplication (eg, pain, flatulence, bloating, diarrhea) did not occur in TIF patients, as assessed by the GSRS.

In Trad et al, the only adverse events mentioned were in 2 TIF patients who required an extra day in the hospital, 1 due to postoperative dizziness and nausea and 1 due to an allergic reaction.

**Discussion of Randomized Trials Comparing TIF to Medical Therapy**

All 4 RCTs of TIF versus medical therapy met investigators’ criteria for a treatment effect of TIF. Three of them had small sample sizes (<100 patients). An important limitation of all the trials is that follow-up of the randomized patients in both treatments groups ended at 6 months. In some of the studies, unblinding and crossover to TIF occurred at 6 months, eliminating the possibility of randomized comparisons beyond 6 months. Although all trials showed a greater treatment effect for the principal outcome of TIF on GERD symptoms, given the methodologic differences between RCTs, it is difficult to ascertain the overall benefit of treatment, even within the 6-month follow-up window.

For example, in Hunter et al, the need to resume PPI therapy before 6 months was considered a treatment failure. However, enrolled patients were not controlled for PPI treatment at baseline. If some patients’ symptoms improved after TIF and resumption of medication, these patients deemed as treatment failures may have achieved some benefit from TIF but were not counted. Similarly, in Hakansson et al, resumption of PPIs after TIF was considered treatment failure. However, in this trial, patients had been previously well controlled. While it is not an optimal outcome if it is necessary to resume PPI, if patients need lower dose or less frequent PPI or have less severe symptoms, they may have derived some benefit from TIF.

The other 2 trials did not count patients who resumed PPIs as treatment failures, but did retain them in their analyses. These trials showed that a proportion of patients resumed PPI therapy in the short term after TIF. However, overall, mean symptom scores of TIF patients were better than the scores of patients on medical therapy, even in Witteman et al, which enrolled patients well controlled in PPI therapy.

However, the longer follow-up in the Witteman trial raises concerns about the validity of the 6-month end point used in the other 3 trials to evaluate TIF. Although symptoms were still better than baseline, there was an increase in the proportion of patient using PPI between 6 months and 12 months, and endoscopy showed several signs of worsening of GERD after 6 months.

**Studies Comparing TIF to Laparoscopic Fundoplication**

Three studies have compared TIF to laparoscopic fundoplication. One was an RCT and 2 were nonrandomized comparative studies. The randomized trial was rated poor using U.S. Preventive Services Task Force criteria, because TIF was performed using a different device in some patients and the reporting lacked details on other aspects of the trial. Moreover, more than half of the patients who had TIF did so using a discontinued device, the trial results may not
generalize specifically to EsophyX. In addition, there was no separate analysis of patients undergoing TIF with the EsophyX device.

The RCT by Svoboda et al compared 34 patients receiving TIF to 18 patients receiving fundoplication. Patients were enrolled if they had chronic GERD symptoms, abnormal esophageal acid exposure test results, partial response to PPI therapy, hiatal hernia less than 2 cm, and no findings associated with severe esophagitis and/or complications.

At 12-month follow-up, 26 (76%) of 34 TIF patients and 14 (78%) of 18 fundoplication patients were available. There was no declared principal outcome of the study. GERD-HRQL scores improved in both groups to a similar extent at 3 months and 12 months (12-month scores, 6.6 for TIF vs 6.7 for fundoplication; p=0.7). In terms of the percentage of subjects with 50% or more improvement in GERD-HRQL scores at 12 months, results were similar (68% for TIF vs 71% for fundoplication; p=0.397) (see Table 3). Fifty percent of TIF subjects were off PPI at 12 months versus 71% of fundoplication subjects (p=0.2). Four serious adverse events occurred: 1 in the TIF group and 3 in the fundoplication group. The adverse event in the TIF group did not occur in a patient who had the procedure using EsophyX. The adverse events in the fundoplication group were unrelated to surgery.

A nonrandomized study by Frazzoni et al compared 10 patients undergoing TIF to 10 patients undergoing laparoscopic fundoplication. Eligible patients had persisting symptoms despite at least 4 weeks of high-dose PPI therapy. Patients with signs of severe esophagitis and extra-esophageal manifestations of GERD were excluded. Patients selected which treatment they wanted. The principal clinical outcome was not specifically declared, but appeared to be a categorical rating (range, 0-3) of heartburn and regurgitation symptoms. Changes in categorical rating of symptom remission were then collapsed into 2 categories, total and subtotal remission (final score of 0 or a 2-point improvement), and partial and no remission (no change in score or a 1-point improvement), based on initial and final score. Assessments of acid exposure and esophageal function at postprocedure endoscopy, manometry, and impedance pH monitoring were also planned.

At baseline, patients had similar levels of acid exposure and reflux as assessed by preprocedure endoscopy and manometry. In terms of clinical outcomes assessed at 3 months, 7 patients undergoing TIF reported only partial/no symptom remission versus 0 patients undergoing fundoplication (p=0.003) (see Table 3). 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 is less effective than fundoplication in improving symptoms of GERD. Adverse perioperative events were not described.

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, but it is not clear how this matching or control was achieved. The indications for each procedure resulted in imbalance in important patient characteristics. 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. Another incidental difference in baseline characteristics was the proportion of patients undergoing a reoperation for GERD: 25% in the TIF group versus 5% and 5% in the 2 fundoplication groups. The principal study outcomes were not specified, but up to 16 measures of various symptoms (rated 0 to 10 for severity and frequency) were assessed at baseline and follow-up.

Evaluation of symptom outcomes occurred at an unstated unknown time postsurgery. An analysis plan was not provided, and it is unclear how statistical testing was performed. Results are displayed in the published article as preoperative and postoperative median values of various symptoms’ severity or frequency for each procedure. It appears as if, qualitatively, most measures of symptoms decreased to low levels (median ranges, 0-2) after all procedures. Quoting from the article: “…there was significant amelioration of symptom frequency and severity and with no significant difference among patients who underwent TIF or …Nissen or Toupet fundoplications.”

The study reported the percentage of patients in each group with symptoms less than once per month (83% of TIF patients, 80% of Nissen fundoplication patients, 92% of Toupet fundoplication patients; p=0.12) (see Table 3). Patient-rated satisfaction was 67% for TIF, 86% for Nissen fundoplication, and 92% for Toupet fundoplication (p value not reported), but described as “similar.” Adverse events were not reported for procedures.

<table>
<thead>
<tr>
<th>Table 3. Study Outcomes Comparing TIF to Laparoscopic Fundoplication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcomes</strong></td>
</tr>
<tr>
<td>Svoboda et al (2011)</td>
</tr>
<tr>
<td>3 months, % improvement GERD-HRQL score &gt;50%</td>
</tr>
<tr>
<td>3 months, % off of PPI</td>
</tr>
<tr>
<td>12 months, % improvement GERD-HRQL score &gt;50%</td>
</tr>
<tr>
<td>12 months, % off of PPI</td>
</tr>
<tr>
<td>Frazzoni et al (2011)</td>
</tr>
<tr>
<td>Percent partial or no symptom remission</td>
</tr>
<tr>
<td>Percent normalization of reflux parameters</td>
</tr>
<tr>
<td>Esophageal acid exposure time</td>
</tr>
<tr>
<td>Distal refluxes</td>
</tr>
<tr>
<td>Proximal refluxes</td>
</tr>
<tr>
<td>Toomey et al (2014)</td>
</tr>
<tr>
<td>Percent with symptoms &lt;1 mo</td>
</tr>
<tr>
<td>Percent satisfied</td>
</tr>
<tr>
<td>Median VAS score postoperative severity of symptoms</td>
</tr>
<tr>
<td>Heartburn post meal</td>
</tr>
<tr>
<td>Heartburn post sleep</td>
</tr>
<tr>
<td>Regurgitation</td>
</tr>
<tr>
<td>Food stuck in throat</td>
</tr>
<tr>
<td>Food stuck in chest</td>
</tr>
<tr>
<td>Bitter taste post meal</td>
</tr>
<tr>
<td>Bitter taste post sleep</td>
</tr>
<tr>
<td>Asthma/cough</td>
</tr>
<tr>
<td>Gas/bloating</td>
</tr>
</tbody>
</table>

Results for Toupet fundoplication are not shown due to different indications for this procedure. GERD-HRQL: Gastroesophageal Reflux Disease Health-Related Quality of Life; NR: not reported; PPI: proton pump inhibitor; VAS: visual analog scale; TIF: transoral incisionless fundoplication.
Discussion of 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. Most TIF patients did not achieve a good result in this study. 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. Demonstration of similarity in outcomes between TIF and fundoplication would require formal design and analysis of the trials as noninferiority trials, with a clear rationale for the noninferiority margin. 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.

Studies Assessing the Durability of TIF
We found 5 case series or reports extending the follow-up in clinical trials that reported patient outcomes at least 2 years beyond the TIF procedure. Presentation and interpretation of these studies is problematic for several reasons. The number of patients reported at a particular time point may not represent the complete number of patients eligible. Some patients underwent further surgical treatment for GERD, and are variously included or not included in the analyses. Reporting of outcomes is not uniform between studies. Some studies only reported certain outcomes (eg, symptom scores at pretreatment baseline and end of follow-up); without intermediate short-term results, such findings cannot distinguish between initial treatment efficacy and durability of the short-term outcomes. Finally, the case series generally do not differentiate results based on the indication for TIF—whether the patient was well-controlled on PPI therapy or not. Outcomes such as resumption of PPI after TIF might be interpreted differently based on whether the patient was well-controlled before treatment.

In 2009, Cadiere et al reported 2-year results of a small case series of patients undergoing TIF. Of the original series of 19 patients, 14 patients were assessed at 2 years. Two of the excluded patients underwent additional surgical treatment. At 2 years, median GERD-HRQL scores improved from 17 to 7 (p=0.004), with 64% having more than 50% reduction in GERD-HRQL scores. Seventy-one percent of patients were not taking daily PPI therapy at 2 years. Twenty-nine percent (4/14) were considered “cured” when defined as no heartburn, no daily PPI use, no hiatal hernia, and no esophagitis. Fifty percent (7/14) were considered “in remission” when defined as reduced heartburn, reduced hiatal hernia, or reduced esophagitis, but requiring occasional use of PPIs. This study did not report 1 year outcomes, so changes in outcome between 1 and 2 years are unknown.

In 2012, Testoni et al reported 2-year outcomes for a case series of patients undergoing TIF. Of the original series of 42 patients, 26 patients had follow-up data at 24 months. Four patients had additional surgical treatment between 12 months and 24 months, and are not included in the analysis. GERD symptoms as measured by the GERD-HRQL and GERD-QUAL scores were...
significantly improved from baseline at all time points. However, these scores reverted toward baseline values at each subsequent time point, but this change was not evaluated with formal statistical testing (see Table 4). PPI use increased over time between 6 months and 24 months; defining responders as those who completely stopped PPI use, the percentage of responders decreased from 60% (21/35) at 6 months to 42% (11/26) at 24 months (p=0.2)

Table 4. Mean GERD Symptom Scores at Baseline and Follow-Up

<table>
<thead>
<tr>
<th></th>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>42</td>
<td>65</td>
<td>127</td>
</tr>
<tr>
<td>GERD-HRQL score</td>
<td>46</td>
<td>25</td>
<td>1.8</td>
</tr>
<tr>
<td>GERD-QUAL score</td>
<td>114</td>
<td>24.2</td>
<td>4.0</td>
</tr>
<tr>
<td>Median GERD-HRQL score</td>
<td>66</td>
<td>7.9</td>
<td>5.2</td>
</tr>
<tr>
<td>Mean GERD-HRQL score</td>
<td>25</td>
<td>6</td>
<td>0.4</td>
</tr>
<tr>
<td>Percent 50% reduction in GERD-HRQL score from baseline</td>
<td>75%</td>
<td>65%</td>
<td>75%</td>
</tr>
<tr>
<td>Percent reporting satisfaction</td>
<td>6%</td>
<td>66%</td>
<td>86%</td>
</tr>
<tr>
<td>Percent patients off daily PPI</td>
<td>26a</td>
<td>66b</td>
<td>108c</td>
</tr>
<tr>
<td>GERD-HRQL dysphagia score</td>
<td>1.8</td>
<td>0.9</td>
<td>4.0</td>
</tr>
<tr>
<td>GERD-HRQL bloating score</td>
<td>2.4</td>
<td>0.3</td>
<td>0.7</td>
</tr>
<tr>
<td>GERD-HRQL painful swallowing score</td>
<td>1.3</td>
<td>0.3</td>
<td>1.3</td>
</tr>
<tr>
<td>GERSS dysphagia score</td>
<td>1.8</td>
<td>0.5</td>
<td>2.1</td>
</tr>
<tr>
<td>GERSS abdominal distention score</td>
<td>5.2</td>
<td>0.7</td>
<td>1.2</td>
</tr>
<tr>
<td>Excess flatulence</td>
<td>2.4</td>
<td>0.2</td>
<td>0.7</td>
</tr>
</tbody>
</table>

GERD: gastroesophageal reflux disease; GERD-HRQL: Gastroesophageal Reflux Disease Health-related Quality of Life; GERSS: Gastroesophageal Reflux Symptom Score; PPI: proton pump inhibitor; RSI: Reflux Symptom Index; TIF: transoral incisionless fundoplication.

a Two-year outcomes excluded 4 patients who underwent surgical treatment between 1 year and 2 years.

b Three-year data includes imputed values for 12 patients who had additional surgery for poor response.

c Two-year data included imputed values for 8 patients who had additional surgery for poor response.

In 2014, Muls et al reported 3-year outcomes for a case series of patients undergoing TIF. Of 86 patients in the original case series, 1- and 3-year follow-ups were available on 66 and 54 patients, respectively. Twelve patients underwent additional surgical treatment between 1 and 3 years; they were included in an intention-to-treat analysis and assigned the worst possible values for all outcomes. This study reported outcomes at baseline, 1 year, and 3 years on the same patients, and permitted the best examination of change in outcomes between the 2 time points. Compared to baseline values, median GERD-HRQL scores improved at both 1- and 3-year follow-ups (see Table 4). The percentage of patients whose scores decreased by 50% or more was 75% at 1 year and 65% at 3 years. The percentage of patients reporting satisfaction was 68% at 1 year and 58% at 3 years. The percentage of patients not using daily PPI decreased from 86% at 1 year to 61% at 3 years. The percent of patients not using any PPI decreased from 70% at 1 year to 52% at 3 years. None of these differences in outcome between 1 year and 3 years were formally evaluated with statistical significance testing.

Contains Public Information
In 2014, Bell et al reported 2-year outcomes of TIF from a multicenter registry. Of 127 patients enrolled, 100 patients had 2-year follow-up data. Another 8 patients who underwent additional surgical treatment between 6 months and 24 months were included in the analysis but designated as treatment failures and assigned pretreatment values for all outcomes. Findings at 12 months (n=123) and 24 months (n=108) showed improvements in all measures of GERD symptoms compared to baseline (p<0.001 for all symptom measures) (see Table 4). Values of some specific GERD symptoms between 12 months and 24 months generally showed no change or some movement back toward baseline, but there was no statistical testing for change between 12 months and 24 months. Some scores showed reversion toward baseline values. Among 98 patients who used PPI daily at baseline, 70% no longer used it daily.

In 2015, Testoni et al reported outcomes for patients undergoing TIF followed for up to 6 years. Most appeared to be the same patients as reported in Testoni et al (2012). The only outcome assessed beyond 3 years in this study is PPI use. Of 49 patients undergoing TIF, variable numbers of patients are reported at each time point. Four patients are mentioned as having undergone additional surgical treatment and 1 is mentioned as having been lost to follow-up. These patients appear to have been excluded from the analysis. If these patients were the only ones excluded from the analysis, results at 6 years represent 14 of 19 possible patients with 6-year follow-up, of whom 4 with poor outcomes have been excluded. At 2 years and 3 years after TIF, GERD-HRQL and GERD-QUAL scores were improved compared to baseline (see Table 5). However, GERD-QUAL scores at 3 years assessed while patients were off PPIs are closer to baseline than the 2-year scores (baseline score, 114; 1-year score, 71; 3-year score, 80), but these differences were not formally statistically evaluated. Defining complete responders as those who completely stopped using PPIs at 1, 2, 3, 4, 5, and 6 years, complete response was observed in 51%, 56%, 53%, 46%, 32%, and 36%, respectively. The proportion of subjects who remained on their baseline dose of PPI was roughly constant throughout the period (range, 14.3%-21.1%) without the appearance of a temporal trend. The increase in use was primarily due to increases in low-dose PPI. Recall that these results excluded 4 patients who underwent additional surgical treatment who presumably would show poor outcomes and PPI use had they remained in the study without additional treatment.

**Table 5. PPI Use After TIF (Testoni et al, 2015)**

<table>
<thead>
<tr>
<th>PPI Use After TIF</th>
<th>6 Months</th>
<th>1 Year</th>
<th>2 Years</th>
<th>3 Years</th>
<th>4 Years</th>
<th>5 Years</th>
<th>6 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>49</td>
<td>49</td>
<td>45</td>
<td>32</td>
<td>24</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>Off PPI</td>
<td>61.2%</td>
<td>51.0%</td>
<td>56.1%</td>
<td>53.1%</td>
<td>45.8%</td>
<td>31.6%</td>
<td>35.7%</td>
</tr>
<tr>
<td>Halved PPI</td>
<td>22.5%</td>
<td>28.6%</td>
<td>31.7%</td>
<td>31.3%</td>
<td>37.6%</td>
<td>47.3%</td>
<td>50.0%</td>
</tr>
<tr>
<td>Daily PPI</td>
<td>16.3%</td>
<td>20.4%</td>
<td>12.2%</td>
<td>15.6%</td>
<td>16.6%</td>
<td>21.1%</td>
<td>14.3%</td>
</tr>
</tbody>
</table>

Data beyond 1 year excluded 4 patients who underwent surgical treatment between 1 year and 2 years. PPI: proton pump inhibitor; TIF: transoral incisionless fundoplication.

**Discussion of Studies Assessing the Durability of TIF**

The evidence base for long-term durability of TIF is limited. Studies of long-term outcomes of TIF often have large losses to follow-up or losses to follow-up cannot be determined from study reporting. Studies varied in how patients who required additional surgery for GERD were handled in the analysis. If excluded from the analysis, then results may be biased by exclusion of patients who did not have good outcomes from TIF.
All 5 studies reported that at 2- to 3-year follow-ups, GERD symptoms were better than at baseline. This included studies of patients who had additional surgery, but who were imputed to have poor outcomes in the analysis. (Bell et al, Muls et al) The study by Bell et al has the largest sample size (N=108) and the 2-year follow-up rate is very good at 85%. The durability of TIF out to 2 years appears to be very good, with very stable symptom scores between 6 months and 2 years.

Very limited evidence beyond 2 years has shown some results consistent with some loss of treatment effectiveness. Increased use of PPIs beyond 2 years occurred in the studies of Muls et al and Testoni et al. In Muls daily use of PPI increased from 14% at 1 year to 39% at 3 years. Accompanying this increase in PPI use was decline in the proportion of subjects whose GERD symptoms indicated that they responded favorably to TIF. In Testoni et al, daily use of PPI did not change much over 6 years, but there was a large change in the proportion of subjects using half-dose or intermittent PPI therapy. Symptom scores at 4 to 6 years were not reported in this study.

Section Summary: Transoral Incisionless Fundoplication (EsophyX)

To determine whether TIF for treating GERD improves the net health outcome, we selected studies that compared TIF to medical therapy, TIF to laparoscopic fundoplication, and studies that assessed long-term TIF outcomes.

For individuals who have GERD who receive TIF, the evidence comparing TIF and medical therapy includes 4 randomized controlled trials (RCTs). These trials varied in selection criteria, comparators, and outcome measures. All studies assessed GERD symptom outcomes at 6 months. One study was rated as good and the others were fair to poor using U.S. Preventive Services Task Force criteria. All 4 trials met their designated end points, showing a treatment effect of TIF relative to medical therapy. In all studies, at least a majority of subjects were able to stay off PPI treatment for the duration of the trial.

For individuals who have GERD who receive TIF, the evidence comparing TIF and fundoplication includes 1 RCT and 2 nonrandomized studies. Each had serious methodologic shortcomings. The RCT included subjects undergoing TIF with a different device. It showed no statistically significant differences between TIF and fundoplication. One nonrandomized study showed that TIF was much less effective than fundoplication. In the third nonrandomized study, indications for TIF and fundoplication varied, resulting in patients with different characteristics undergoing the different procedures. This study showed no statistically significant differences in outcomes between TIF and fundoplication.

For individuals who have GERD who receive TIF, the evidence evaluating durability of treatment effects includes five case series reported patient outcomes at 2 years or beyond. Studies varied in the proportion of patients followed long term. All studies showed GERD symptoms had improved at the last follow-up over baseline. Only 2 studies reported outcomes at 3 years or beyond. They showed increases in PPI therapy use beyond 3 years and some loss of TIF treatment effectiveness. These findings comparing outcomes at different follow-up times were not formally analyzed.

Although all 4 RCTs have shown GERD symptoms improve with TIF compared to medical therapy, analysis of outcomes was limited to 6 months postprocedure. Differences between trials
in patient selection criteria, intervention comparators, and outcome measures complicate the evaluation of the magnitude of treatment benefit. Studies comparing TIF and fundoplication are inadequate to determine relative efficacy. Finally, due to a small evidence base, the duration of treatment benefit of TIF is uncertain.

The evidence is not sufficient to demonstrate that TIF improves the net health outcome compared to fundoplication. Studies comparing TIF to fundoplication are small and have numerous methodological weaknesses. Although studies comparing TIF to medical therapy report improved outcomes, longer term follow up is needed to assess the clinical significance and durability of results.

**Transesophageal Radiofrequency (ie, Stretta Procedure)**

The available evidence consists of a meta-analysis and 4 small RCTs, all 4 of which include a sham placebo control, along with numerous uncontrolled case series.

**Systematic Review and Meta-Analyses**

A systematic review and meta-analysis was published by Lipka et al in 2014 (preprint). Four RCTs with a total of 165 patients were included in the meta-analysis. These trials are described in greater detail in the next section. Three trials compared Stretta versus sham, and 1 trial compared Stretta with PPI therapy. The overall quality of evidence was considered to be very low with a high risk of bias. The pooled results showed no significant difference between Stretta and sham or PPI management for the measured outcomes. The mean difference (control minus Stretta) in the percent time that pH was less than 4 was 1.56 (95% CI, -2.56 to 5.69). The mean difference for esophageal sphincter pressure was -0.32 mm Hg (95% CI, -2.66 to 2.02). The mean difference in health-related quality of life from 2 studies was -5.24 (95% CI, -12.95 to 2.46). The relative risk for the ability to discontinue PPIs was 0.87 (95% CI, 0.75 to 1.00). This meta-analysis is limited by heterogeneity in the included studies, which may be 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 (2 RCTs, 18 case series) with a total of 1441 patients. This review analyzed the within-subjects results following treatment only. The control groups of available clinical trials were not included for comparison. Analysis of the 9 studies (525 patients) that reported subjective heartburn scores showed a significant decrease from 3.55 to 1.19 at a mean of 24.1 months. Analysis of the 9 studies (433 patients) that reported GERD-HRQL scores showed an improvement from 26.11 to 9.25 at a mean follow-up of 19.8 months. Analysis of the 6 studies (299 patients) that reported SF-36 Physical Component Summary scores showed an improvement from 36.45 to 46.12 at a mean follow-up of 9.5 months. For the 11 studies that measured esophageal pH, significant improvements were found in the Johnson-DeMeester score (44.37 to 28.53), the esophageal acid exposure time (10.29% to 6.51%), and lower esophageal sphincter pressure (16.54 to 20.24). 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.

**RCTs Comparing Transesophageal Radiofrequency vs Sham**

The 2003 TEC Assessment included 1 randomized, sham-controlled trial by Corley et al. This trial enrolled patients with symptoms at least partially responsive to PPIs, a pH study showing abnormal acid exposure, and the usual exclusions including severe esophagitis or significant anatomic defect. The sham procedure involved balloon inflation but no needle deployment or
energy delivery. A total of 64 patients were randomized, and partial or complete 6-month follow-up data were available on 56 patients. The results of this trial were inconsistent. Although improvement in heartburn symptoms, quality of life, and general physical quality of life was observed in the active treatment group compared with the sham group, there were no differences in medication usage and esophageal acid exposure. Thus in terms of the objective measures of GERD, the findings are equivocal. The large proportion of sham-treated patients successfully reducing medication use points to possible placebo effect of the procedure.

Aziz et al reported a 12-month randomized, double-blind, sham-controlled trial in 36 patients whose GERD was controlled with PPIs.24 Patients were randomly assigned to receive RF, which could be repeated if there was a less than 75% improvement in GERD-HRQL scores at 4 months, or a sham procedure. At 12 months, 17% of patients in the single-session group, 50% in the double-session group, and 0% of the sham-treated patients had discontinued PPIs. Statistically significant improvements in GERD-HRQL were observed in all 3 treatment groups: In the single-session RF group, GERD-HRQL scores improved from a mean of 30 at baseline to 14 posttreatment; in the double-session RF group, GERD-HRQL scores improved from 31 to 11; and in the sham group, GERD-HRQL scores improved from 30 to 25. Mean total esophageal acid exposure time decreased in the active treatment groups (from 9.4 to 6.7 minutes in the single-session group [p<0.01], from 8.8 to 5.2 minutes in the double-session group [p<0.01]) but not in the sham group. The clinical relevance of these changes is uncertain. Serious adverse events occurred in 3 patients following RF treatment; 1 patient developed pneumonia and in 2 patients developed prolonged gastroparesis.

Arts et al reported a double-blind randomized crossover study of Stretta and sham treatment in a small trial with 22 GERD patients.23 The initial sham treatment in 11 patients did not affect any of the outcome measures. Three months after the RF procedure, the symptom score was significantly improved (14.7 to 8.3), and gastroesophageal junction compliance was significantly decreased (17.8 vs 7.4 mL/mm Hg). The quality-of-life score for bodily pain improved from 49.5 to 24.0. No changes were observed in PPI use, esophageal acid exposure, or lower esophageal sphincter pressure after RF. The decrease in compliance of the gastroesophageal junction was reversed by a smooth muscle relaxant, suggesting that the effect of RF on gastroesophageal junction compliance was not due to fibrosis.

In an unblinded randomized trial by Coron et al, a total of 43 PPI-dependent GERD patients either continued the effective dose of their PPI or received the RF procedure (Stretta).26 At 6 months, significantly more patients in the treatment group than the control group were able to discontinue or decrease their PPI use by at least 50%, a difference that was not maintained at 12 months. Some authors have suggested that PPI discontinuation rather than dose reduction is a more meaningful outcome measure. In this study, the number of patients able to discontinue PPI medication did not differ between groups.

**Controlled Trials Comparing Transesophageal Radiofrequency vs Laparoscopic Fundoplication**

In 2015, Liang et al reported a prospective comparison of laparoscopic Toupet fundoplication (n=80) versus the Stretta procedure (n=85).28 Of the 165 patients treated, 125 (76%) completed the 3-year follow-up (65 fundoplication, 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 (laparoscopic fundoplication: 72.3% vs Stretta: 68.3%; \( p=.627 \)) and had similar improvements in belching, hiccup, cough, and asthma. The Stretta procedure was less effective than laparoscopic fundoplication in improving symptoms of heartburn (mean improvement, 2.53 vs 4.05; \( p=0.01 \)), regurgitation (mean improvement, 2.41 vs 4.03; \( p=0.004 \)), and chest pain (mean improvement, 2.96 vs 5.50; \( p=0.005 \)). Significantly more patients in the Stretta group underwent reoperation (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 these differences were not statistically significant. This study lacked randomization and had high loss to follow-up. While symptom scores were comparable at baseline, the study may have been subject to selection bias related to treatment choice of, which affected baseline differences for other variables.

**Durability of Transesophageal Radiofrequency**

Ten-year follow-up after the Stretta procedure was reported by Noar et al.\(^{29}\) All patients had daily recurring symptoms of heartburn and regurgitation despite twice-daily PPI use. Of a total of 217 patients treated, 149 had reached 10-year follow-up. Of those, 50 were lost to follow-up (11 were deceased), resulting in 99 patients in the cohort. Of the 99 patients with 10-year follow-up, 72% showed normalization of GERD-HRQL scores, 64% had a 50% or greater reduction in PPI use, and 41% eliminated PPIs completely. Comparison of results out to 4 years in the total cohort (n=217) and completers only (n=99) showed no evidence of bias associated with non-completers. In a subset of 51 patients who underwent repeat endoscopy at 10 years or later, only 5 of the 33 patients who had dysplasia at study entry had remaining metaplasia. In the 18 patients without metaplasia at study entry, there was no change in esophageal histology.

A 5-year prospective observational study with 138 of 152 patients was reported by Liang et al in 2014.\(^{30}\) Symptoms of heartburn, regurgitation, chest pain, cough, and asthma were all decreased significantly compared with baseline (\( p<0.001 \)). More patients were completely off PPI therapy at 5 years (42.8%) than at 6 months (27.5%). Bloating was observed in 12 (8.7%) of patients after the Stretta procedure. No reoperations were reported.

**Section Summary: Transesophageal Radiofrequency (ie, Stretta Procedure)**

Four small RCTs report improvements in symptoms and quality of life following treatment with RF energy, however, a meta-analysis of these same studies found no significant improvement in outcomes. Nonrandomized studies show maintenance of efficacy at 3 to 10 years, although symptom relief with RF energy may be lower than with fundoplication and reoperations greater. Larger RCTs with longer follow-up are needed to better define the risks and benefits of this procedure.

**Injection/ Implantation of Prosthetics or Bulking Agents**

**Durasphere**

The available evidence for this device consists of 1 case series. One open-label pilot study\(^{31}\) of 10 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, 7 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 1 RCT. 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 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 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 (2 perforations, 1 pulmonary infiltrate related to a perforation, 1 severe chest pain). The primary efficacy end point was 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 the 2 groups. The study was terminated early due to a lack of efficacy.

Polymethylmethacrylate Beads
The available evidence for this device consists of 1 case series. A 2001 publication on transesophageal submucosal implantation of polymethylmethacrylate beads consisted of a case series of 10 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 (ie, drug therapy, laparoscopic fundoplication). Well-designed trials should use standardized outcome measures to examine both subjective (eg GERD-Health-Related Quality of Life scores) and objective (eg, esophageal acid exposure) effects on health outcomes.

Summary of Evidence
For individuals who have gastroesophageal reflux disease (GERD) who receive transoral incisionless fundoplication (TIF), the evidence includes 4 randomized controlled trials (RCTs) evaluating TIF and medical therapy, 1 RCT and 2 nonrandomized studies of TIF versus fundoplication, and 5 case series that reported patient outcomes at 2 years or beyond. Relevant outcomes are symptoms, change in disease status, quality of life, medication use, and treatment-related morbidity. Although all 4 RCTs showed GERD symptoms improved with TIF compared to medical therapy, analysis of outcomes was limited to 6 months postprocedure. Differences between trials in patient selection criteria, intervention comparators, and outcome measures complicate the evaluation of the magnitude of treatment benefit. Studies comparing TIF and fundoplication 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 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 report improvements in symptoms and quality of life following treatment with radiofrequency energy, however, a meta-analysis of these same studies found no significant improvement in outcomes. Nonrandomized studies show maintenance of efficacy at 3 to 10 years, although symptom relief may be lower than after fundoplication, and reoperations greater. Larger RCTs with longer follow-up 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 are 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 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–Health-Related Quality of Life 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 RF (Stretta®) as a treatment of GERD, input was received from 1 physician specialty society (2 reviewers) and 3 academic medical centers while this policy was under review for 2015. Input was mixed on treatment of GERD with transesophageal RF 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 TIF using EsophyX, input was received from 2 physician specialty societies and 4 academic medical centers while this policy was under review in 2011. The reviewers agreed that TIF is sufficiently different from laparoscopic Nissen fundoplication to warrant evaluation as a separate procedure. The reviewers considered TIF (ie, EsophyX®) to be investigational for the treatment of GERD.

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. ASGE gave a number of recommendations based on moderate or high-quality evidence for the endoscopic evaluation of GERD. ASGE suggested, based on low-quality evidence, that antireflux therapy be considered for selected patients with uncomplicated GERD.
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
The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) provided evidence-based guidelines on endoluminal treatments for GERD in 2013. SAGES gave a weak recommendation based on low-quality evidence for the EsophyX procedure, stating that long-term data are not yet available and that further studies are required to define optimal techniques and most appropriate patient selection criteria, and to further evaluate device and technique safety. SAGES gave a strong recommendation based on high-quality evidence that Stretta is considered appropriate therapy for patients being treated for GERD who are 18 years of age or older, who have had symptoms of heartburn, regurgitation, or both for 6 months or more, who have been partially or completely responsive to antisecretory pharmacologic therapy, and who have declined laparoscopic fundoplication.

American Society of General Surgeons
The American Society of General Surgeons (ASGS) issued a position statement on transoral fundoplication in 2011 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.”

American Gastroenterological Association
The 2008 Medical Position Statement of the American Gastroenterological Association makes no recommendation for or against “the use of currently commercially available endoluminal antireflux procedures in the management of patients with an esophageal syndrome” based on insufficient evidence (grade insufficient).

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-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. 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 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. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.\(^\text{39}\)

The 2004 Guidance from NICE 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 for consent and for audit or research.”\(^\text{40}\)

**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 6.

**Table 6. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
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<tbody>
<tr>
<td><strong>Ongoing</strong></td>
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<tr>
<td>NCT01118585(^a)</td>
<td>Prospective Outcome Evaluation of Transoral Incisionless Fundoplication (TIF) for the Treatment of Gastroesophageal Reflux Disease (GERD): The TIF Registry Study</td>
<td>500</td>
<td>Dec 2016</td>
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<tr>
<td>NCT01110811(^a)</td>
<td>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</td>
<td>60</td>
<td>Mar 2017</td>
</tr>
<tr>
<td>NCT02211105(^a)</td>
<td>Laparoscopic Nissen Fundoplication (LNF) Surgery Versus Transoral Incisionless Fundoplication (TIF): Anti- Reflux Treatment Registry</td>
<td>500</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT01682265</td>
<td>Stretta in Reflux Uncontrolled by Intake of Inhibitors of Protons Pump (IPP)-The SIRUP Trial-Multicentric, Randomized, Double Blind, Prospective Study</td>
<td>60</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT02366169(^a)</td>
<td>A Worldwide Post-Market Surveillance Registry to Assess the Medigus Ultrasonic Surgical Endostapler (MUSE™) System for the Treatment of GERD</td>
<td>200</td>
<td>Dec 2019</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>CPT/HCPCS</th>
<th>Description</th>
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<tbody>
<tr>
<td>43201</td>
<td>Esophagoscopy, flexible, transoral; with directed submucosal injection(s), any substance</td>
</tr>
<tr>
<td>43210</td>
<td>Esophagogastroduodenoscopy, flexible, transoral; with esophagogastic fundopasty, partial or complete, includes duodenoscopy when performed</td>
</tr>
<tr>
<td>43212</td>
<td>Esophagoscopy, flexible, transoral; with placement of endoscopic stent (includes pre- and post-dilatation and guide wire passage, when performed)</td>
</tr>
<tr>
<td>43236</td>
<td>Esophagogastroduodenoscopy, flexible, transoral; with directed submucosal injection(s), any substance</td>
</tr>
<tr>
<td>43257</td>
<td>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</td>
</tr>
<tr>
<td>43266</td>
<td>Esophagogastroduodenoscopy, flexible, transoral; with placement of endoscopic stent (includes pre- and post-dilation and guide wire passage, when performed)</td>
</tr>
<tr>
<td>43499</td>
<td>Unlisted procedure, esophagus</td>
</tr>
<tr>
<td>43659</td>
<td>Unlisted laparoscopy procedure, stomach</td>
</tr>
</tbody>
</table>

- There is a 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

<table>
<thead>
<tr>
<th>12-15-2009</th>
<th>In Header Section:</th>
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<tbody>
<tr>
<td></td>
<td>Changed title From: Endoscopic gastroplasty for gastroesophageal reflux disease (GERD) and weight reduction To: Transesophageal Endoscopic Therapies for Gastroesophageal Reflux Disease</td>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No change in policy intent was made, however, wording was updated to current version From:</td>
</tr>
<tr>
<td></td>
<td>“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:</td>
</tr>
<tr>
<td></td>
<td>1. Transesophageal endoscopic gastroplasty (i.e., the Endocinch procedure)</td>
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</tbody>
</table>
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."
- Revised 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
- 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) (i.e., 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

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<th>Rationale section updated</th>
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<td>Added &quot;See Also: Injectable Bulking Agents for the Treatment of Urinary and Fecal Incontinence&quot;</td>
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<td>Corrected Professional and Institutional Current Effective Date from January 1, 2016 back to July 21, 2015.</td>
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<tr>
<td>02-09-2016</td>
<td>Description section updated</td>
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<tr>
<td></td>
<td>Coding notations updated</td>
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</tr>
<tr>
<td></td>
<td>Added &quot;Experimental / Investigational for all diagnoses related to this medical policy.&quot; as this was erroneously left off of prior versions.</td>
<td></td>
</tr>
<tr>
<td>03-10-2017</td>
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<tr>
<td></td>
<td>Coding notations updated</td>
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REFERENCES


34. ASGE Standards of Practice Committee, Muthusamy VR, Lightdale JR, et al. The role of endoscopy in the management of GERD. Gastrointest Endosc. 2015;81(6):1305-1310. PMID 25863867


Other References