Prior Authorization Review
Panel MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
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Plan: Aetna Better Health	**Submission Date**: 10/01/2018
Policy Number: 0213	**Effective Date:** **Revision Date:**
Policy Name: Gastroesophageal Reflux Disease (GERD): Treatment Devices	

Type of Submission – Check all that apply:

- ☐ **New Policy**
- ☒ **Revised Policy***
- ☐ **Annual Review – No Revisions**

***All revisions to the policy must be highlighted using track changes throughout the document. Please provide any clarifying information for the policy below:**

CPB 0213 Gastroesophageal Reflux Disease (GERD): Treatment Devices

Clinical content was last revised 05/13/2016. Additional non-clinical updates were made by Corporate since the last PARP submission, as documented below.

Revision and Update History since last PARP submission:
05/24/2018 - This CPB has been updated with additional background information and references.
02/28/2019 – Next tentative scheduled review date by Corporate
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Name of Authorized Individual (Please type or print):	**Signature of Authorized Individual:**
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(https://www.aetna.com/)

Gastroesophageal Reflux Disease (GERD): Treatment Devices

Number: 0213

Please see amendment for Pennsylvania Medicaid at the end of this CPB.

Policy

I. Aetna considers the Bard EndoCinch Suturing System (C.R. Bard Inc., Murray Hill, NJ) experimental and investigational for the management of members with gastro-esophageal reflux disease (GERD) and all other indications because there is insufficient published scientific evidence to support the effectiveness of these interventions, especially with respect to long-term outcomes.

II. Aetna considers the StomaphyX or EsophyX (EndoGastric Solutions, Inc., Redmond, WA) experimental and investigational for the management of members with gastro-esophageal reflux disease (GERD) and all other indications because there is insufficient published scientific evidence to support the effectiveness of these interventions, especially with respect to long-term outcomes.

Policy History

Last Review
05/24/2018
Effective: 03/16/1998
Next Review: 02/28/2019

Review History

Definitions

Additional Information

Clinical Policy Bulletin Notes

III. Aetna considers the Stretta System (Curon Medical, Sunnyvale, CA) experimental and investigational for the management of members with gastro-esophageal reflux disease (GERD) and all other indications because there is insufficient published scientific evidence to support the effectiveness of these interventions, especially with respect to long-term outcomes.

IV. Aetna considers the use of the Angelchik anti-reflux prosthesis experimental and investigational for the management of GERD and all other indications because it has not been shown to be as safe and effective as other options for the treatment of GERD or other indications.

V. Aetna considers the use of Enteryx experimental and investigational for the management of GERD and all other indications because it has not been established as an effective option for the treatment of GERD or other indications.

VI. Aetna considers the use of the Endoscopic Plicator System (NDO Surgical, Inc., Mansfield, MA) and the Syntheon ARD Plicator (Syntheon, Miami, FL) experimental and investigational for the management of GERD and all other indications because it has not been established as an effective option for the treatment of GERD and other indications.

VII. Aetna considers the LINX Reflux Management System (a sphincter augmentation device) (Torax Medical, Shoreview, MN) experimental and investigational for the management of GERD and all other indications because it has not been established as an effective option for the treatment of GERD and other indications.

VIII. Aetna considers the Durasphere (Carbon Medical Technologies, St Paul, MN), the Gatekeeper Reflux Repair System (Medtronic, Inc., Minneapolis, MN), an endoscopically-implanted injectable esophageal prosthesis, and the Plexiglas polymethylmethacrylate (PMMA) microspheres (Arkema Inc., Bristol, PA) experimental and investigational for the management of GERD and all other indications because it has not been established as an effective option for the treatment of GERD and other indications.

IX. Aetna considers electrical stimulation of the lower esophageal sphincter (e.g., the EndoStim) for the treatment of GERD experimental and investigational because its effectiveness has not been established.

See also
CPB 0728 - Barrett's Esophagus (../700_799/0728.html).

Background

Gastroesophageal reflux disease (GERD), also known as reflux esophagitis, is probably the most prevalent clinical condition that arises from the gastrointestinal (GI) tract. There are 2 principal factors involved in esophageal reflux: (i) the GI contents and (ii) the anti-reflux mechanism, which is comprised of the lower esophageal sphincter (LES) and the anatomic configuration of the gastroesophageal junction. Reflux occurs when the gradient between the LES pressure and the intra-gastric pressure is compromised as a result of a transient or sustained reduction in the former, or an elevation in the latter. Most patients with GERD have decreased LES pressures. However, some patients have normal LES pressures, but their sphincters relax inappropriately, thus resulting in refluxes. Treatments for gastroesophageal reflux disease (GERD) are designed to improve the function of the

lower esophageal sphincter (LES). The objectives are to eliminate symptoms, heal esophagitis, prevent recurrence of symptoms or progression of disease. The initial treatment of GERD is geared toward reducing esophageal refluxes. Antacids, H2-receptor antagonists, as well as dietary and lifestyle modifications have been used for such purposes. For patients who fail initial treatment, proton pump inhibitors (e.g., lansoprazole and omeprazole) should be tried. When these standard medical therapies fail, surgery may be considered.

Anti-reflux surgery is required in only 1 to 2 % of all patients with GERD. These procedures are designed to raise the pressure within the LES by wrapping a portion or all of the cardia stomach around the esophagus. With the advent of laparoscopic anti-reflux surgery, the 2 most common procedures are the Nissen fundoplication and the Toupet partial fundoplication. The most commonly used surgical procedure, Nissen fundoplication (open or laparoscopic), is the mobilization of the lower end of the esophagus and plication of the fundus of the stomach around it. Dependent on the skill and experience of the operating surgeon, anti-reflux surgery has been reported to have an efficacy rate of 90 %. These operations are usually performed on the day of hospital admission and take about 90 mins. In general, patients are discharged from the hospital on the second post-operative day and can return to work in 7 to 10 days. Other surgical options include Belsey partial fundoplication as well as Collis gastroplasty combined with Belsey partial fundoplication. However, anti-reflux surgery can be associated with complications. The most common complications are dysphagia and an inability to belch or vomit, occurring in 4 to 11 % of patients.

A number of minimally invasive devices are marketed to provide a treatment option to patients who have failed standard medical therapies, or individuals who decide against or could not afford drug therapy. However, there is insufficient scientific data to support the effectiveness of these devices.

Well-designed studies are needed to show that these procedures reduce or eliminate the use of anti-GERD medications. Comparative studies with standard drug therapy and traditional surgical procedures may shed some light on the role these devices play in the treatment of GERD. Some of the issues that have to be addressed are: (i) what are the long-term outcomes of these procedures, and (ii) do patients need retreatment, and if so, how often?

In a review on endoscopic and laparoscopic treatment of GERD, Watson and Immanuel (2010) staetd that for selected patients, there is an established role for the surgical treatment of reflux, and possibly an emerging role for endoscopic anti-reflux procedures. Randomized trials have compared medical versus surgical management, laparoscopic versus open surgery and partial versus total fundoplications. However, the evidence base for endoscopic procedures is limited to some small sham-controlled studies, and uncontrolled cohort studies. Laparoscopic fundoplication has been shown to be an effective anti-reflux operation. It facilitates quicker convalescence and is associated with fewer complications, but has a similar longer term outcome compared with open anti-reflux surgery. In most randomized trials, anti-reflux surgery achieves at least as good control of reflux as medical therapy, and these studies support a wider application of surgery for the treatment of moderate-to-severe reflux. Laparoscopic partial fundoplication is an effective surgical procedure with fewer side effects, and it may achieve high rates of patient satisfaction at late follow-up. Many of the early endoscopic anti-reflux procedures have failed to achieve effective reflux control, and they have been withdrawn from the market.
Newer procedures have the potential to fashion a surgical fundoplication. However, at present there is insufficient evidence to establish the safety and efficacy of endoscopic procedures for the treatment of GERD, and no endoscopic procedure has achieved equivalent reflux control to that achieved by surgical fundoplication.

Bredenoord (2010) stated that it is estimated that approximately 30 % of the GERD patients is not satisfied about the effect of proton pump inhibitor (PPI) on their symptoms. Esophageal hyper-sensitivity, persistent non-acid reflux and incomplete acid suppression all can play a role in the pathogenesis of persistent GERD symptoms. More powerful PPIs are now being developed, resulting in a more prolonged and profound acid suppression. New prokinetics and inhibitors of transient lower esophageal sphincter relaxations (TLESRs) can potentially reduce both acid and non-acid reflux and drugs that reduce hyper-sensitivity are possibly helpful for the treatment of non-erosive reflux disease. Whether these drugs will make it to the markets will mainly depend on their side effect profile and their ability to have an additional beneficial effect over the current gold standard therapy as it likely that a new anti-reflux drug will be used in combination with PPIs. Over the last decade various endoscopic anti-reflux techniques have been introduced, most of them have been withdrawn soon after introduction due to lack of effect or after the occurrence of severe side-effects. Several endoluminal plication techniques and endoluminal RF ablation therapy are still available and being evaluated in research centers; but more data on safety and efficacy is needed before a more widespread use can be advised.

A systematic evidence review prepared for the Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S) (McLoughlin et al, 2006) reached the following conclusions about endoscopic treatments of GERD: "The scope, applicability, efficacy and cost effectiveness of endoscopic anti-reflux therapies for the treatment of GORD have not been established. These procedures may provide an alternative treatment for selected patients with mild to moderate GORD who are dependent on medication and are reluctant or unable to undergo surgery. However, a substantial placebo effect has been demonstrated in sham controlled trials, and endoscopic results were generally inferior when compared with laparoscopic fundoplication. Doubts

about the durability of the therapeutic effect remain since the follow-up period in most studies was short."A systematic evidence review prepared for the Agency for Healthcare Research and Quality (Ip et al, 2005) reached similar conclusions about the need for reliable evidence about endoscopic treatments for GERD. The assessment found that data on comparative endoscopic treatments with continued (or intensified) use of PPIs are needed to better understand their efficacy compared to an established standard. The report also noted the need for more efficacy and safety data on new endoscopic approaches tested against a sham procedure with adequate follow-up.

Other reviews of the evidence have reached similar conclusions about the unproven status of endoscopic treatments for GERD, Schwarz and Smout (2007) reported that endotherapy has shown the potential to treat (uncomplicated) GERD, but that some procedures have failed or proven unsafe. The authors concluded: "Further developments and studies are necessary to determine what modifications to these techniques are required to produce optimal efficacy and durability. Until then, widespread clinical use of endotherapy for GORD should probably be avoided." Triadafilopoulos (2007) noted that future comparative studies with pre-determined clinically significant end points, validated outcome measures, prolonged follow-up, and complete complication registries will eventually determine the precise role of endoscopic therapies for patients with GERD.

In a review on endoscopic anti-reflux procedures, Pace et al (2008) concluded that none of the proposed anti-reflux therapies has fulfilled the criteria of efficacy, safety, cost, durability and, possibly, of reversibility. There is at present no definite indication for endoscopic therapy of GERD.

Endocinch:

EndoCinch Suturing System is suggested for endoscopic placement of sutures in the soft tissue of the esophagus and stomach and for approximation of tissue.

The Food and Drug Adminsitration (FDA) cleared for marketing via a 510 (k) application minimally invasive devices for the treatment of refractory GERD including: (i) the Bard EndoCinch Suturing System (BESS), and (ii) the Stretta System. The BESS entails insertion of a thin, flexible endoscopic tube into the patient's esophagus. The end of the scope holds a tiny device, much like a miniature sewing machine, which places stitches in 2 different locations near the LES. The suturing material is then tied to effectively tighten the valve and prevent reflux. The procedure requires no incisions and usually no general anesthesia. It is performed on an outpatient basis, and patients usually can return to work the next day.

Jafri and colleagues (2009) analyzed existing endoscopy-based interventions for GERD. The focus is on the effectiveness of available procedures and to delineate goals for future research. These investigators noted that recent evaluations of the EndoCinch system reveal poor long-term results and no significant improvement over sham therapy due to poor apposition of mucosa with stitches. Recent studies with transoral incisionless fundoplication demonstrate improvement in GERD symptoms, quality of life, esophageal acid exposure, esophagitis, resting LES pressure and medication use. The SRS endoscopic stapling system creates a partial fundoplication wrap, and a preliminary study demonstrated improved symptoms and acid exposure. The Stretta system delivers RF energy to the gastro-esophageal junction. A large prospective series demonstrates sustained improvement in GERD symptoms, quality of life and PPI therapy elimination after RF ablation at the gastro-esophageal junction. A sham-controlled study showed improvement in symptoms at 6 months. The authors concluded that

EndoCinch plication requires further study and modification of technique before it can be recommended for general clinical use. Transoral incisionless fundoplication is a very promising procedure in its early stages of development. They stated that further evaluation of procedure safety and durability is needed. Radiofrequency ablation therapy has been re-introduced and may have potential in patients with refractory GERD.

In a systematic review, Chen et al (2009) evaluated the safety and effectiveness of endoscopic procedures for GERD. Randomized controlled trials and non-randomized comparative studies with at least 10 patients in each study arm, and case series studies of at least 10 patients, were included. A total of 33 studies examining 7 endoscopic procedures (Stretta procedure, Bard EndoCinch, Wilson-Cook Endoscopic Suturing Device, NDO Plicator, Enteryx, Gatekeeper Reflux Repair System and Plexiglas) were included in the review. Of the 3 procedures that were tested against sham controls (Stretta procedure, Bard EndoCinch and Enteryx), patient outcomes in the treatment group were either as good as, or significantly better than, those of control patients in terms of heartburn symptoms, quality of life and medication usage. However, for the 2 procedures that were tested against laparoscopic fundoplication (Stretta procedure and Bard EndoCinch), outcomes for patients in the endoscopic group were either as good as, or inferior to, those for the laparoscopic group. The authors concluded that currently there is insufficient evidence to determine the safety and effectiveness of endoscopic procedures for GERD, especially in the long-term.

StomaphyX:

In March 2007, the FDA granted 510(k) premarketing clearance to the StomaphyX (EndoGastric Solutions, Inc.), an endoluminal fastener and delivery system used to tighten esophageal tissue. The FDA clearance indicated that the

StomaphyX is substantially equivalent to EndoCinch. In September 2007, the FDA granted 510(k) premarketing clearance to the EsophyX System with SerosaFuse Fastenter (Endogastric Solutions, Inc.) as being substantially equivalent to the StomaphyX and EndoCinch devices. The EsophyX System is designed to perform a transoral incisionless fundoplication procedure using to reconstruct a valve at the gastro-esophageal junction through transoral delivery of multiple fasteners. Cadiere et al (2008) reported on the outcome of a short-term, uncontrolled study of the EsophyX system for treating GERD. A total of 86 patients with chronic GERD treated with proton pump inhibitors (PPIs) were enrolled. Exclusion criteria included an irreducible hiatal hernia greater than 2 cm. At 12 months, 73 % of study subjects had 50 % or greater improvement in GERD health-related quality of life scores, and 81 % of study subjects discontinued PPI use. However, less than half (37 %) of study subjects had normalization of esophageal acid exposure. Serious adverse events consisted of 2 esophageal perforations upon device insertion and 1 case of post-operative intraluminal bleeding. The investigators reported that other adverse events were mild and transient.

Transoral Incisionless Fundoplication and EsophyX:

Transoral Incisionless Fundoplication (TIF) with EsophyX is inserted through the patient's mouth under visual guidance of an endoscope, the EsophyX device is purportedly used to construct a durable antireflux valve with SerosaFuse Fasteners and tighten the LES, supposedly reestablishing a barrier to reflux and restoring the competency of the gastroesophageal junction.

An assessment of endoluminal gastroplication for GERD by the National Institute for Clinical Excellence (2005) concluded that "[c]urrent evidence on the safety and efficacy of endoluminal gastroplication for gastro-oesophageal reflux disease (GORD) does not appear adequate for this procedure

to be used without special arrangements for consent and for audit or research." Specialist advisors to NICE expressed concerns about the long-term effectiveness of this procedure.

In a retrospective study, Bergman and co-workers (2008) examined the safety and effectiveness of the first generation EsophyX system in patients with GERD who had undergone endolumenal fundoplication with the device. At follow-up, PPI usage was elicited and 2 validated questionnaires were administered measuring GERD health-related quality of life (range of 0 to 50) and symptom severity (range of 0 to 72). In limited preliminary evaluation, the initial North American experience with endolumenal fundoplication using the EsophyX device is that it appears to be safe and provides moderate effectiveness in treating the symptoms of GERD. Moreover, the authors stated that further studies comparing this technique with conventional medical and surgical therapies are necessary.

The American Society of General Surgeons' position statement on "Natural orifice surgery and transoral incisionless fundoplication" (ASGS, 2009) stated that "ASGS supports the continued development and refinement of this procedure as well as other appropriate natural orifice procedures performed by adequately trained general surgeon specialists". While the ASGS Board of Trustees issued a favorable position statement regarding transoral incisionless fundoplication (TIF); its recommendation does not appeared to be based from a full-fledged technology assessment of the procedure.

In a retrospective study, Barnes et al (2011) evaluated the clinical outcomes in 124 consecutive gastro-esophageal reflux disease (GERD) patients who underwent transoral incisionless fundoplication (TIF) using the second generation Esophyx device (Esophyx2) at 2 community hospitals. Out of 123 patients treated successfully, 110 gave consent (74 % females, median age 60 [range of 21 to 87] years, BMI 27.5 [19.0 to 47.9]). At a median 7-month follow-up (range of 5 to

17), typical and atypical symptom scores were normalized in 75 % to 80 % of patients, PPIs were completely discontinued by 93 %, and 83 % were satisfied with their current health condition. Endoscopy in 53 patients revealed Hill grade I tight valves in 89 % of the cases, reduced hiatal hernia in 33/34 (97 %), and healed reflux esophagitis in 25/30 (83 %). Based on global analysis, 72 % of the patients were in remission, 20 % improved symptomatically, and only 8 % had ongoing GERD. These results supported the safety and efficacy of TIF as well as encouraged its application as an alternative treatment of GERD refractory to PPIs. The drawbacks of this study were its retrospective nature (symptom data at baseline were based on retrospective recall) and short-term follow-up. Furthermore, the lack of pH measuring systems at the authors' institutions prevented these researchers from measuring esophageal acid exposure before and after TIF.

Bell and Freeman (2011) retrospectively evaluated the safety and effectiveness of a rotational/longitudinal esophagogastric TIF with the second generation Esophyx device using subjective and objective outcomes. A total of 37 consecutive patients on anti-secretory medication and with proven GERD and limited hiatal hernia underwent TIF for persistent GERD symptoms. Five patients were re-operated for failed laparoscopic fundoplication. Of the 37 treated patients, 57 % were female. The median age was 58 (range of 20 to 81) years and body mass index (BMI) was 25.5 (range of 15.9 to 36.1) kg/m(2). Sixty-eight percent indicated GERD-associated cough, asthma, or aspiration as a primary complaint and 32 % complained of heartburn or regurgitation. The TIF procedures created tight wraps of 230˚to 330˚extending 3-4 cm above the Z-line. Two complications occurred: 1 mediastinal abscess treated laparoscopically and 1 post-operative bleeding requiring transfusion. At 6 (range of 3 to 14) months median follow-up, TIF resulted in a significant improvement of both atypical and typical symptoms in 64 % and 70 to 80 % of patients, respectively, as indicated by the corresponding GERD health-related quality of life (HRQL) and reflux symptom

index (RSI) score reduction by 50 % or more compared to baseline on proton pump inhibitors (PPIs). No patient reported problems with dysphagia, bloating, or excess flatulence, and 82 % were not taking any PPIs. Reflux characteristics were significantly improved and normalized in 61, 89, and 56 % of patients in terms of acid exposure, number of refluxates, and DeMeester scores, respectively. TIF was effective in treating GERD in 75 % of patients among whom 54 % were in a complete "remission" and 21 % were "improved". The remaining 25 % were considered failures, and 5 (13.5 %) patients underwent revision. The authors concluded that rotational/longitudinal esophagogastric fundoplication using the EsophyX device significantly improved symptomatic and objective outcomes in over 70 % of patients at median 6-month follow-up. Post-fundoplication side effects were not reported after TIF. This was a small, retrospective study with short-term follow-up; its findings need to be validated by well-designed studies.

Testoni et al (2012) assessed the long-term effect of TIF using the second generation Esophyx device in patients with symptomatic GERD. TIF 2.0 fundoplication was done in 42 consecutive patients. All were studied with GERD-HRQL and GERD-QUAL questionnaires, upper gastrointestinal (GI) endoscopy, esophageal manometry, and 24-hr pH impedance before and at 6, 12, and 24 months after TIF. In all, 35 patients completed 6-month follow-up; 21 (60.0 %) completely stopped proton pump inhibitor (PPI) therapy, 6 (17.1 %) more than halved it, and 8 (22.9 %) continued with the same dose as before the procedure. There were 26 patients with complete 24-month follow-up; 11 (42.3 %) completely stopped PPI therapy, 7 (26.9 %) more than halved it, and 8 (30.8 %) were taking the same dose as before the procedure. Hiatal hernia and ineffective esophageal motility seemed to raise the risk of recurrence of symptoms ($p = 0.02$ and $p < 0.001$, respectively). The number of fasteners deployed during TIF was the only factor predictive of successful outcome ($p = 0.018$). The authors concluded that TIF using the EsophyX

device allowed withdrawal or reduction of PPI in about 77 % of patients at 6-month follow-up and about 69 % at 24 months. Larger number of fasteners deployed during TIF was predictive of positive outcome; pre-TIF ineffective esophageal motility and hiatal hernia raised the risk of recurrence of GERD symptoms, but were not significant from a prospective point of view. The major drawback of this small study was its uncontrolled design. Also, while 77 % of patients stopped or at least halved PPI use at 6-month follow-up; this proportion dropped to about 69 % at 24-month evaluation, raising concerns regarding how long fundoplication lasts with the current technique. The authors stated that "[i]n light of these results and awaiting randomized controlled studies on larger series, the TIF procedure can at present be offered as a complement to medical therapy or an alternative to surgery only in selected patients with small or no hiatal hernia, who refuse surgery or do not want long-term PPI therapy, or are intolerant or partial responders to PPI".

In a retrospective study, Trad et al (2012) evaluated safety, symptom resolution, patient satisfaction, and medication use 1 to 2 years after TIF using the second generation Esophyx device in patients with GERD and/or laryngopharyngeal reflux (LPR) symptoms. A total of 34 patients with a confirmed diagnosis of GERD symptoms that were inadequately controlled by anti-secretory medications, and who where either dissatisfied with their current therapy or not willing to continue taking medication, underwent TIF using EsophyX at the authors' community-based hospital. Follow-up assessments were completed in 28 patients. Median age of the study group was 57 years (range of 23 to 77), BMI was 25.7 (18.3 to 36.4) kg/m(2), and 50 % were female. All patients had documented chronic GERD for a median 5 years (1 to 20) and refractory symptoms to PPIs. Hiatal hernia was present in 75 % (21/28) of patients, and 21 % (6/28) had erosive esophagitis (LA grade A or B). Transoral incisionless fundoplication was performed following a standardized TIF-2 protocol and resulted in reducing hiatal hernia and restoring the natural anatomy of the

gastroesophageal (GE) junction (Hill grade I). There were no post-operative complications. At a median 14-months follow-up, 82 % (23/28) of patients were off daily PPIs (64 % completely off PPIs), and 68 % (19/28) were satisfied with their current health condition compared to 4 % before TIF. Median GERD-HRQL scores were significantly reduced to 4 (0 to 25) from 26 (0 to 45) before TIF ($p < 0.001$). Heartburn was eliminated in 65 % (17/26) and improved by greater than 50 % in 86 % (24/28) of patients. Regurgitation was eliminated in 80 % (16/20) of patients. Atypical LPR symptoms such as hoarseness, coughing, and throat clearing were eliminated in 63 % (17/27) of patients as measured by Reflux Symptom Index scores. The authors concluded that these findings in 28 patients confirmed the safety and effectiveness of TIF, documenting symptomatic improvement of GERD and LPR symptoms and clinically significant discontinuation of daily PPIs in 82 % of patients. Limitations of this study included its retrospective, single-center design, small sample size and a lack of follow-up comparative pH/impedance monitoring data. The authors are currently enrolling patients in a prospective, multi-center TIF Registry.

Svoboda et al (2011) stated that natural orifice transluminal surgery (NOTES) has been introduced in endoscopic surgery as a new system offering the advantage of a less invasive procedure. Gastro-esophageal reflux disease appears to be the most promising application of NOTES treatment. The aims of our study were to evaluate the safety and efficacy of this procedure and length of hospital stay. Patients indicated for surgery of GERD were randomly assigned (ratio 2:1) to TIF ($n = 34$) using the first generation Esophyx device and control group, where gold standard Nissen laparoscopic fundoplication was performed (NLF group, $n = 18$). For TIF, the Plicator method was initially used for 18 patients, but the company terminated production in 2008 without a follower. During the last 2 years the EsophyX method was used for 16 patients. After the evaluation of 34 TIF patients and 18 NLF patients we observed similar efficacy of TIF procedures

compared with NLF after 3 and 12 months. The hospital stay was significantly shorter ($p < 0.0001$) in TIF group (average of 2.9 +/- 0.8 days) than in NLF group (6.4 +/ - 0.7). The TIF procedure was safe; 1 serious adverse event in the TIF group and 3 in the NLF group were observed. The authors concluded that both NOTES TIF procedures were, after the initial learning curve, safe and effective methods for treatment of GERD, allowing substantial shortening of hospital stay. The effect of both procedures was sustained over 12 months. Moreover, they noted that longer follow-up is necessary to verify efficacy for more years.

Zagol and Mikami (2011) evaluated transoral fundoplication devices for GERD that have been commercially available within the last 5 years. Literature databases including Medline and PubMed were searched from January 2005 to November 2010. Both blinded and unblinded randomized studies were evaluated. These investigators reviewed the literature for evaluations of primary transoral endoluminal fundoplication devices which included EndoCinch, NDO Plicator, Esophyx, and Stretta. Reviews of all studies with greater than 20 patients were evaluated to assess the efficacy and safety of transoral fundoplication devices. These endoluminal devices were primary matched against sham procedures. The EndoCinch and Stretta procedures were the only devices compared to laparoscopic fundoplication, the current standard for surgical management of GERD. The authors concluded that the field of endoluminal treatment of GERD has gained popularity over the last several years. Endoluminal treatment of GERD has been shown to be safe and effective in recent studies. The authors still believe more randomized prospective studies need to be carried out to determine if endoluminal therapies will be a durable option for patients with GERD. Continuing research will further the advancement of endoluminal GERD procedures in the future. Also, Frazzoni et al (2011) concluded that in patients with refractory GERD,

EsophyX fundoplication is significantly less effective than laparoscopic fundoplication in improving reflux parameters and accordingly, in inducing symptom remission.

The Agency for Healthcare Research and Quality's updated evidence report on "Treatment options for GERD or acid reflux disease" (AHRQ, 2011) compared the risks and benefits of treatments for GERD. The report stated that "[t]hree types of endoscopic treatments are EndoCinch™, Stretta®, and EsophyX™. These treatments are very new and are not as common as medicines or surgery to treat GERD. People receiving one of these treatments may be in a study to see how well it works. There are not enough studies to say how well endoscopic treatments (EndoCinch™, Stretta®, and EsophyX™) work to control the symptoms of GERD". Regarding the EndoCinch procedure, the AHRQ assessment (Ip, et al., 2011) concluded that the quality of evidence was "low", consisting of two sham-controlled studies and 6 noncomparative cohort studies. The AHRQ report found that no consistent differences between EndoCinch and sham were reported, and that significant improvements in heartburn, qualtiy of life, and esophagitis healing were found in some but not all cohort studies. The AHRQ assessment (Ip, et al., 2011) found the strength of evidence for the EsophyX procedure was "insufficient," consisting of five small cohort studies. The reported proportion of patients who were off PPIs at the end of the followup period ranged from 47 to 71%. Significant improvement of quality as measured by the GERD-HRQL scale was reported by 2 of 5 studies. The AHRQ assessment (Ip, et al., 2011) found "insufficient" evidence for the.Stretta procedure, consisting of one sham-controlled study and 7 noncomparative cohort studies. In the randomized controlled trial, the proportion of patients who stopped or decreased PPI use was significantly greater in the Stretta group than the control group at 6 months (but it was not significant at 1 year). No significant differences in heartburn symptoms, quality of life, acid exposure, and esophagitis

outcomes were found. The majority of cohort studies found significant improvements in GERD symptoms, quality of life, and medication use.

In a prospective, open-label, multi-center, single-arm study, Bell et al (2012) attempted to validate previously reported safety and symptomatic outcomes of TIF: (i) evaluate the relative benefit of TIF within different GERD subgroups, and (ii) determine predictors of success in community settings. Between January 2010 and February 2011, a total of 100 consecutive patients who underwent TIF procedures using the second generation Esophyx device at 10 centers were enrolled in this study. Symptom improvement and objective outcomes of TIF were analyzed at 6-month follow-up. One hundred TIF procedures were performed. No complications were reported. Median GERD symptom duration was 9 years (range of 1 to 35 years) and median duration of PPI use was 7 years (1 to 20 years). Maximal medical therapy resulted in incomplete symptom control for 92 % of patients; GERD-HRQL total score was normalized in 73 %. Median heartburn and regurgitation scores improved significantly, from 18 (range of 0 to 30) and 15 (range of 0 to 30) on PPIs before TIF to 3 (range of 0 to 25) and 0 (range of 0 to 25), respectively; $p < 0.001$. Median Reflux Symptom Index scores were reduced after TIF from 24 (range of 14 to 41) to 7 (range of 0 to 44); $p < 0.001$. Eighty percent of patients were completely off PPIs after TIF versus 92 % of patients on PPIs before TIF. Pre-operative factors associated with clinical outcomes were less severe heartburn (total GERD-HRQL less than or equal to 30, $p = 0.02$) and the presence of esophagitis ($p < 0.02$). The authors concluded that TIF is safe and effective in multiple community-based settings in the treatment of medically refractory GERD, as demonstrated by an absence of complications, excellent symptom relief, and complete cessation of PPIs at 6-month follow-up. The main drawbacks of this study were its non-randomized nature and short-term

follow-up. Furthermore, TIF is not as effective in primary symptom response as traditional laparoscopic fundoplication.

Muls et al (2013) prospectively evaluated the long-term safety and durability of TIF using the first generation Esophyx device in a multi-center setting. A longitudinal per protocol (PP) and a modified intention-to-treat (mITT) analysis at 1 and 3 years consisted of symptom evaluation using the GERD-HRQL questionnaire, medication use, upper GI endoscopy, and pH-metry. Of 79 patients previously reported at 1 year, 12 were lost to follow-up, and 1 died from an unrelated cause. The remaining 66 patients were followed-up and analyzed (mITT). Of 66 patients, 12 underwent revisional procedures, leaving 54 patients for PP analysis at a median of 3.1 years (range of 2.9 to 3.6). No adverse events related to TIF were reported at 2- or 3-year follow-up. On PP analysis, median GERD-HRQL score off PPIs improved significantly to 4 (range of 0 to 32) from both off (25 [13 to 38], $p < 0.0001$) and on (9 [0 to 22], $p < 0.0001$) PPIs. Discontinuation of daily PPIs was sustained in 61 % (mITT) and 74 % (PP) of patients. Of 11 patients with pH data at 3 years (PP), 9 (82 %) remained normal. Based on mITT analysis, 9/23 (39 %) remained normal at 3 years. The authors concluded that the clinical outcomes at 3 years following TIF, patient satisfaction, healing of erosive esophagitis, and cessation of PPI medication support long-term safety and durability of the TIF procedure for those with initial treatment success. Moreover, they noted that although complete normalization of pH studies occurred in a minority of patients, successful cases showed long-term durability. Furthermore, they stated that “the steep learning curve with the EsophyX device may negatively influence the results of this study. Perhaps, multi-center studies with surgeons who are through their learning curve with a focus primarily on physiological outcomes may further define the role of TIF in the management of chronic GERD in the future”.

The Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (2013) identified the Stretta, Esophyx, Linx, and EndoStim as procedures that are under research and offered at specialist centers performing suitable registered research projects.

Yew and Chuah (2013) discussed the past and present status of anti-reflux endoluminal therapy. Currently, there are 3 commonly employed anti-reflux endoluminal procedures: (i) fundoplication or suturing techniques (EndoCinch, NDO, and EsophyX), (ii) intramural injection or implant techniques enhancing LES volume and/or strengthening compliance of the LES-Enteryx and Gatekeeper), and (iii) RF ablation of LES and cardia. EndoCinch plication requires further study and modification of technique before it can be recommended because of durability issues.Esophyx, the TIF, may reduce hiatal hernias and increase LES length. Preliminary studies have shown promising reduction in symptoms and medication use but evidence concerning safety and long-term durability is still pending. The safety issue with injection technique is the main concern as evident from the incidences of implant withdrawals after reported major adverse events. Future research with cautious monitoring is required before any new implant material can be recommended for commercial application. Radiofrequency ablation therapy is regaining popularity in treating refractory symptoms despite PPI use due to improved efficacy, durability, and safety after years of refinement of protocol.

Toomey et al (2014) undertook a case-controlled registry study of three cohorts of 20 patients undergoing TIF or laparoscopic Nissen or Toupet fundoplications from 2010 to 2013 controlling for age, body mass index, and preoperative DeMeester scores. All patients were prospectively followed. Median data are reported. The investigators reported that patients undergoing TIF had significantly shorter operative times (in minutes: 71 vs 119 and 85, respectively, $P < 0.001$) and length

of stay (in days: 1, 2, and 1, respectively, P < 0.001). The authors stated that, no matter the approach, patients reported dramatic and similar reduction in symptom frequency and severity (e.g., heartburn 8 to 0, P < 0.05). At follow-up, 83 per cent of patients after TIF, 80 per cent after Nissen, or 92 per cent after Toupet fundoplications had symptoms less than once per month (P = 0.12).

Kim and colleagues (2013) noted that while acid suppression with PPIs remains the mainstay of treatment of GERD, some patients showed refractory response to PPIs, necessitating further intervention. After increasing dosage of PPIs and other kinds of pharmacological intervention adopting prokinetics or others, variable endoscopic treatments were introduced for the treatment of these refractory cases. Implantation of reabsorbable or synthetic materials in the distal esophagus was tried in vain and is expelled from the market due to limited efficacy and serious complication. The authors stated that RF energy delivery (Stretta) and TIF (EsophyX) are actively tried currently.

Hakansson et al (2015) reported on a double-blind sham-controlled study of TIF in GERD patients who were chronic PPI users. The investigators studied patients with objectively confirmed GERD and persistent moderate to severe GERD symptoms without PPI therapy. Of 121 patients screened, the investigators randomised 44 patients with 22 patients in each group. Those allocated to TIF had the TIF2 procedure completed during general anaesthesia by the EsophyX device with SerosaFuse fasteners. The sham procedure consisted of upper GI endoscopy under general anaesthesia. Neither the patient nor the assessor was aware of the patients' group affiliation. The primary effectiveness end-point was the proportion of patients in clinical remission after 6-month follow-up. Secondary outcomes were: PPI consumption, oesophageal acid exposure, reduction in Quality of Life in Reflux and Dyspepsia and Gastrointestinal Symptom Rating Scale scores and healing of reflux esophagitis. The time

(average days) in remission offered by the TIF2 procedure (197) was significantly longer compared to those submitted to the sham intervention (107), $p < 0.001$. After 6 months 13/22 (59 %) of the chronic GERD patients remained in clinical remission after the active intervention. Likewise, the secondary outcome measures were all in favour of the TIF2 procedure. The authors stated that no safety issues were raised. Limitations of this study included its small size and limited duration of follow-up.

Testoni et al (2015) assessed the long-term effect of TIF 2.0 on pathological reflux and symptoms in GERD patients with daily dependence on PPI. Fifty patients underwent TIF. All underwent GERD-HRQL and GERD-QUAL questionnaires, upper GI endoscopy, esophageal manometry, and 24-h pH-impedance before and 6, 12, and 24 months after TIF, and subsequent yearly clinical re-evaluation. Patients were followed for up to 6 years (mean of 52.7 ± 19.7 months). In all, 83.7, 79.6, 87.8, and 84.4 % of patients stopped or halved the PPI therapy 6, 12, 24, and 36 months after TIF. Three-year figure remained stable up to 6 years. Symptom scores off PPI were significantly lower at 6, 12, 24, and 36 months. At 6 months, Hill's grade I of the newly created valve persisted in all pre-procedure Hill's grade I patients, in 66.7 % of grade II and 58.3 % of grade III. This figure remained substantially unchanged at 12 and 24 months, too. Impedance monitoring indicated significantly fewer total and acid refluxes after treatment ($p = 0.01$). Factors predicting good outcomes were pre-procedure Hill's grade I-II, no hiatal hernia or hernia less than or equal to 2 cm ($p = 0.03$), absence of ineffective esophageal motility ($p < 0.0001$), and number of fasteners deployed ($p = 0.01$). This small, single-center study needs to be replicated in larger multi-center studies.

Hunter et al (2015) performed a prospective, sham-controlled trial to determine if TF reduced troublesome regurgitation to a greater extent than PPIs in patients with GERD. The investigators screened 696 patients with troublesome

regurgitation despite daily PPI use with 3 validated GERD-specific symptom scales, on and off PPIs. Those with at least troublesome regurgitation (based on the Montreal definition) on PPIs underwent barium swallow, esophagogastroduodenoscopy, 48-hour esophageal pH monitoring (off PPIs), and high-resolution esophageal manometry analyses. Patients with GERD and hiatal hernias less than or equal to 2 cm were randomly assigned to groups that underwent TF and then received 6 months of placebo (n = 87), or sham surgery and 6 months of once- or twice-daily omeprazole (controls, n = 42). Patients were blinded to therapy during follow-up period and reassessed at 2, 12, and 26 weeks. At 6 months, patients underwent 48-hour esophageal pH monitoring and esophagogastroduodenoscopy. By intention-to-treat analysis, TF eliminated troublesome regurgitation in a larger proportion of patients (67%) than PPIs (45%) (P = .023). A larger proportion of controls had no response at 3 months (36%) than subjects that received TF (11%; P = .004). Control of esophageal pH improved after TF (mean 9.3 % before and 6.3 % after; p < 0.001), but not after sham surgery (mean 8.6 % before and 8.9 % after). Subjects from both groups who completed the protocol had similar reductions in GERD symptom scores. Severe complications were rare (3 subjects receiving TF and 1 receiving the sham surgery).

Trad et al (2015) reported on a short-term multicenter randomized study compared the efficacy of TIF against PPIs in controlling these symptoms in patients with small hiatal hernias. Between June and August 2012, 63 patients were randomized at 7 US community hospitals. Patients in the PPI group were placed on maximum standard dose (MSD). Patients in the TIF group underwent esophagogastric fundoplication using the EsophyX device. Primary outcome was elimination of daily troublesome regurgitation or extraesophageal symptoms. Secondary outcomes were normalization of esophageal acid exposure (EAE), PPI usage and healing of esophagitis. Of 63 randomized patients (40 TIF

and 23 PPI), 3 were lost to follow-up leaving 39 TIF and 21 PPI patients for analysis. At 6-month follow-up, troublesome regurgitation was eliminated in 97 % of TIF patients versus 50 % of PPI patients, relative risk (RR) = 1.9, 95 % confidence interval (CI): 1.2 to 3.11 (p = 0.006). Globally, 62 % of TIF patients experienced elimination of regurgitation and extraesophageal symptoms versus 5% of PPI patients, RR = 12.9, 95% CI = 1.9-88.9 (P = .009). EAE was normalized in 54% of TIF patients (off PPIs) versus 52% of PPI patients (on MSD), RR = 1.0, 95 % CI: 0.6 to 1.7 (p = 0.914); 90 % of TIF patients were off PPIs.

A review by Lo and Mashimo (2015) noted that, "although these results seem promising, additional research raises the issue of poor efficacy and early treatment failure after TIF". The authors noted that results of TIF have been "mixed" with a few cases requiring surgical intervention. The authors noted that there is also concern over damage to adjacent structures such as the vagal nerves during relatively blind endoscopic suturing. The authors stated that further study is needed to identify the most appropriate subjects for these devices.

Witteman et al (2015) evaluated effectiveness of TIF compared with proton pump inhibition in a population consisting of GERD patients controlled with PPIs who opted for an endoscopic intervention over lifelong drug dependence. Patients with chronic GERD were randomized (2:1) for TIF or continuation of PPI therapy. American Society of Anesthesiologists greater than 2, body mass index (BMI) greater than 35 kg/m(2), hiatal hernia greater than 2 cm, and esophageal motility disorders were exclusion criteria. Primary outcome measure was GERD-related quality of life. Secondary outcome measures were esophageal acid exposure, number of reflux episodes, PPI usage, appearance of the gastro-esophageal valve, and healing of reflux esophagitis. Cross-over for the PPI group was allowed after 6 months. A total of 60 patients (TIF: n = 40; PPI: n = 20, mean BMI of 26 kg/m(2), 37 males) were included. At 6 months,

GERD symptoms were more improved in the TIF group compared with the PPI group ($p < 0.001$), with a similar improvement of distal esophageal acid exposure ($P=0.228$) compared with baseline. The pH normalization for TIF group and PPI group was 50% and 63%, respectively. All patients allocated for PPI treatment opted for crossover. At 12 months, quality of life remained improved after TIF compared with baseline ($p < 0.05$), but no improvement in esophageal acid exposure compared with baseline was found ($p = 0.171$) and normalization of pH was accomplished in only 29 % in conjunction with deteriorated valve appearances at endoscopy and resumption of PPIs in 61 %. The authors concluded that although TIF resulted in an improved GERD-related quality of life and produced a short-term improvement of the anti-reflux barrier in a selected group of GERD patients, no long-term objective reflux control was achieved.

Trad et al (2017) reported on the TF EsophyX versus Medical PPI Open Label (TEMPO) trial, which was conducted in seven US sites. Between June and August 2012, the investigators enrolled patients with small (less than 2 cm) or absent hiatal hernias who suffered from troublesome GERD symptoms while on PPI therapy for at least 6 months and had abnormal esophageal acid exposure (EAE). Randomization was to TF group (n = 40) or to PPI group (n = 23). Following evaluation at 6 months, all remaining PPI patients (n = 21) elected to undergo cross-over to TF; 52 patients were assessed at 3 years for (i) GERD symptom resolution using three GERD-specific quality of life questionnaires, (ii) healing of esophagitis using endoscopy, (iii) EAE using 48-h Bravo testing, and (iv) discontinuation of PPI use. Two patients who underwent revisional procedures by year 3 were included in the final analysis. At 3-year follow-up, elimination of troublesome regurgitation and all atypical symptoms was reported by 90 % (37/41) and 88 % (42/48) of patients, respectively. The mean Reflux Symptom Index score improved from 22.2 (9.2) on PPIs at screening to 4 (7.1) off PPIs 3 years

post-TF, p < 0.0001. The mean total % time pH <4 improved from 10.5 (3.5) to 7.8 (5.7), p = 0.0283. Esophagitis was healed in 86 % (19/22) of patients. At the end of study, 71 % (37/52) of patients had discontinued PPI therapy. All outcome measures remained stable between 1-, 2-, and 3-year follow-ups.

Sami Trad (2016) noted TIF performed with the EsophyX device is a totally endoscopic procedure with the objectives to mechanically repair a defective gastro-esophageal valve and to reduce small hiatal hernias. The recent publication of randomized controlled trials (RCTs) and long-term follow-up data offers the opportunity to re-evaluate this treatment modality and its role in the management of patients with chronic gastro-esophageal reflux disease (GERD). Randomized controlled trials have confirmed the ability of TIF to eliminate troublesome GERD symptoms, heal esophagitis, and improve distal esophageal acid exposure in appropriately selected patient populations. These studies establish TIF's superiority to conventional medical therapy, especially in clinical scenarios where proton-pump inhibitors (PPIs) fail to provide complete symptom relief across the spectrum of classic and atypical GERD manifestations, including regurgitation and laryngopharyngeal reflux. Long-term data indicated sustained positive outcomes and durability up to 6 years after procedure. These results were achieved with a low rate of serious adverse events and usually without introducing troublesome dysphagia, gas bloat, or flatulence. The authors concluded that based on the most recent data, TIF appeared to be a valuable treatment alternative for the management of appropriately selected patients with moderate-to-severe chronic GERD symptoms.

Huang et al (2017) stated that the effectiveness of TIF performed with the EsophyX device and its long-term outcomes in GERD are debated. These investigators performed a systematic review with meta-analysis of studies evaluating the role of TIF in GERD. A systematic search of

Embase, Scopus, PubMed, and the Cochrane Library Central was performed. All original studies reporting outcomes in GERD patients who underwent TIF were identified. Only RCTs evaluating the effectiveness of TIF, and prospective observational studies reporting outcomes after TIF were included. A total of 18 studies (963 patients) published between 2007 and 2015 were identified, including 5 RCTs and 13 prospective observational studies. The pooled relative risk of response rate to TIF versus PPIs/sham was 2.44 (95 % confidence interval [CI]: 1.25 to 4.79, p = 0.0009) in RCTs in the intention-to-treat analysis. The total number of refluxes was reduced after TIF compared with the PPIs/sham group. The esophageal acid exposure time and acid reflux episodes after TIF were not significantly improved; PPIs usage increased with time and most of the patients resumed PPIs treatment at reduced dosage during the long-term follow-up. The total satisfaction rate after TIF was about 69.15 % in 6 months. The incidence of severe adverse events consisting of gastro-intestinal (GI) perforation and bleeding was 2.4 %. The authors concluded that TIF is an alternative intervention in controlling GERD-related symptoms with comparable short-term patient satisfaction. Moreover, they stated that long-term results showed decreased effectiveness with time; patients often resume PPIs at reduced doses in the near future.

Also, an UpToDate review on "Surgical management of gastroesophageal reflux in adults" (Schwaitzberg, 2016) does not mention Esophyx/transoral incisionless fundoplication/TIF as a therapeutic option.

Stefanidis and colleagues (2017) stated that TIF using the EsophyX device has been shown to be effective and safe in patients with gastro-esophageal reflux disease (GERD); however, the subset of patients that would mostly benefit from this technique remains unknown. These researchers evaluated the long-term efficacy and safety of the TIF procedure in patients with a history of esophagitis or proven chronic GERD who have achieved symptom control with the

administration of proton pump inhibitors (PPIs), but did not wish to continue receiving medications for life. A total of 45 patients with typical GERD symptoms (heartburn, regurgitation, chest pain) and a history of esophagitis grade A and B or proven GERD by esophageal pH monitoring underwent TIF using EsophyX. Patients with eosphagitis C and D or those with large hiatal hernias (greater than 2 cm in length) were excluded. The primary clinical effectiveness measure was GERD symptom elimination at follow-up based on normalization of the GERD health related quality of life (GERD-HRQL) questionnaire. After a median follow-up period of 59 months (36 to 75) the median GERD-HRQL scores improved significantly from 27 (2 to 45) at baseline to 4 (0 to 26) ($p < 0.001$) in the 44 patients completing the study. Heartburn was eliminated in 12 out of the 21 patients included (57.1 %), regurgitation was eliminated in 15 out of the 17 patients included (88.2 %) and finally chest pain was eliminated in 5 patients out of the 6 patients included (83.3 %). Overall, 32 patients out of the 44 patients (72.7 %) that completed the study follow-up reported elimination of their main symptom, without the need for PPI administration (none PPI usage). Furthermore, 6 more patients (13.6 %), 5 with heartburn, and 1 with regurgitation reported half PPI dose taken for less than 50 % of the preceding follow-up period (occasional PPI usage), while 6 more patients (4 with heartburn, 1 with regurgitation, and 1 with chest pain) reported full or half PPI dose taken for more than 50 % of the preceding follow-up period (daily PPI usage). The authors concluded that creation of an esophagogastric fundoplication using the EsophyX device abolished reflux symptoms in 72.7 % of PPI-responsive GERD patients at a median 59 month follow-up.

Kethman and Hawn (2017) noted that GERD is the most common gastro-intestinal (GI) disorder of the esophagus. It is a chronic, progressive disorder that presents most typically with heartburn and regurgitation and atypically with chest pain, dysphagia, chronic cough, globus, or sore throat. The mainstay for diagnosis and characterization of the disorder is

esophagoduodenoscopy (EGD), high-resolution esophageal manometry, and symptom-associated ambulatory esophageal pH impedance monitoring. Additional studies that can be useful in certain clinical presentations include gastric scintigraphy and oral contrast upper GI radiographic series. Refractory GERD can be surgically managed with various techniques. In obese individuals, laparoscopic Roux-en-Y gastric bypass should be considered due to significant symptom improvement and lower incidence of recurrent symptoms with weight loss. Otherwise, laparoscopic Nissen fundoplication is the preferred surgical technique for treatment of this disease with concomitant hiatal hernia repair when present for either procedure. The short-term risks associated with these procedures include esophageal or gastric injury, pneumothorax, wound infection, and dysphagia. Emerging techniques for treatment of this disease include the Linx Reflux Management System, EndoStim LES Stimulation System, EsophyX and MUSE endoscopic fundoplication devices, and the Stretta endoscopic ablation system. Outcomes after surgical management of refractory GERD are highly dependent on adherence to strict surgical indications and appropriate patient-specific procedure selection.

Furthermore, an UpToDate review on “Surgical management of gastroesophageal reflux in adults” (Schwaitzberg, 2018) states that “A number of methods for treating GERD endoscopically have been developed. Their efficacy (particularly long-term) is still being defined”.

Stretta:

Stretta System is an endoscopic radiofrequency (RF) energy delivery system that uses a special single-use catheter to deliver constant tissue temperature for collagen contraction, purportedly resulting in tissue shrinkage and tightening of the gastroesophageal junction.

The Stretta System uses radiofrequency (RF) energy to treat GERD. The procedure involves insertion of a flexible catheter with needle electrodes for energy delivery down the patient's esophagus (patient is conscious but sedated). Precisely controlled RF energy is delivered to create lesions in the muscle of the LES and gastric cardia. The resorption of these lesions over the following weeks creates a tighter LES and a less compliant cardia. The tighter valve is thought to provide significantly increased resistance to gastric reflux. The procedure takes approximately 1 hour or less. Patients undergoing the procedure can get back to normal activities the next day.

Triadafilopoulos and Utley (2001) reported that temperature-controlled endoluminal radiofrequency energy delivery (the Stretta procedure) has been demonstrated in several studies to be safe and effective for the treatment of GERD and is a promising new technology for this chronic disorder. In a recent review, Katz (2002) noted that 2 endoscopic procedures were recently approved by the FDA for treatment of GERD: radiofrequency energy delivery to the gastro-esophageal junction, and transoral flexible endoscopic suturing. The author concluded that these techniques should be used selectively until more data are available and until results are compared to the safe and highly effective medical therapies. This is in agreement with Koop (2002) who stated that a number of new endoscopic techniques for the treatment of GERD have been developed, but the future for these is unclear.

Galmiche and des Varannes (2003) reviewed the literature on endoluminal therapies for GERD, and reached the following conclusions about the Stretta procedure:

- Although some surgeons propose use of the Stretta procedure for patients with severe, refractory, or complicated GERD, clinical studies of the Stretta procedure

have excluded these patients. "Virtually all trials of these new therapeutic approaches have enrolled PPI-dependent patients without severe esophagitis. Patients refractory to PPIs, those with hiatus hernia larger than 2 cm, those with severe esophagitis, as well as obese individuals, have usually been excluded from these trials".

- No studies have involved direct comparisons with other established medical or surgical therapies.
- Some concern has also been expressed about the potential impact of these procedures on definitive management of GERD. For instance, it is possible that previous endoscopic therapy might complicate or reduce the effectiveness of subsequent procedures.
- Some severe, although very rare, complications (including perforations) have been observed, especially during early experience with the Stretta procedure.
- Studies have been short-term; the long-term effectiveness of the procedure is unknown.
- Studies of radiofrequency catheterization (Stretta) have largely been uncontrolled.
- The only controlled study (Corley, 2002) of the Stretta procedure has been published in abstract form only, and has failed to confirm that the results of uncontrolled studies regarding significant reductions in acid exposure and symptom relief.

Gamiche and des Varannes (2003) concluded: "In our opinion, endoscopic treatment for GERD needs to be done in reference centers with highly skilled staff, and not outside the framework of well-designed prospective, and appropriately controlled studies. Comparative studies of the cost-effectiveness of endoscopic therapy should include medical strategies such as intermittent or on-demand PPI therapy. Assessment of relevant outcome measures, including economic endpoints and long-term efficacy, are required before these novel approaches are used in routine practice."

Another published evidence review (Hochberger et al, 2003) reached similar conclusions about the Stretta procedure: "While many of these techniques have shown good results in preliminary studies, long-term results are not yet available and therefore all such procedures have to be considered experimental. Their effectiveness will need to be compared with that of established treatment forms."

A technology assessment of the Stretta procedure (Kahrilas, 2003), reached a similar conclusion: "Thus, within the framework of GERD subgroups discussed earlier, this author concludes that the current role of Stretta in clinical practice (circa January 2003) is as follows. Clear indications for Stretta treatment are nil because of the paucity of controlled data available, the limited follow-up currently available on treated patients, and the confusing nature of the data that are available. This opinion is in sharp disagreement with the FDA 510(k) summary statement on Stretta concluding that, "the risk-benefit profile (of Stretta) is substantially equivalent to that of fundoplication surgery." Because there are no clear indications for the procedure, it is the opinion of this author that all Stretta treatments rendered at this time should be done in the setting of clinical trials."

In a prospective, randomized trial, Coron et al (2008) compared RF (Stretta procedure) and a PPI strategy in PPI-dependent patients. Patients with PPI-dependent typical reflux symptoms were randomly allocated to either RF or PPI regimen alone. The primary endpoint, evaluated at 6-month, was defined as the possibility for the patient to stop or to decrease PPI use to less than 50 % of the effective dose required at baseline. In the RF group, 18/20 patients stopped (n = 3) or decreased (n = 15) PPI use as compared to 8/16 in the PPI group (p = 0.01). None of the control patients could stop PPI. Health-related quality of life scores were not different between groups. No significant change in oesophageal acid exposure (OAE) was noted between baseline and 6-months after RF. No severe complication was

reported. The authors concluded that RF energy delivery is a safe and effective therapeutic option, allowing reduction in or discontinuation of PPI therapy in patients with PPI-dependent symptoms, without loss of quality of life. However, in a majority of patients, PPI therapy can not be completely stopped. The effectiveness of RF does not seem to be related to a decrease in OAE. This was a small study with short-term follow-up. These findings need to be validated by well-designed studies with larger number of subjects and longer follow-up.

Aziz et al (2010) noted that GERD is a prevalent disorder that often requires long-term medical therapy or surgery. Radiofrequency energy delivery has been shown in several studies to improve GERD symptoms and quality of life for approximately 2/3 of patients. The authors proposed that increasing the dose of Stretta would further improve the response to this therapy. For this study, 36 patients were randomized into 3 groups: (i) group A; 12 patients underwent a single session Stretta procedure, (ii) group B; 12 patients under went a sham Stretta procedure (mirror of the active procedure in all aspects except there was no deployment of the electrodes), and (iii) group C; 12 patients underwent a single Stretta treatment followed by repeat Stretta if GERD health-related quality of life (HRQL) was not 75 % improved after 4 months. For each patient, 56 RF lesions were created per session. The principal outcome was GERD HRQL improvement. The secondary outcomes were medication use, LES basal pressure, endoscopic grade of esophagitis, and OAE by pH probe. The Stretta procedure was completed successfully for all the patients in both active treatment groups. At 12 months, the mean HRQL scores of those off medications, the LES basal pressure, the 24-hr pH scores, and the PPI daily dose consumption were significantly improved from baseline in both Stretta groups ($p < 0.01$). The double Stretta was numerically but not significantly better than the single Stretta for mean HRQL, mean 24-hr pH, mean LES

pressure, and PPI use. Seven patients in the double Stretta treatment group had normalized their HRQL at 12 months compared with 2 patients in the single-treatment group ($p = 0.035$). The sham patients had a small but statistically significant decrease in their daily PPI dosages ($p < 0.05$) and mean HRQL scores ($p < 0.05$). No serious complications (bleeding, perforation, or death) occurred. However, 2 patients experienced significant delayed gastric emptying after the second Stretta treatment. The authors concluded that the Stretta procedure significantly reduced GERD HRQL, use of PPI drugs, OAE, LES pressure, and grade of esophagitis compared with the sham procedure. The double Stretta therapy had numerically superior outcomes for most parameters and a significantly more frequent normalization of HRQL scores compared with the single Stretta. These findings need to be validated by well-designed studies with larger number of subjects and longer follow-up.

An appraisal by the National Institute for Health and Clinical Excellence (NICE, 2009) concluded: "The evidence on safety and efficacy of endoscopic radiofrequency (RF) ablation for gastro-oesophageal reflux disease (GORD) is inadequate and there are inconsistencies in the evidence on efficacy." The Committee noted that improvements in subjective outcomes in the published series were not supported by objective outcomes (pH and pressure measurements). They also noted that symptomatic improvement may result from denervation caused by the procedure, making the lower esophagus insensitive to potentially harmful acid reflux, as opposed to true reflux control. More recently, updated NICE guidance (2013) concluded: “The evidence on the safety of endoscopic radiofrequency ablation for gastroesophageal reflux disease (GORD) 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.”

Noar and colleagues (2014) stated that patients with GERD often seek alternative therapy for inadequate symptom control, with over 40 % not responding to medical treatment. These researchers evaluated the long-term safety, efficacy, and durability of response to RF treatment (Stretta) of the lower esophageal sphincter. Using an intent-to-treat analysis, these researchers prospectively assessed 217 patients with medically refractory GERD before and after Stretta. There was no concurrent control group in the study. Primary outcome measure was normalization of GERD HRQOL in 70 % or greater of patients at 10 years. Secondary outcomes were 50 % reduction or elimination of PPIs and 60 % or greater improvement in satisfaction at 10 years. Successful treatment was defined as achievement of secondary outcomes in a minimum of 50 % of patients. Complications and effect on existing co-morbidities were evaluated. The results of a 10-year study were reported. The primary outcome was achieved in 72 % of patients (95 % CI: 65 to 79). For secondary outcomes, a 50 % or greater reduction in PPI use occurred in 64 % of patients, (41 % eliminating PPIs entirely), and a 60 % or greater increase in satisfaction occurred in 54 % of patients. Both secondary end-points were achieved. The most common side effect was short-term chest pain (50 %). Pre-existing Barrett's metaplasia regressed in 85 % of biopsied patients. No cases of esophageal cancer occurred. The authors concluded that in this single-group evaluation of 217 patients before and after Stretta, GERD HRQOL scores, satisfaction, and PPI use significantly improved and results were immediate and durable at 10 years. The major drawbacks of this study include the following: (i) this was a non-randomized, single-center, open-label prospective trial; (ii) there was no inclusion of long-term pH and motility data, and no Nissen fundoplication (NF) comparison arm; (iii) due to the long study period, patient migration and associated difficulty in assessing GERD via validated questionnaires, it was difficult to collect complete 10-year data; (iv) the data presented were only 10-year data and

perhaps 15- and 20-year data may be needed to show continued durability of response; (v) not all 10-year patients had undergone final endoscopic screening, which limited the ability to definitively conclude that the procedure may influence the rate of esophageal cancer or course of Barrett's esophagus; and (vi) the study did not directly address the potential cost benefits, which may merit further study.

Lipka et al (2015) noted that a RF ablation technique known as Stretta was recommended by the Society of American Gastrointestinal and Endoscopic Surgeons as an alternative treatment for GERD. However, RCTs of the effectiveness of Stretta have produced conflicting findings, and those from previous systematic reviews were compromised as a result of deficiencies in study conduct and reporting of findings. These investigators performed a systematic review and meta-analysis to evaluate all evidence on the effectiveness of Stretta for the management of GERD. They searched MEDLINE and the Cochrane Central Register of Controlled Trials (The Cochrane Library) from inception until February 28, 2014, along with other databases, for RCTs of Stretta in patients with GERD. Primary outcomes were physiologic parameters of GERD, including normalization of esophageal pH values and augmentation of lower esophageal sphincter pressure (LESP). Secondary outcomes were health-related quality of life (HRQOL) and ability to stop the use of proton pump inhibitors (PPIs). For quality assurance purposes, 2 investigators were involved throughout the study. Data were pooled under a random-effects model. The systematic review was performed as per the standards of the Cochrane collaboration. These researchers collected data from 4 trials and a total of 165 patients (153 patients were analyzed). Three trials compared Stretta vs sham, and 1 trial compared Stretta with PPI therapy. The overall quality of evidence was very low. The pooled results showed no difference between Stretta and sham or management with PPI in patients with

GERD for the outcomes of mean (%) time the pH was less than 4 over a 24-hour time course, LESP, ability to stop PPIs, or HRQOL. The authors concluded that in a meta-analysis of trials, they found that Stretta for patients with GERD did not produce significant changes, compared with sham therapy, in physiologic parameters, including time spent at a pH less than 4, LESP, ability to stop PPIs, or HRQOL.

Hopkins et al (2015) commented that "published reviews of the literature are conflicted in their recommendations of Stretta in the management of GERD. The literature suggests that the Stretta procedure has an acceptable safety profile and may be effective in reducing symptom burden and quality of life scores up to 8 years post-intervention. However, there does not appear to be any sustained improvement in objective outcomes and there is no evidence that Stretta results in improved outcomes as compared to surgical intervention."

A clinical trial on “Stretta In Reflux Uncontrolled by IPP (SIRUP)” that is currently recruiting participants. This trial is designed to compare the Stretta procedure and the sham procedure efficiency 6 months post-procedure in reflux uncontrolled by intake of inhibitors of protons pump (IPP) patients. (Last verified 4/2014).

Enteryx:

In addition to the EndoCinch and Stretta procedures, there are other endoscopic procedures being evaluated for the treatment of GERD. Enteryx (Boston Scientific Corp, Natick, MA) is a chemically inert, non-carcinogenic, hypoallergenic, non-antigenic, radio-opaque compound that is available in a liquid organic state but becomes solid on hydration (or placement in tissue). It has been used in the treatment of arterio-venous malformations, peripheral vascular disease, and hypervascular head and neck cancers. It can be injected into the LES under fluoroscopic and endoscopic guidance. The endoscopist can ensure that the injections are into the

muscular layer because a ring appears at the LES on radiograph. This ring persists as long as the material is in the LES. On April 22, 2003, Enteryx was approved by the FDA for the treatment of patients with GERD who require and respond to PPIs. The pre-market approval (PMA) of Enteryx was recommended by the Gastroenterology and Urology Devices Advisory Panel of the FDA with 10 conditions including a post-market study to be performed as a placebo-sham controlled trial that also examine the effects of re-treatment.

In a pilot study of patients with GERD who required continuous therapy with a PPI (n = 15), Deviere et al (2002) examined the safety and effectiveness of Enteryx (ethylene-vinyl-alcohol polymer) in the management of these patients. Enteryx was injected into the muscle of the gastric cardia. Primary endpoints were the safety of the procedure, the effect on LES pressure and the stability of the injected material. A secondary endpoint was the effect on heartburn score after discontinuation of treatment with a PPI. The authors concluded that Enteryx implantation in the muscle of the cardia is feasible and safe. It leads to a sustained increase in resting LES pressure. This is associated with a sustained improvement in heartburn score for patients who previously required continuous therapy with a PPI. The authors stated that further studies are needed to delineate the potential clinical applications and long-term outcomes of this technique.

In a multi-center, single-arm study (n = 85), Johnson and associates (2003) evaluated the safety and effectiveness of Enteryx for the treatment of GERD. These patients had heartburn symptoms that were responsive to PPI therapy. At 6 months following Enteryx implantation, PPI use was eliminated in 74 % and reduced by greater than 50 % in 10 % of patients. Mean total esophageal acid exposure time was 9.5 % pre-therapy and 6.7 % at 6 months. Mean LES length increased from 2.0 cm at baseline to 3.0 cm post-therapy. There were no clinically serious adverse events. Transient mild-to-moderate chest pain commonly occurred after implantation.

These investigators concluded that endoscopic implantation of Enteryx is a safe and effective therapy for eliminating or decreasing the need for PPI medications, improving GERD symptoms and patient quality of life, and decreasing esophageal acid exposure among patients suffering from GERD. The authors stated that studies evaluating the benefits of Enteryx implantation compared with sham procedures as well as those that examine the long-term effectiveness and durability of Enteryx are in progress.

Although many patients had improvements in their symptoms and medication requirements, objective evaluations of the esophagus performed during the clinical trial showed evidence of persistent acid reflux in 61 % of patients and low-grade inflammation in 37 % of patients at 12 months. The most common adverse event observed in patients undergoing Enteryx treatment was pain beneath the breastbone that usually diminished within 2 weeks. Other common side effects included temporary difficulty with swallowing (20 %), fever (12 %), sore throat (11 %), and gas/bloating/belching (7 %).

Current evidence for the use of Enteryx is limited to pilot studies as well as small trials that lack appropriate control groups and long-term follow-up data. Thus, the clinical value of Enteryx is uncertain at this time. It should be noted that the FDA has issued a warning to physicians to stop using Enteryx because it has been connected to serious health problems and, in at least 1 case, death. On September 23, 2005, Boston Scientific Corporation initiated a voluntary recall of all Enteryx procedure kits and Enteryx single pack injectors because of reports that improper injection procedures can lead to serious patient injury and death.

An assessment conducted by the National Institute of Clinical Excellence (2004) concluded that current evidence on the safety and efficacy of endoscopic injection of bio-compatible polymer for GERD does not appear adequate for this procedure to be used without special arrangements for

consent and for audit or research. This is in agreement with that of 2004 Blue Cross Blue Shield Technology Evaluation Center (TEC)'s assessment on transesophageal endoscopic treatments for GERD, which stated that endoscopic suturing, radiofrequency energy delivery, or implantation of inert polymers for treatment of GERD do not meet the TEC criteria.

Gatekeeper:

More recently, the National Institute for Health and Clinical Excellence (NICE, 2007) evaluated the Gatekeeper Reflux Repair System (Medtronic, Minneapolis, MN), a hydrogel prosthesis that is implanted endoscopically into the LES. The NICE guidance concluded that there is limited evidence of short-term efficacy on endoscopic augmentation of the LES using hydrogel implants for the treatment of GERD. This evidence also raises concerns about the procedure's safety. "Therefore, this procedure should not be used without special arrangements for consent and for audit." The Gatekeeper Reflux Repair System clinical program was suspended in late 2005 before FDA approval due to concerns over efficacy.

The AGA's institute medical position statement on the use of endoscopic therapy for GERD (Falk et al, 2006) stated that "most studies of endoscopic therapy have only limited follow-up information of a relatively small number of patients. Thus, the durability of these technologies beyond 1 to 2 years remains unclear. Short-term and long-term safety issues are unresolved, but serious adverse events led to the voluntary withdrawal of Enteryx by the manufacturer in September 2005 and suspension of the Gatekeeper clinical program in late 2005. The economics of all techniques for the patient, practitioner, and society are unknown. While newer devices and improvements in endoscopic antireflux techniques may yield better and more durable treatment outcomes, current data suggest that there are no definite indications for

endoscopic therapy for GERD at this time. Both practitioners and patients need to be aware of the limitations in the evidence that exist with these devices at present".

Spicak (2007) stated that 3 types of endoscopic methods in several modifications have been developed for the treatment of GERD: (i) radiofrequency therapy (Stretta procedure) is available both in Europe and the United States and more than 5,000 patients have been treated to date; (ii) injection therapy requires the injection of bulking agents or implantation of bioprosthesis into the LES zone. Both Enteryx was withdrawn from the market in 2005, and Gatekeeper was suspended before FDA approval; (iii) suturing/plication therapy is based on the plication at the level of the LES, and most of all techniques resemble the principle of surgical treatment. Despite sophisticated technologies and promising short-term results, all these techniques are associated with inconsistencies, controversies, and relevant adverse affects. According to current practice, use of endoscopic methods is justifiable only as part of clinical trials.

In a prospective, randomized, sham-controlled, single-blinded, international multi-center study, Fockens et al (2010) evaluated if endoscopic implantation of an injectable esophageal prosthesis, the Gatekeeper Reflux Repair System (GK), is safe and effective for controlling GERD. A total of of 204 patients were assigned to 3 groups: (i) 60 lead-in, (ii) 96 GK, and (iii) 48 sham patients. The sham patients were allowed to cross-over to the GK treatment arm or exit the study at 6 months. The primary end points were (i) reduction in serious device- and procedure-related adverse device effects compared with a surgical composite complication rate, and (ii) reduction in heartburn symptoms 6 months after the GK procedure compared with the sham procedure. The secondary end point was improved esophageal pH (total time pH was less than 4) 6 months after

the GK procedure compared with baseline. A planned interim analysis was performed after 143 patients were enrolled (25 lead-in, 75 GK, and 43 sham patients), and the GK study was terminated early due to lack of compelling efficacy data. Four reported serious adverse events had occurred (2 perforations, 1 pulmonary infiltrate related to a perforation, and 1 severe chest pain) at termination of the study with no mortality or long-term sequelae. Heartburn symptoms had improved significantly at 6 months compared with baseline in the GK group ($p < 0.0001$) and the sham group ($p < 0.0001$), but no significant between-group difference in improvement was observed ($p = 0.146$). Esophageal acid exposure had improved significantly at 6 months compared with baseline in the GK group ($p = 0.021$) and the sham group ($p = 0.003$), but no significant between-group difference in improvement was observed ($p = 0.27$). The authors concluded that the GK procedure was associated with some serious but infrequent complications. No statistically significant difference in outcomes was observed between the treatment and control groups at 6 months compared with baseline.

Durasphere:

In a pilot study, Ganz et al (2009) evaluated the long-term safety and effectiveness of Durasphere (Carbon Medical Technologies, St Paul, MN), a new injectable bulking agent, in the treatment of mild-moderate GERD. A total of 10 GERD subjects, confirmed by pH monitoring, on daily PPI therapy, hiatal hernia less than 3 cm, and no or mild erosive esophagitis were enrolled in this study. Subjects received endoscopic injection with Durasphere at the gastro-esophageal junction. Outcome measures included change in symptom scores, PPI use, pH scores, and endoscopic findings; safety profile was monitored. Nine of 10 patients completed the 12-month trial. There were no adverse events. The procedure was well-tolerated with minimal patient discomfort and no dysphagia. At 12 months 70 % of patients discontinued all antacid medication completely; 90 % of

patients reduced PPI use by greater than 50 %. DeMeester scores improved from a mean of 44.5 at baseline to 26.5 at 12 months; 4 patients achieved normal pH scores. There was no esophagitis at 12 months, and no erosion, ulceration or sloughing of material was noted at any injection site. The Durasphere material did not appear to migrate. The authors concluded that Durasphere appears to be a promising new injectable bulking agent for the treatment of mild-moderate GERD, with demonstrable efficacy and no significant adverse events in a small cohort. Drawbacks of this study were its non-randomized study design without a control group and small number of subjects.

Plexiglas Polymethylmethacrylate (PMMA) Microbeads:

Feretis et al (2001) noted that a gelatinous implant containing polymethylmethacrylate (PMMA) beads is successfully used to augment the diminished thickness of the chorium in patients with skin defects and wrinkles. These investigators examined if submucosal injection of PMMA microspheres into the lower esophageal folds decreases the severity of symptoms and acid reflux in patients with GERD. Endoscopic submucosal implantation of PMMA was carried out in 10 patients with GERD who were either refractory to or dependent on PPIs. Symptom severity score, 24-hour pH monitoring, upper GI endoscopy, and endoscopic ultrasonography were performed to evaluate the efficacy of implantation. A significant decrease in the symptom severity score and mean total time with esophageal pH less than 4 was noted after the implantation of PMMA ($p < 0.05$); 7 of 10 patients were taking no medication after PMMA implantation. There were no serious procedure-related complications. The authors concluded that endoscopic implantation of PMMA into the submucosa of the lower esophageal folds may be a new method for treating GERD. Moreover, they stated that further studies are needed to determine the long-term effectiveness of the procedure.

Neuhauser et al (2003) stated that therapeutic options for GERD include lifestyle modifications, medical therapy, laparoscopic anti-reflux surgery, and 3 more recent options: (i) injection therapy to the LES, (ii) endoscopic sewing procedures, and (iii) radio frequency ablation therapy. Medical therapy is effective in most patients but not always successful with advanced disease. Up to 70 % of subjects do not have adequate nocturnal control of gastric acid secretion with 20 mg of omeprazole given twice-daily. Patients who do not tolerate medical therapy, who respond inadequately, or who want to avoid life-long drug therapy are candidates for alternate treatments. Studies on endoscopic procedures such as PMMA injection, the Stretta procedure, and endoscopic suturing techniques all suffer from having small study groups for each procedure, unknown durability, short follow-up, and the absence of randomized, controlled trilas. Limitations on endoscopic techniques are esophageal motility disorders, severe esophagitis, and larger hiatal hernias. Laparoscopic anti-reflux surgery remains a well-established, durable alternative to long-term medical therapy. It has the benefits of convenience, safety, minimal complications, improved quality of life, and low cost. Alternative methods will have to earn their place against this gold standard.

Plicator:

The Plicator System (NDO Surgical Inc., Mansfield, MA) is another new treatment option for GERD. It consists of the reusable Plicator instrument, a single-use cartridge containing a suture-based implant, and a specially designed endoscopic tissue retractor. This system allows the physician to create a full-thickness plication at the gastro-esophageal junction, permitting serosa-to-serosa tissue healing and a re-structuring of the normal anti-reflux barrier. The Plicator procedure is an outpatient procedure performed using direct endoscopic visualization and under conscious sedation. The Plicator System was cleared by the FDA in April 2003 through a 510(k)

application. The most common side effect associated with the Plicator procedure is pharyngitis (41 %), which resolved spontaneously within several days after the procedure.

There is only limited clinical data on the effectiveness of the Plicator System. In a pilot study, Chuttani et al (2003) reported that full-thickness plication (the Plicator procedure) was performed successfully in 6 of 7 patients, with 1 procedure aborted because of difficulty in sedating the patient. Mean procedure time was 21 mins. Mild epigastric pain was reported by 2 patients and difficulty with eructation by 1 patient; all symptoms resolved spontaneously within 7 days of the procedure. Endoscopy at 6 months revealed an intact plication in all patients. At 1 year after the procedure, patients reported sustained reduction in heartburn scores. One patient, who did not experience significant relief of symptoms, ultimately underwent successful laparoscopic Nissen fundoplication at 6 months after the procedure. At 1 year after the procedure, 3 of 5 patients were not taking anti-GERD medications. The authors concluded that endoscopic full-thickness plication is feasible, safe and, and appeared to reduce symptoms and medication use associated with GERD. Findings of this study need to be validated by prospective, randomized controlled studies.

An assessment prepared for the California Technology Assessment Forum (CTAF) concluded that the Stretta, Endocinch, and Enterx endoluminal treatments for GERD do not meet CTAF's assessment criteria (Feldman, 2004). The assessment explained that, in the case of Enterx and Bard EndoCinch, the current literature does not include any randomized trial data, so it is not possible to fully evaluate the safety and efficacy of these procedures. In addition, with the Bard EndoCinch, questions remain about the safety of the procedure and the training required to perform it under conditions of routine clinical practice. CTAF found that, although the Stretta procedure had been evaluated in a randomized, controlled clinical trial (Corley et al, 2003), the

trial did not enroll patients who were refractory to medical therapy, so it is not possible to conclude from this trial if Stretta will be an acceptable alternative to surgery for patients with refractory symptoms on appropriate medical therapy. Although the study showed that the Stretta procedure was successful in returning patients back to a similar level of symptoms they had at baseline on medications, the procedure did not improve esophageal acid exposure, esophageal erosions or LES pressure, all presumably risk factors for developing later complications from GERD. The assessment found that it does not seem advisable to recommend that patients discontinue a safe and effective treatment that has been proven to reduce acid exposure (i.e., medications) in favor of one that does not (Stretta).

Ozawa et al (2005) stated that endoscopic treatments (e.g., the EndoCinch method, the NDO Plicator method, the Wilson-Cook Medical's Endoscopic Suturing Device, the Stretta System, the Enteryx procedure, and Medtronic's Gatekeeper Reflux Repair System) for GERD are still in the development phase. They further noted that the safety, effectiveness, durability, cost-effectiveness, indications of endoscopic treatments, and possible combination with other treatments must be thoroughly evaluated in randomized controlled trials. This is in agreement with the observations of Annese et al (2005) who stated that the use of endoscopic treatment for GERD should be limited to clinical trials, which should incorporate the provision of comprehensive and unbiased information to study patients as well as de Hoyos and Fernando (2005) who noted that endoscopic therapies for GERD are being rapidly introduced, despite lack of long-term follow-up and randomized trials.

Rothstein et al (2006) examined the effectiveness of endoscopic full-thickness plication for the treatment of GERD in comparison with a sham procedure. Patients with symptomatic GERD requiring maintenance PPI therapy were entered into a randomized, single-blind, prospective, multi-

center trial. A total of 78 patients were randomly assigned to undergo endoscopic full-thickness restructuring of the gastric cardia with transmural suture, while 81 patients underwent a sham procedure. Group assignments were revealed following the 3-month evaluation. The primary end point was greater than or equal to 50 % improvement in GERD HRQL score. Secondary end points included medication use and esophageal acid exposure. By intention-to-treat analysis, at 3 months, the proportion of patients achieving greater than or equal to 50 % improvement in GERD-HRQL score was significantly greater in the active group (56 %) compared with the sham group (18.5 %; $p < 0.001$). Complete cessation of PPI therapy was higher among patients in the active group than in the sham group by intention-to-treat analysis (50 % versus 24 %; $p = 0.002$). The percent reduction in median percent time pH less than 4 was significantly improved within the active group versus baseline (7 versus 10, 18 %, $p < 0.001$) but not in the sham group (10 versus 9, -3 %, $p = 0.686$). Between-group analysis revealed the active therapy to be superior to the sham in improving median percent time pH less than 4 ($p = 0.010$). There were no perforations or deaths. The authors concluded that endoscopic full-thickness plication more effectively reduces GERD symptoms, PPI use, and esophageal acid exposure than a sham procedure.

An editorial (Shaheen, 2006) accompanying the study by Rothstein and colleagues outlined the limitations of the study. It stated that the Plicator procedure shows promise as a treatment option for patients with mild GERD seeking an alternative to long-term acid-suppressive therapy. Furthermore, Shaheen stated there are issues to be dealt with concerning the acceptance of endoscopic anti-reflux devices such as safety, efficacy and durability. In regards to the study, Shaheen also stated that some head-to-head data with alternative treatment measure would be helpful. No study has truly compared the results of PPI therapy to endoscopic anti-reflux devices. Shaheen concluded that the study still leaves uncertainty as to where to position endoscopic anti-reflux

procedures in the patient with GERD. Since there is a lack of data, there is no claim to superiority, or even equivalency, of these devices to the best medical or surgical therapy for GERD. Until the questions regarding safety, efficacy, and durability outlined above become clearer, the routine use of these devices in PPI responsive patients outside the realm of clinical studies can not be recommended.

In an open-label, prospective, multi-center study, von Renteln and colleagues (2008) evaluated the safety and effectiveness of placing multiple transmural sutures for the treatment of GERD. Subjects with symptomatic GERD who require daily maintenance PPI therapy. Study exclusions were hiatal hernia greater than 3 cm, grades III and IV esophagitis, Barrett's epithelium, and esophageal dysmotility. A total of 41 patients received 2 or more transmural sutures placed linearly in the anterior gastric cardia approximately 1 cm below the gastro-esophageal junction. Six months following the procedure, median GERD-health-related quality of life (HRQL) improved 76 % compared with off-medication baseline (6.0 versus 25.0, $p < 0.001$), with 75 % of patients (32/40) achieving over 50% improvement in their baseline GERD-HRQL score. Six months after the procedure, daily PPI therapy was eliminated in 70 % of patients (28/40). Heartburn symptoms improved 80 % compared with off-medication baseline (16.0 versus 84.0, $p < 0.001$). Median esophagitis grade improved 75 % compared with baseline (0.0 versus 1.0, $p = 0.005$). Esophageal pH assessed as median distal esophageal-acid exposure (percentage time pH less than 4.0) improved 38 % compared with baseline (9.0 versus 11.0, $p < 0.020$; nominal p value for a single statistical test: significance removed upon the Bonferroni adjustment for multiple testing of data) and manometric outcomes were also improved compared with baseline (median LES resting pressure improved 25 % [10.0 versus 6.0, $p < 0.017$; nominal p value for a single statistical test: significance removed upon the Bonferroni adjustment for multiple testing of data]) and median amplitude of contraction improved 11 % (70.0 versus 62.0, $p <$

0.037; nominal p value for a single statistical test: significance removed upon the Bonferroni adjustment for multiple testing of data). The authors concluded that endoscopic full-thickness plication with multiple serially placed implants was safe and effective in reducing GERD symptoms, medication use, esophageal-acid exposure, and esophagitis. The limitations of this study were small sample size, and a lack of randomized comparison with a single implant group.

Angelchik Anti-Reflux Prosthesis:

The Angelchik anti-reflux prosthesis was approved (PMA) by the FDA in 1979. It is a soft, collar-shaped, silicone elastomer shell filled with silicone gel, with an internal diameter of 3.1 cm. It is placed around the esophagus under the diaphragm and above the stomach, and is secured by 2 reinforced Teflon straps around the gastro-esophageal junction. The alleged advantage of the Angelchik device is the simplicity of the procedure -- its placement requires only limited dissection, thus decreasing the operating time. Since its introduction, more than 25,000 prostheses have been inserted into patients worldwide. Early faulty design had caused breakage of the circumferential strap, and led to migration of the device. Modification of the original strap to 2 re-inforced, non-circumferential straps by the manufacturer appears to have minimized the migration problem. However, complications as a consequence of implantation of the Angelchik prosthesis have been reported in as many as 10 to 20 % of patients. An American Medical Association's DATTA evaluation of the Angelchik prosthesis found that this device has not been established as safe and effective for routine use in the treatment of GERD. Long-term studies concluded that the Angelchik device causes long-term dysphagia in many patients, severe enough to require its removal in 25 % of these patients. Thus, its continual use can not be recommended.

LINX Reflux Management System:

LINX Reflux Management System uses a small flexible band of interlinked titanium beads with magnetic cores that are laparoscopically placed around the esophagus, just above the stomach. The LINX system purportedly expands by swallowing, allowing food and liquid to pass normally into the stomach. The magnetic attraction then closes the LES, supposedly preventing reflux.

In a feasibility study, Bonavina et al (2010) evaluated the safety and efficacy of the LINX Reflux Management System (Torax Medical, Shoreview, MN), a laparoscopically implanted sphincter augmentation device, for the treatment of GERD. The device, designed to prevent reflux due to abnormal opening of the LES, was laparoscopically implanted at the gastro-esophageal junction in 44 patients. At baseline, all patients had abnormal esophageal acid exposure on 24-hr pH monitoring and improved, but persistent, typical GERD symptoms while on acid suppression therapy with PPIs. The device comprises a miniature string of inter-linked titanium beads, with magnetic cores, placed around the gastro-esophageal junction. The magnetic bond between adjacent beads augments sphincter competence. The beads temporarily separate to accommodate a swallowed bolus, allow belching or vomiting, and re-approximate to augment the LES in the closed position. Patients were evaluated after surgery by GERD Health-Related Quality of Life symptom score, PPI usage, endoscopy, esophageal manometry, and 24-hr esophageal pH monitoring. The total mean GERD Health-Related Quality of Life symptom scores improved from a mean baseline value of 25.7 to 3.8 and 2.4 at 1- and 2-year follow-up, representing an 85 % and 90 % reduction, respectively ($p < 0.0001$). Complete cessation of PPI use was reported by 90 % of patients at 1 year and by 86 % of patients at 2 years. Early dysphagia occurred in 43 % of the patients and self-resolved by 90 days. One device was laparoscopically explanted for persistent dysphagia without disruption of the anatomy or function of the cardia. There were no device migrations, erosions, or induced mucosal

injuries. At 1 and 2 years, 77 % and 90 % of patients had a normal esophageal acid exposure. The mean percentage time pH was less than 4 decreased from a baseline of 11.9 % to 3.1 % ($p < 0.0001$) at 1 year and to 2.4 % ($p < 0.0001$) at 2 years. Patient satisfaction was 87 % at 1 year and 86 % at 2 years. The authors concluded that the new laparoscopically implanted sphincter augmentation device eliminates GERD symptoms without creating undue side effects and is effective at 1 and 2 years of follow-up. The findings of this small feasibility study need to be validated by well-designed studies.

Ganz and colleagues (2013) evaluated the safety and effectiveness of a new magnetic device to augment the LES. These investigators prospectively assessed 100 patients with GERD before and after sphincter augmentation. The study did not include a concurrent control group. The primary outcome measure was normalization of esophageal acid exposure or a 50 % or greater reduction in exposure at 1 year. Secondary outcomes were 50 % or greater improvement in quality-of-life related to GERD and a 50 % or greater reduction in the use of PPIs at 1 year. For each outcome, the pre-specified definition of successful treatment was achievement of the outcome in at least 60 % of the patients. The 3-year results of a 5-year study were reported. The primary outcome was achieved in 64 % of patients (95 % confidence interval [CI]: 54 to 73). For the secondary outcomes, a reduction of 50 % or more in the use of PPIs occurred in 93 % of patients, and there was improvement of 50 % or more in quality-of-life scores in 92 %, as compared with scores for patients assessed at baseline while they were not taking PPIs. The most frequent adverse event was dysphagia (in 68 % of patients post-operatively, in 11 % at 1 year, and in 4 % at 3 years). Serious adverse events occurred in 6 patients, and in 6 patients the device was removed. The authors concluded that in this single-group evaluation of 100 patients before and after sphincter augmentation with a magnetic device, exposure to esophageal acid decreased, reflux symptoms improved, and use of PPIs decreased. Moreover, they stated that follow-up studies

(prospective, randomized trials with appropriate controls) are needed to confirm these preliminary findings and evaluate longer-term safety.

In a multi-center, prospective, single-arm study, Lipham et al (2012) examined the long-term safety and effectiveness of the LINX reflux management system. A total of 44 patients underwent a laparoscopic surgical procedure for placement of the LINX System around the gastro-esophageal junction (GEJ). Each patient's baseline GERD status served as the control for evaluations post-implant. Long-term efficacy measures included esophageal acid exposure, GERD quality-of-life measures, and use of PPIs. Adverse events and long-term complications were closely monitored. For esophageal acid exposure, the mean total % time pH less than 4 was reduced from 11.9 % at baseline to 3.8 % at 3 years ($p < 0.001$), with 80 % (18/20) of patients achieving pH normalization (less than or equal to 5.3 %). At greater than or equal to 4 years, 100 % (23/23) of the patients had improved quality-of-life measures for GERD, and 80 % (20/25) had complete cessation of the use of PPIs. There have been no reports of death or long-term device-related complications such as migration or erosion. The authors concluded that sphincter augmentation with the LINX Reflux Management System provided long-term clinical benefits with no safety issues, as demonstrated by reduced esophageal acid exposure, improved GERD-related quality of life, and cessation of dependence on PPIs, with minimal side effects and no safety issues. Patients with inadequate symptom control with acid suppression therapy may benefit from treatment with sphincter augmentation. The major drawbacks of this study were its small sample size (only 23 patients were available at 4 years) and the lack of a comparison group.

Moreover, the NICE's guidance on "Laparoscopic insertion of a magnetic bead band for gastro-oesophageal reflux disease" (2012) considered insertion of a magnetic bead band for the treatment of GERD to be an innovative concept which,

if shown to be safe and effective in further studies, could be a useful addition to the treatment options. The report stated that "The evidence on the safety and efficacy of laparoscopic insertion of a magnetic bead band for gastro-oesophageal reflux disease (GORD) is limited in quantity. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research …. NICE encourages further research and collaborative data collection on laparoscopic insertion of a magnetic bead band for GORD".

A technology brief on the LINX device for the Australian Safety and Efficacy of New Interventional Procedures - Surgical (ASENIP-S, 2013) concluded: "The findings of the two clinical trials reported in this Technology Brief illustrate promising results for the use of the LINX® Reflux Management System in treating patients with GORD. In particular, the device's ability to be removed if required and the lower rate of side effects, compared with conventional surgical intervention, make the device a favourable treatment alternative (provided its utility in patients with significant oesophagitis and hiatal hernia can be determined). However, the evidence base for this technology is in its infancy and it is not currently possible to determine the safety and effectiveness of the LINX® device. Future studies should be comparative (ideally randomised), with broader patient populations and without industry sponsorship. Particular outcomes of interest for future studies should include the durability of the device (i.e. the lifespan of the magnets), its ability to reduce the likelihood of complications of GORD (i.e., Barrett's oesophagus and cancer) and patient QoL. In addition, regulatory approval of the LINX® Reflux Management System in Australia does not appear to be imminent, and the cost of the device is likely to be a barrier to its uptake in clinical practice at this time."

Ganz et al (2013) prospectively assessed 100 patients with GERD before and after sphincter augmentation. The study did not include a concurrent control group. The primary outcome measure was normalization of esophageal acid exposure or a

50 % or greater reduction in exposure at 1 year. Secondary outcomes were 50 % or greater improvement in quality of life related to GERD and a 50 % or greater reduction in the use of PPIs at 1 year. For each outcome, the pre-specified definition of successful treatment was achievement of the outcome in at least 60 % of the patients. The 3-year results of a 5-year study were reported. The primary outcome was achieved in 64 % of patients (95 % CI: 54 to 73). For the secondary outcomes, a reduction of 50 % or more in the use of PPIs occurred in 93 % of patients, and there was improvement of 50 % or more in quality-of-life scores in 92 %, as compared with scores for patients assessed at baseline while they were not taking PPIs. The most frequent adverse event was dysphagia (in 68 % of patients post-operatively, in 11 % at 1 year, and in 4 % at 3 years). Serious adverse events occurred in 6 patients, and in 6 patients the device was removed. The authors concluded that the current study was designed so that the direct effects of the sphincter augmentation device on each patient's exposure to esophageal acid, use of PPIs, and symptom control could be measured before and after the implantation. This design was limited in that it did not allow direct comparisons with other forms of therapy. These researchers stated that prospective, randomized trials with larger samples and longer-term follow-up are needed to confirm these early results and assess longer-term safety.

Bonavina et al (2013a) stated that the LINX Reflux Management System is designed to provide a permanent solution to GERD by augmenting the sphincter barrier with a standardized, reproducible laparoscopic procedure that does not alter gastric anatomy and is easily reversible. Two single-group trials confirmed that a magnetic device designed to augment the LES can be safely and effectively implanted using a standard laparoscopic approach. The device decreased esophageal acid exposure, improved reflux symptoms and quality of life, and allowed cessation of PPIs in the majority of patients.

The expert panel convened by the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) Technology and Value Assessment Committee (2013) concluded the following:

- The incidence of initial dysphagia following LINX implantation is high. Difficulty swallowing was more commonly reported at 12 and 24 months following LINX implantation than at baseline. Patients should be advised about the possibility that it may be more difficult to swallow following surgery, and that this symptom may persist.
- The LINX device may provide an option currently lacking in clinical practice for patients with medically refractory GERD who have not yet progressed to end-stage reflux disease with associated complications.
- Direct comparative studies between the LINX procedure and Nissen fundoplication will be needed
- On the basis of the available evidence, the LINX device should be an option available to patients and providers for the management of medically refractory GERD.

On the other hand, the American College of Gastroenterology (ACG)'s guidelines on "Diagnosis and management of gastroesophageal reflux disease" (Katz et al, 2013) did not agree with the expert opinion rendered by the SAGES Technology and Value Assessment Committee. The ACG guidelines stated that "Endoscopic therapies for GERD have been developed but have not demonstrated long-term efficacy. These therapies included radiofrequency augmentation to the lower esophageal sphincter, silicone injection into the lower esophageal sphincter, and endoscopic suturing of the LES. None of these therapies demonstrated long-term improvement in esophageal pH levels or the ability for patients to stop antireflux therapy and were subsequently removed from the US marketplace. Recent alternative approaches have included transoral incisionless

fundoplication, a suturing device designed to create a full thickness gastroesophageal valve from inside the stomach. Unfortunately long-term data regarding efficacy of this device are limited to a small number of subjects and short duration of follow-up. A recent study suggested that at 36 months of follow-up, the majority of patients had required additional medical therapy or a revisional fundoplication. Sphincter augmentation using the LINX Reflux system constructed of titanium beads has shown efficacy up to 4 years in the reduction of the amount of pathologic esophageal acid exposure in a small number of subjects. This device has been approved by the FDA based on a clinical study in 100 GERD patients. This study found that performance of LINX resulted in consistent symptom relief and pH control with markedly fewer side effects than traditional laparoscopic fundoplication in well-selected patients. More data are required before widespread usage can be recommended. The usage of current endoscopic therapy or transoral incisionless fundoplication cannot be recommended as an alternative to medical or traditional surgical therapy".

In a randomized, multi-center, open label, cross-over study, Trad et al (2014) examined if transoral fundoplication (TF) could further improve clinical outcomes in partial responders to high-dose (HD) proton-pump inhibitor (PPI) therapy and evaluated durability of TF. In 7 United States centers, patients with hiatal hernia less than or equal to 2 cm and abnormal esophageal acid exposure (EAE) were randomized to TF (n = 40) or HD PPIs (n = 23) group. At 6-month follow-up, PPI patients underwent cross-over. These researchers assessed clinical outcomes 6-month post TF in cross-over patients (COP), as compared to 6-month of HD PPI therapy, and 12-month outcomes in patients initially randomized to TF. The primary outcome was symptom control evaluated by Reflux Disease Questionnaire and Reflux Symptom Index. Secondary outcomes included healing of esophagitis, normalization of EAE and PPI use after TF. These investigators analyzed 21 COP and 39 TF patients.

McNemar's test or Fisher exact test was used to compare proportions. Of 63 randomized patients, 3 were lost to follow-up, leaving 39 TF and 21 COP for analyses. In the COP, TF further improved control of regurgitation and of atypical symptoms achieved after 6 months of HD PPIs. Of 20 patients with GERD symptoms after 6 months of high-dose PPI therapy, 6 5% (13/20) reported global elimination of troublesome regurgitation and atypical symptoms post TF off PPIs; 67 % (6/9) reported no troublesome regurgitation. Esophagitis further healed in 75 % (6/8) of patients; 71 % of COP patients were off PPIs 6 months following TF. Normalization of EAE decreased from 52 % after HD PPIs (on PPIs) to 33 % after TF (off PPIs), p = 0.388. In the original TF group, 12-month post TF, 77 % of patients achieved complete symptom control, 82 % ceased PPI therapy, 100 % healed esophagitis and 45 % normalized EAE. The authors concluded that these findings indicated that in patients with incomplete symptom control on high-dose PPI therapy TF may provide further elimination of symptoms and esophagitis healing. In the original TF group, the clinical outcomes of TF remained stable between 6- and 12-month follow-up.

This was a relatively small study (n = 60 including 21 cross-over patients). Furthermore, the authors noted that there were several limitations to this study: (i) this was an open-label, pre-planned cross-over, non-blinded trial, which may carry a certain unintended bias; (ii) although symptomatic control in the TF group improved at 12-month compared to 6-month, a residual placebo effect could still have impacted the reported results, (iii) the lack of pH impedance testing and systematic high-resolution manometry data prevented these researchers from clarifying the presumed effects of TF on patients with non-acid and proximal reflux, and on number of TLESRs, and (iv) for the association analysis, these researchers combined the TF and the cross-over patient to increase the sample size. They believe that these analyses should be repeated on a larger patient population.

In a single-center, prospective case-series study, Bonavina et al (2013b) evaluated their clinical experience during a 6-year period with an implantable device that augments the lower esophageal sphincter for gastro-esophageal reflux disease (GERD). The device uses magnetic sphincter augmentation (MSA) to strengthen the anti-reflux barrier. A total of 100 consecutive patients underwent laparoscopic MSA for GERD between March 2007 and February 2012 were included in this report. Clinical outcomes for each patient were tracked post implantation and compared with pre-surgical data for esophageal pH measurements, symptom scores, and PPI use. Median implant duration was 3 years (range of 378 days to 6 years). Median total acid exposure time was reduced from 8.0 % before implant to 3.2 % post implant ($p < 0.001$). The median GERD Health Related Quality of Life score at baseline was 16 on PPIs and 24 off PPIs and improved to a score of 2 ($p < 0.001$). Freedom from daily dependence on PPIs was achieved in 85 % of patients. There have been no long-term complications, such as device migrations or erosions. Three patients had the device laparoscopically removed for persistent GERD, odynophagia, or dysphagia, with subsequent resolution of symptoms. The authors concluded that magnetic sphincter augmentation for GERD in clinical practice provides safe and long-term reduction of esophageal acid exposure, substantial symptom improvement, and elimination of daily PPI use. For candidates of anti-reflux surgery who have been carefully evaluated before surgery to confirm indication for MSA, MSA has become a standard treatment at these researchers' institution because control of reflux symptoms and pH normalization can be achieved with minimal side effects and preservation of gastric anatomy. The main drawback of this study was its single-center, case-series design.

Louie et al (2014) stated that in 2012 the United States Food and Drug Administration approved implantation of a magnetic sphincter to augment the native reflux barrier based on single-series data. These researchers sought to compare their initial

experience with magnetic sphincter augmentation (MSA) with laparoscopic Nissen fundoplication (LNF). A retrospective case-control study was performed of consecutive patients undergoing either procedure who had chronic gastrointestinal esophageal disease (GERD) and a hiatal hernia of less than 3 cm. A total of 66 patients underwent operations (34 MSA and 32 LNF). The groups were similar in reflux characteristics and hernia size. Operative time was longer for LNF (118 versus 73 mins) and resulted in 1 return to the operating room and 1 re- admission. Pre-operative symptoms were abolished in both groups. At 6 months or longer post-operatively, scores on the Gastroesophageal Reflux Disease Health Related Quality of Life scale improved from 20.6 to 5.0 for MSA versus 22.8 to 5.1 for LNF. Post-operative DeMeester scores (14.2 versus 5.1, p = 0.0001) and the percentage of time pH was less than 4 (4.6 versus 1.1; p = 0.0001) were normalized in both groups but statistically different. MSA resulted in improved gassy and bloated feelings (1.32 versus 2.36; p = 0.59) and enabled belching in 67 % compared with none of the LNFs. The authors concluded that MSA resulted in similar objective control of GERD, symptom resolution, and improved quality of life compared with LNF. MSA appeared to restore a more physiologic sphincter that allows physiologic reflux, facilitates belching, and creates less bloating and flatulence. This device has the potential to allow individualized treatment of patients with GERD and increase the surgical treatment of GERD. The main drawbacks of this study were its retrospective nature, small sample size and short follow-up.

Loh et al (2014) examined if the LINX Reflux management system is an effectives treatment for patients with symptoms of GERD not controlled by PPI. A total of 48 LINX-related papers were identified using the reported search, of which 3 represented the best evidence to answer the clinical question. The authors, journal, date and country of publication, patient group, study type, relevant outcomes and results of these papers were tabulated. All 3 studies were prospective case studies. They demonstrated that LINX is an effective

treatment for GERD patients with good short- and medium-term outcomes and an acceptable safety profile. The authors concluded that further studies are needed to determine its long-term outcomes and its relative efficacy as compared to other established treatments.

Min and Ganz (2014) noted that GERD is a common and progressive condition manifested by heartburn or regurgitation. Although Nissen fundoplication has been and remains the gold standard for procedural therapy for GERD, 2 newer interventions have gained popularity: (i) magnetic sphincter augmentation (MSA), which entails the placement of a self-expanding magnetic ring around the GE junction, and (ii) TIF, an endoscopic approach that creates a neogastroesophageal valve near the fundus. Collective data gathered from 4 studies published within the past year suggested that the 3 modalities share comparable effectiveness in pH monitoring and patient satisfaction, TIF may have a lower PPI cessation rate, and Nissen fundoplication required longer recovery time and had a more serious adverse effects profile. The authors stated that large, prospective, randomized controlled studies are needed to reliably compare the 3 procedures.

Lipham et al (2015) stated that anti-reflux surgery with a magnetic sphincter augmentation device (MSAD) restores the competency of the LES with a device rather than a tissue fundoplication. As a regulated device, safety information from the published clinical literature can be supplemented by tracking under the Safe Medical Devices Act. These investigators examined the safety profile of the MSAD in the first 1,000 implanted patients. They compiled safety data from all available sources as of July 1, 2013. The analysis included intra- and peri-operative complications, hospital re-admissions, procedure-related interventions, re-operations, and device malfunctions leading to injury or inability to complete the procedure. Over 1,000 patients worldwide had been

implanted with the MSAD at 82 institutions with median implant duration of 274 days. Event rates were 0.1 % intra- and peri-operative complications, 1.3 % hospital re-admissions, 5.6 % endoscopic dilations, and 3.4 % re-operations. All re-operations were performed non-emergently for device removal, with no complications or conversion to laparotomy. The primary reason for device removal was dysphagia. No device migrations or malfunctions were reported. Erosion of the device occurred in 1 patient (0.1 %). The authors concluded that the safety analysis of the first 1,000 patients treated with MSAD for GERD confirmed the safety of this device and the implantation technique. The overall event rates were low based on data from 82 institutions. They stated that the MSAD is a safe therapeutic option for patients with chronic, uncomplicated GERD. The main drawbacks of this study included: (i) typical patients treated with MSAD generally do not have a large hiatal hernia or other co-morbidities, such as Barrett's esophagus, strictures, or motility disorders to the same extent as patients who typically undergo fundoplication, and (ii) the reliance on health professionals to consistently report events occurring outside of a clinical study to the manufacturer and/or FDA.

In a multi-center, prospective, observational study, Riegler et al (2015) evaluated the magnetic sphincter augmentation device (MSAD) and laparoscopic fundoplication (LF) in clinical practice. Data collection included baseline characteristics, reflux symptoms, PPI use, side effects, and complications. Post-surgical evaluations were collected at 1 year. At report, 249 patients (202 MSAD patients and 47 LF patients) had completed 1-year follow-up. The LF group was older and had a greater frequency of large hiatal hernias and Barrett's esophagus than the MSAD group ($p < 0.001$). The median GERD-health related quality of life score improved from 20.0 to 3.0 after MSAD and 23.0 to 3.5 after LF. Moderate or severe regurgitation improved from 58.2 to 3.1 % after MSAD and 60.0 to 13.0 % after LF ($p = 0.014$). Discontinuation of PPIs

was achieved by 81.8 % of patients after MSAD and 63.0 % after LF (p = 0.009). Excessive gas and abdominal bloating were reported by 10.0 % of patients after MSAD and 31.9 % following LF (p ≤ 0.001). Following MSAD, 91.3 % of patients were able to vomit if needed, compared with 44.4 % of those undergoing LF (p < 0.001). Re-operation rate was 4.0 % following MSAD and 6.4 % following LF. The authors concluded that anti-reflux surgery should be individualized to the characteristics of each patient, taking into consideration anatomy and propensity and tolerance of side effects. Both MSAD and LF showed significant improvements in reflux control, with similar safety and re-operation rates. In the treatment continuum of anti-reflux surgery, MSAD should be considered as a first-line surgical option in appropriately selected patients without Barrett's esophagus or a large hiatal hernia in order to avoid unnecessary dissection and preserve the patient's native gastric anatomy. MSAD is an important treatment option and will expand the surgeon's role in treating GERD. This was an observational study; its findings need to be validated by randomized controlled trials.

Furthermore, an UpToDate review on " Surgical management of gastroesophageal reflux in adults" (Schwaitzberg, 2014) states that " LINX prosthesis -- In 2013, the US Federal Drug Administration (FDA) approved the LINX Reflux Management System for lower esophageal sphincter augmentation. Eligible patients for the procedure include those with inadequate symptom control with acid suppression therapy, including those patients with mild to moderate GERD and a hiatal hernia less than 3 cm. The device is a ring made up of a series of rare earth magnets that have sufficient attraction to increase the LES closure pressure, but allow for food passage with swallowing. Results from early studies at four years are encouraging".

An assessment by the ECRI Institute (2013) of the Linx procedure judged the quality of studies to be low. Commenting on the pivotal studies by Ganz, et al., and Lipham, et al., the

ECRI report stated that weaknesses of these studies include inconsistent and incomplete results reporting (Ganz et al. reported intent-to-treat [ITT] at one year, not at subsequent follow-ups, patients were lost to follow-up; Lipham reported findings on the basis of patients left at follow-up, not ITT), and post-hoc analyses on an unclear number of patients. Both studies took baseline esophageal pH level measurements while patients were off PPI therapy, so no pre-post pH comparison data for PPI therapy and Linx are available. The ECRI reported also noted that results in the text of articles did not consistently correspond to results in tables.

An AHRQ Horizon Scanning Report on peptic ulcer disease and dyspepsia (ECRI, 2013) commented that: "Experts thought this intervention has potential to improve patient health, although comparative studies evaluating Linx with other minimally invasive GERD procedures have not been conducted. Experts noted that although this intervention is likely to be accepted by patients, clinicians may be hesitant because of the small amount of data on safety and efficacy and the lack of long-term data on safety and efficacy."

Sheu and Rattner (2015) evaluated the current data on the safety, effectiveness, and indications for MSA using the LINX device to treat GERD. The LINX device has demonstrated excellent safety and GERD efficacy in several recent non-blinded, single-arm studies with strict inclusion criteria and up to 3 years follow-up. Dysphagia has been the most common adverse effect occurring after LINX. Other gastro-intestinal side-effects seen after laparoscopic fundoplication (bloating, gas, and inability to belch) may be less common after LINX. The authors concluded that the LINX device is a safe, well-tolerated, and effective therapy for GERD in the short-term. They stated that MSA should be considered for selected GERD patients without significant anatomic or motility defects; however, the long-term safety and effectiveness of LINX -- both alone and in comparison to current GERD therapies -- remains to be determined.

In a prospective, multi-center, pilot study, Saino et al (2015) evaluated safety and effectiveness of the magnetic sphincter augmentation device (MSAD) for 5 years. Prior to MSAD placement, patients had abnormal esophageal acid and symptoms poorly controlled by proton pump inhibitors (PPIs). Patients served as their own control, which allowed comparison between baseline and post-operative measurements to determine individual treatment effect. At 5 years, gastro-esophageal reflux disease (GERD)-Health Related Quality of Life (HRQL) questionnaire score, esophageal pH, PPI use, and complications were evaluated. Between February 2007 and October 2008, a total of 44 patients (26 males) had an MSAD implanted by laparoscopy, and 33 patients were followed-up at 5 years. Mean total percentage of time with pH less than 4 was 11.9 % at baseline and 4.6 % at 5 years ($p < 0.001$), with 85 % of patients achieving pH normalization or at least a 50 % reduction. Mean total GERD-HRQL score improved significantly from 25.7 to 2.9 ($p < 0.001$) when comparing baseline and 5 years, and 93.9 % of patients had at least a 50 % reduction in total score compared with baseline. Complete discontinuation of PPIs was achieved by 87.8 % of patients. No complications occurred in the long-term, including no device erosions or migrations at any point. The authors concluded that based on long-term reduction in esophageal acid, symptom improvement, and no late complications, the findings of this study showed the relative safety and effectiveness of magnetic sphincter augmentation (MSA) for GERD.

The main drawbacks of this study included no comparison treatment group and loss of patients during the 5-year follow-up (only 33 patients were available for 5-year follow-up). Esophageal pH data were completed by all sites at 1 year, but not all sites continued to perform esophageal pH monitoring past the 1-year follow-up. Long-term manometric data to characterize any changes in esophageal motility would have been informative; but were not part of the protocol past the 1-year follow-up. No significant findings were found during

follow-up to make continued manometric evaluations clinically necessary. For the clinical study, only patients with normal motility were eligible for MSAD implantation, defined as esophageal amplitude of at least 35 mm Hg and at least 70 % effective swallows. In clinical practice, these investigators have adhered to implanting only patients with normal motility. Normal esophageal motility is necessary to facilitate propulsion of a food bolus through the esophageal body in order to push open the magnetic device and allow passage through the LES and into the stomach. In clinical practice, one author has developed a barium esophagram protocol to evaluate for adequate motility related to MSAD and limited the use of manometry to those patients found to have abnormal passage of a solid bolus by video esophagram. The protocol involves evaluations in the upright, prone, and supine positions while the patient swallows liquid as well as solid food bolus (i.e., contrast-coated hamburger). These preliminary findings from a pilot study need to be validated by well-designed studies.

Ganz et al (2016) performed a prospective study of the safety and efficacy of a magnetic device in 100 adults with GERD for 6 months or more, who were partially responsive to daily PPIs and had evidence of pathologic esophageal acid exposure, at 14 centers in the United States and The Netherlands. The magnetic device was placed using standard laparoscopic tools and techniques; 85 subjects were followed up for 5 years to evaluate quality of life, reflux control, use of PPIs, and side effects. The GERD-HRQL questionnaire was administered at baseline to patients on and off PPIs, and after placement of the device; patients served as their own controls. A partial response to PPIs was defined as a GERD-HRQL score of 10 or less on PPIs and a score of 15 or higher off PPIs, or a 6-point or more improvement when scores on versus off PPI were compared. Over the follow-up period, no device erosions, migrations, or malfunctions occurred. At baseline, the median GERD-HRQL scores were 27 in patients not taking PPIs and 11 in patients on PPIs; 5 years after device placement this score decreased to 4. All patients used PPIs at

baseline; this value decreased to 15.3 % at 5 years. Moderate or severe regurgitation occurred in 57 % of subjects at baseline, but only 1.2 % at 5 years. All patients reported the ability to belch and vomit if needed. Bothersome dysphagia was present in 5 % at baseline and in 6 % at 5 years. Bothersome gas-bloat was present in 52 % at baseline and decreased to 8.3 % at 5 years. The authors concluded that augmentation of the lower esophageal sphincter with a magnetic device provided significant and sustained control of reflux, with minimal side effects or complications. No new safety risks emerged over a 5-year follow-up period. They stated that these findings validated the long-term safety and effectiveness of the MSA device for patients with GERD.

The major drawbacks of this study were: (i) all of the centers were high-volume esophageal center, and high-volume surgeons with extended proficiency in dissection of the diaphragmatic hiatus, performing laparoscopic fundoplication and early adopters of magnetic sphincter augmentation (MSA) technology. This may limit the applicability of the results outside of high-volume esophageal centers, (ii) the lack of an objective post-operative GERD control measure -- esophageal pH testing and manometry were not performed beyond 1 year. Manometry data have been reported previously with no significant change in any manometric parameter. Esophageal pH results at 1 year showed that the majority of the patients had normalization of esophageal acid exposure along with symptomatic improvement and discontinuation of PPIs. Longer-term pH data would have strengthened the conclusions, and (iii) the lack of a comparison group.

While the studies by Saino et al (2015) and Ganz et al (2016) provided long-term outcomes, both of them had limitations. Moreover, they do not address the critical issues that comparisons of LINX with either fundoplication or comparisons with medical therapy are needed.

In a retrospective, case-control study, Warren et al (2016a) evaluated the manometric changes, function, and impact of MSA on the LES (n = 121). Inclusion criteria consisted of a confirmed diagnosis of GERD by an abnormal esophageal pH study (BMI less than 35 kg/m2, hiatal hernia less than 3 cm, and absence of endoscopic Barrett disease). Manometric changes, pH testing, and PPI use were assessed preoperatively and 6 and 12 months after MSA. MSA was associated with an overall increase in the median LES resting pressure (18 pre-MSA versus 23 mm Hg post-MSA; p = 0.0003), residual pressure (4 versus 9 mm Hg; p < 0.0001), and distal esophageal contraction amplitude (80 versus 9 0mm Hg; p = 0.02). The percent peristalsis remained unaltered (94 % versus 87 %; P = 0.71). Overall, patients with a manometrically defective LES were restored 67 % of the time to a normal sphincter with MSA. Those with a structurally defective or severely defective LES improved to a normal LES in 77 % and 56 % of patients, respectively. Only 18 % of patients with a normal pre-operative manometric LES deteriorated to a lower category. The authors concluded that MSA results in significant manometric improvement of the LES without apparent deleterious effects on the esophageal body. A manometrically defective LES can be restored to normal sphincter, whereas a normal LES remains stable. The authors noted that this study had several drawbacks: (i) the data were pooled and, though prospectively collected and retrospectively analyzed, it is from several different studies and multiple organizations, (ii) there was no standardized protocol for conducting or interpreting manometry. Also, it is recognized that assessment of LES length with high resolution manometry is controversial as it may not be as

reliable as stationary pull through manometry. However, given its broad utilization in many centers the data should be applicable, (iii) the original manometry files were not reviewed and re-interpreted due to the complexity of acquiring files from multiple systems in multiple centers over time. Nevertheless, the centers contributing data were experienced esophageal centers and have experienced personnel interpreting these files, and (iv) this was an evaluation of median and mean values and may not be directly applicable to a 1-on-1 comparison. As well, collective differences likely average out in a large group, but when applied to a specific patient, may have a greater error for clinical decision-making.

Warren et al (2016b) stated that magnetic sphincter augmentation (MSA) has emerged as an alternative surgical treatment of GERD. The safety and effectiveness of MSA has been previously demonstrated, although adequate comparison to Nissen fundoplication (NF) is lacking, and required to validate the role of MSA in GERD management. A multi-institutional retrospective cohort study of patients with GERD undergoing either MSA or NF was carried out. Comparisons were made at 1 year for the overall group and for a propensity-matched group. A total of 415 patients (201 MSA and 214 NF) underwent surgery. The groups were similar in age, gender, and GERD-HRQL scores but significantly different in pre-operative obesity (32 versus 40 %), dysphagia (27 versus 39 %), DeMeester scores (34 versus 39), presence of microscopic Barrett's (18 versus 31 %) and hiatal hernia (55 versus 69 %). At a minimum of 1-year follow-up, 354 patients (169 MSA and 185 NF) had significant improvement in GERD-HRQL scores (pre to post: 21-3 and 19-4); MSA patients had greater ability to belch (96 versus 69 %) and vomit (95 versus 43 %) with less gas bloat (47 versus 59 %). Propensity-matched cases showed similar GERD-HRQL scores and the differences in ability to belch or vomit, and gas bloat persisted in favor of MSA. Mild dysphagia was higher for MSA (44

versus 32 %). Resumption of daily PPIs was higher for MSA (24 versus 12, p = 0.02) with similar patient-reported satisfaction rates. The authors concluded that MSA for uncomplicated GERD achieved similar improvements in quality of life and symptomatic relief, with fewer side effects, but lower PPI elimination rates when compared to propensity-matched NF cases. They stated that in appropriate candidates, MSA is a valid alternative surgical treatment for GERD management. The main drawbacks of this study were its retrospective design, short-term (1 year) follow-up, lack of an objective post-operative GERD control measure (e.g., post-operative pH), higher dysphagia, and lower PPI elimination rates, and all of the centers were high-volume esophageal centers, and high-volume surgeons with extended proficiency in dissection of the diaphragmatic hiatus, performing laparoscopic fundoplication, and early adopters of MSA technology. This may limit the applicability of the results outside of high-volume esophageal centers.

Reynolds et al (2016) compared charges, complications, and outcome of MSA versus laparoscopic Nissen fundoplication (LNF) at 1 year. This was a retrospective analysis of all patients who underwent MSA or LNF for the treatment of GERD between January 2010 and June 2013. Patient charges were collected for the surgical admission. These researchers also collected data on 30-day complications and symptom control at 1 year assessed by GERD-HRQL score and PPI use. There were 119 patients included in the study, 52 MSA and 67 LNF. There was no significant difference between the mean charges for MSA and LNF ($48,491 versus $50,111, p = 0.506). There were significant differences in OR time (66 minutes MSA versus 82 minutes LNF, p < 0.01) and LOS (17 hours MSA versus 38 hours LNF, p < 0.01). At 1-year follow-up, mean GERD-HRQL was 4.3 for MSA versus 5.1 for LNF (p = 0.47) and 85 % of MSA patients versus 92 % of LNF patients were free from PPIs (p = 0.37). MSA patients reported less gas bloat symptoms (23 versus 53 %, p ≤ 0.01) and inability to belch (10 versus 36 %, p ≤ 0.01) and vomit (4

versus 19 %, p ≤ 0.01). The authors concluded that the side effect profile of MSA was better than LNF as evidenced by less gas bloat and increase ability to belch and vomit. They stated that LNF and MSA are comparable in symptom control, safety, and overall hospital charges. The charge for the MSA device is offset by less charges in other categories as a result of the shorter operative time and LOS. The main drawbacks of this study were its retrospective design, short-term (1 year) follow-up, the primary outcome was a difference in charges, and the study was not adequately powered for the secondary outcome -- it was not powered to detect a difference in PPI use of less than 10 %.

Asti et al (2016) stated that only a minority of patients with GERD are offered a surgical option. This is mostly due to the fear of potential side effects, the variable success rate, and the extreme alteration of gastric anatomy with the current gold standard, the laparoscopic Nissen fundoplication. It has been reported that laparoscopic Toupet fundoplication (LTF) and laparoscopic sphincter augmentation using a magnetic device (LINX) can treat reflux more physiologically and with a lower incidence of side-effects and reoperation rate. In an observational cohort study, these researchers presented the first comparing quality of life in patients undergoing LTF versus LINX. Consecutive patients undergoing LTF or LINX over the same time period were compared by using the propensity score full matching method and generalized estimating equation. Criteria of exclusion were greater than 3 cm hiatal hernia, grade C-D esophagitis, ineffective esophageal motility, body mass index (BMI) greater than 35, and previous upper abdominal surgery. The primary study outcome was quality of life measured with the GERD-HRQL questionnaire. Secondary outcomes were PPI use, presence of gas-related symptoms or dysphagia, and reoperation-free probability. Between March 2007 and July 2014, a total of 238 patients with GERD met the criteria of inclusion in the study. Of these, 103 underwent an LTF and 135 a LINX procedure. All patients had a minimum 1-year follow-up. Over time, patients in both

groups had similar GERD-HRQL scores (odds ratio [OR] 1.04, confidence interval [CI]: 0.89 to 1.27; p=0.578), PPI use (OR 1.18, CI: 0.81 to 1.70; p=0.388), gas-related symptoms (OR 0.69, CI: 0.21 to 2.28; p=0.542), dysphagia (OR 0.62, CI: 0.26 to 1.30; p=0.241), and reoperation-free probability (stratified log-rank test=0.556). In 2 concurrent cohorts of patients with early stage GERD undergoing LTF or LINX and matched by propensity score analysis, health-related quality of life significantly improved and GERD-HRQL scores had a similar decreasing trend over time up to 7 years of follow-up. The authors concluded that LTF and LINX provide similar disease-specific quality of life over time in patients with early stage GERD. The limitations of this study were: (i) the GERD-HRQL is a validated, but still subjective test, and the LINX procedures were not standardized regarding crural repair, (ii) hidden bias typical of an observational study cannot be excluded due to unmeasured and unmeasurable confounding factors, and (iii) the PS model could be biased, and these researchers did not consider possible measurable time-dependent confounders. Moreover, the authors stated that "Despite the sensitivity analysis showed negligible residual bias, we need to be cautious in interpreting the overall study results … Further research is needed to investigate correlation between longitudinal quality of life data with objective long-term outcome of these procedures". Rona and associates (2017) evaluated outcomes of MSA in patients with hiatal hernias greater than or equal to 3 cm. These researchers retrospectively reviewed all patients who underwent MSA at their institutions over a 6-year period. Information obtained consisted of patient demographics, symptoms of GERD, pre-operative GERD-HRQL scores, peri-operative details, and implantation of the MSA device. Primary end-points included post-operative GERD-HRQL scores, PPI use, symptom change, and procedure-related complications. A large hiatal hernia was defined as a hernia measuring greater than or equal to 3 cm by intra-operative measurement. A total of 192 patients were reviewed. Median follow-up was 20 months (3 to 75). Mean GERD-HRQL scores in the overall population

before and after MSA were 18.9 and 5.0, respectively ($p < 0.001$). In the majority of patients symptoms improved or resolved ($n = 177$, $p < 0.001$); 52 patients (27.0 %) had a hiatal hernia greater than or equal to 3 cm (range of 3 to 7). Their mean GERD-HRQL score decreased from 20.5 to 3.6 ($p < 0.001$) following MSA. When compared to patients with smaller hernias, patients with large hiatal hernias had decreased post-operative PPI requirement (9.6 versus 26.6 %, $p = 0.011$) and lower mean post-operative GERD-HRQL scores (3.6 versus 5.6, $p = 0.027$). The percent of patients requiring post-operative intervention for dysphagia was similar (13.5 versus 17.9 %, $p = 0.522$), as was the incidence of symptom resolution or improvement (98.1 versus 91.3 %, $p = 0.118$). The authors concluded that MSA in patients with large hiatal hernias demonstrated decreased post-operative PPI requirement and mean GERD-HRQL scores compared to patients with smaller hernias. The incidence of symptom resolution or improvement and the percentage of patients requiring intervention for dysphagia were similar. They stated that short-term outcomes of MSA were encouraging in patients with GERD and large hiatal hernias. The authors noted that there were several limitations to this study: (i) data were gathered retrospectively and is potentially subject to both selection and information biases as this review spanned over a 6-year period, (ii) after successful introduction of the LINX device into their clinical practice, their understanding of its potential for patients with large hiatal hernias evolved and they began expanding their patient selection to those with hiatal hernias of greater than or equal to 3 cm over the last 2 years of the study. Thus, patients in their large hiatal hernia group had a shorter follow-up time compared to those in their control group. Consequently, the improved post-operative outcomes with respect to PPI requirement and GERD-HRQL scores seen in the large hiatal hernia group may be secondary to a relatively shorter follow-up period. Long- term follow-up with objective post-operative measures of reflux and screening for hiatal hernia recurrence are needed to

confirm the durability of MSA in this patient population. These investigators stated that although their results were encouraging and may broaden the application of MSA, prospective trials comparing MSA and Nissen fundoplication are needed to reveal the optimal surgical therapy in patients with gastro-esophageal reflux and large hiatal hernias.

Patti (2016) reviewed the pathophysiology, clinical presentation, diagnostic evaluation, and treatment of GERD. A search of PubMed was conducted for the years spanning 1985 to 2015 and included the following terms: heartburn, regurgitation, dysphagia, gastroesophageal reflux disease, cough, aspiration, laryngitis, GERD, GORD, endoscopy, manometry, pH monitoring, proton pump inhibitors, open fundoplication, and laparoscopic fundoplication. Only articles in English were included. The author concluded that lifestyle modifications, PPIs, and laparoscopic fundoplication are proven treatment modalities for GERD; endoscopic procedures have not been proven as effective.

An UpToDate review on “Approach to refractory gastroesophageal reflux disease in adults” (Fass, 2016) states that “Another surgical approach is laparoscopic sphincter augmentation using a device comprised of a string of magnetized beads. The device is implanted at the lower esophageal sphincter to maintain closure of a weak lower esophageal sphincter, preventing reflux. The beads then separate when the patient swallows to allow passage of a food or liquid bolus. In one prospective study, 100 patients with GERD that was partially responsive to PPIs underwent implantation of a magnetic esophageal sphincter device. At 3-year follow-up, a 50 % or greater reduction in esophageal acid exposure was achieved in 64 % of patients and 87 % of patients reported complete cessation of PPI use. The most frequent adverse event was dysphagia, which occurred in 68 % of patients. Serious side effects occurred in 6 % of

individuals. However, randomized controlled trials are needed to confirm these results and to assess the long-term safety of magnetic devices to treat refractory GERD".

Chen and colleagues (2017) noted that the efficacy of MSA and its outcomes for GERD are uncertain. These researchers analyzed the efficacy of 2 treatments: (i) NF, and (ii) MSA for GERD. They carried out a meta-analysis using 4 databases. All studies from 2005 to 2016 were included. Pooled effect was calculated using either the fixed or random effects model. A total of 4 trials included 624 patients and aimed to evaluate the differences in PPI use, complications, and adverse events. MSA had a shorter operative time (MSA and NF: RR = -18.80, 95 % CI: -24.57 to -13.04, and p = 0.001) and length of stay (RR = -14.21, 95 % CI: -24.18 to -4.23, and p = 0.005). Similar PPI use, complication (p = 0.19), and severe dysphagia for dilation were shown in both groups. Although there was no difference between the MSA and NF in the number of adverse events, the incidence of post-operative gas or bloating (RR = 0.71, 95 % CI: 0.54 to 0.94, and p = 0.02) showed significantly different results. However, there was no significant difference in ability to belch and ability to vomit. The authors concluded that MSA can be recommended as an alternative treatment for GERD according to their short-term studies, especially in main-features of gas-bloating, due to shorter operative time and less complication of gas or bloating. Moreover ,they stated that there are still many unanswered questions whether MSA is still appropriate for hiatal hernias that are more than 3 cm, whether the long-term outcomes of MSA are same as the short-time outcomes, whether the incidence of LINX device removed and erosion will increase as time goes on, and so on. They stated that it is very important and necessary to perform RCTs to compare the efficacy of MSA compared to NF in short-term and long-term. These investigators stated that the main drawbacks of this study included 2 trials that did not match the size of hiatal hernias, the less number of tails included, and none of RCT trials.

Skubleny and associates (2017) stated that the LINX® magnetic sphincter augmentation system (MSA) is a surgical technique with short-term evidence demonstrating efficacy in the treatment of medically refractory or chronic GERD. Currently, the Nissen fundoplication is the gold-standard surgical treatment for GERD. These investigators noted that they were the first to systematically review the literature and perform a meta-analysis comparing MSA to the Nissen fundoplication. A comprehensive search of electronic databases (e.g., Medline, Embase, SCOPUS, Web of Science and the Cochrane Library) using search terms "Gastroesophageal reflux or heartburn" and "LINX or endoluminal or magnetic" and "fundoplication or Nissen" was completed. All randomized controlled trials (RCTs), non-randomized comparison study and case series with greater than 5 patients were included. A total of 547 titles were identified through primary search, and 197 titles or abstracts were screened after removing duplicates. Meta-analysis was performed on post-operative quality of life (QOL) outcomes, procedural efficacy and patient procedural satisfaction; 3 primary studies identified a total of 688 patients, of whom 273 and 415 underwent Nissen fundoplication and MSA, respectively. MSA was statistically superior to LNF in preserving patient's ability to belch (95.2 versus 65.9 %, $p < 0.00001$) and ability to emesis (93.5 versus 49.5 %, $p < 0.0001$). There was no statistically significant difference between MSA and LNF in gas/bloating (26.7 versus 53.4 %, $p = 0.06$), post-operative dysphagia (33.9 versus 47.1 %, $p = 0.43$) and proton pump inhibitor (PPI) elimination (81.4 versus 81.5 %, $p = 0.68$). The authors concluded that magnetic sphincter augmentation appeared to be an effective treatment for GERD with short-term outcomes comparable to the more technically challenging and time-consuming Nissen fundoplication. Moreover, they stated that long-term comparative outcome data past 1 year are needed in order to further understand the efficacy of magnetic sphincter augmentation.

An assessment of the procedure by the National Institute for Health and Care Excellence (NICE, 2017) found that there were no safety concerns but that available data were short term.. "There is limited evidence of short-term efficacy, but evidence of long-term efficacy is inadequate in quality and quantity."

Bariatric Surgical Procedures for GERD:

Laparoscopic adjustable gastric banding (LAGB) involves the surgical insertion of a hollow band around the stomach near its upper end, creating a small pouch and a narrow passage into the larger remainder of the stomach. The band is inflated with a saline solution and can be tightened or loosened over time to change the size of the passage by increasing or decreasing the amount of saline. The procedure has been suggested to ease the symptoms of GERD. Examples of US Food and Drug Administration (FDA) approved adjustable bands include LAP-BAND and Realize.

Roux-en-Y Gastric Bypass (RYGBP) (open or laparoscopic) is commonly known as "gastric bypass." A small stomach pouch is created to restrict food intake. A Y-shaped section of the small intestine is attached to the pouch to allow food to bypass the lower stomach, the duodenum and the first portion of the jejunum. This reduces the amount of calories and nutrients the body absorbs. Long-limb Roux-en-Y gastric bypass is similar to standard RYGBP, except that the limb through which food passes is long, which purportedly eases symptoms of GERD.

REZA Band:

REZA Band is a non-medication, non-surgical device that was designed to reduce the symptoms of acid reflux. The device is worn around the neck while sleeping and reportedly applies slight external pressure to the cricoid cartilage region (right

below the Adam's apple). This purportedly increases the internal pressure in the upper esophageal sphincter (UES); thereby decreasing acid reflux into the esophagus.

Medigus:

Medigus Ultrasonic Surgery Endostapler (MUSE) utilizes a disposable flexible endoscope that is inserted through the mouth. The system combines a miniaturized video camera, a surgical stapler and ultrasonic sights for alignment. It has been suggested that the use of this device can help restore a normal gastroesophageal valve through anterior fundoplication via endoluminally placed staples.

Electrical Stimulation of the Lower Esophageal Sphincter (EndoStim):

In an open-label, single-center trial, Rodríguez and colleagues (2015) examined the 2-year safety and effectiveness of LES electrical stimulation therapy (EST) in GERD patients. Subjects responsive partially to PPIs with off-PPI GERD HRQL of greater than or equal to 20, 24-hour esophageal pH less than or equal to 4.0 for greater than 5 % of the time, hiatal hernia less than or equal to 3 cm, and esophagitis LA grade C or lower participated in this trial. Bipolar stitch electrodes and a pulse generator (EndoStim BV, The Hague, The Netherlands) were implanted laparoscopically; LES-EST at 20 Hz, 215 μs, 3to 8 mAmp was delivered over 30-minute sessions, 6 to 12 sessions per day, starting on day 1 after implantation. Patients were evaluated using GERD-HRQL, symptom diaries, Short Form-12, and esophageal pH testing at regular intervals. Stimulation sessions were optimized based on residual symptoms and esophageal pH at follow-up. A total of 25 patients (mean age of [SD] = 52 [12] years; 14 men) were implanted successfully; 23 patients participated in the 2-year extension trial, and 21 completed their 2-year evaluation. At 2 years, there was improvement in their median GERD-HRQL on LES-EST compared with both their on-PPI (9

versus 0; p = 0.001) and off-PPI (23.5 versus 0; p < 0.001) baseline scores. Median 24-hour distal esophageal acid exposure improved from 10 % at baseline to 4 % (per-protocol analysis; p < 0.001) at 2 years with 71 % demonstrating either normalization or a greater than or equal to 50 % decrease in their distal esophageal acid exposure. All except 5 patients (16/21) reported complete cessation of PPI use; only 2 patients were using a PPI regularly (greater than or equal to 50 % of days). There was significant improvement in sleep quality and daily symptoms of heartburn and regurgitation on LES-EST. At baseline, 92 % of the subjects (22/24) reported that they were "unsatisfied" with their condition off-PPI and 71 % (17/24) on-PPI compared with 0 % (0/21) "unsatisfied" at the 24-month visits on LES-EST. There were no device- or therapy-related serious adverse events and no untoward sensation or dysphagia reported with LES-EST. The authors suggested that LES-EST is safe and effective for treating patients with GERD over a period of 2 years; LES-EST resulted in a significant and sustained improvement in GERD symptoms, and esophageal acid exposure and eliminated PPI use in majority of patients (16 of 21). The main drawbacks of this study were its open-label, single-center design (lack of a control group) and its small sample size (n = 25). Furthermore, this study excluded patients with moderate and large (greater than 3 cm) hiatal hernias, LES end-expiratory pressures less than 5 mmHg, and those with severe (grade D) esophagitis or long segment Barrett esophagus. These patients tend to have more severe esophageal motor dysfunction and are more likely to suffer from medically refractory GERD. Thus, effectiveness of LES-EST in these subgroups need to be established. The authors stated that “Sham-controlled trials comparing EST with no stimulation and comparative effectiveness trials compared with maximal medical therapy and anti-reflux surgery may help to better establish the role of LES stimulation in the management of GERD”.

In an editorial that accompanied the afore-mentioned study, Attwood (2015) stated that “So is Endostim too good to be true? Only controlled clinical trials will fully reveal the truth”.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

Code	Code Description
Electrical stimulation of the lower esophageal sphincter (e.g., the EndoStim) - no specific code:	
43210	Esophagogastroduodenoscopy, flexible, transoral; with esophagogastric fundoplasty, partial or complete, includes duodenoscopy when performed
43257	Esophagogastroduodenoscopy, flexible, transoral; with delivery of thermal energy to the muscle of lower esophageal sphincter and/or gastric cardia, for treatment of gastroesophageal reflux disease [Stretta System]
43284	Laparoscopy, surgical, esophageal sphincter augmentation procedure, placement of sphincter augmentation device (ie, magnetic band), including cruroplasty when performed
43285	Removal of esophageal sphincter augmentation device
ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):	
K21.0	Gastro-esophageal reflux disease with esophagitis
K21.9	Gastro-esophageal reflux disease without esophagitis

The above policy is based on the following references:

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Amendment to
Aetna Clinical Policy Bulletin Number:
0213 Gastroesophageal Reflux Disease (GERD): Treatment Devices

There are no amendments for Medicaid.