The GERD Device Market: At the Crossroads

by MARY THOMPSON

KEY POINTS

- The GERD device market has a long history of technology failures that continues to weigh negatively on provider and payor perceptions and has raised the clinical evidence bar.

- One company that survived the tough early years is EndoGastric Solutions (EGS), which made a pivotal decision several years back to put more of its resources into conducting rigorous clinical studies.

- Those efforts culminated in a new Category I CPT code covering transoral (incisionless) esophagogastric fundoplasty, which went into effect in January, and that milestone, coupled with negative reports on the potential harms of long-term PPI drug use, is finally creating some tailwinds in this field.

- The challenge for EGS and the other GERD device competitors going forward will be to successfully distance themselves from this market’s checkered past and convince payors that their technologies are safe, work well, and improve the economics of GERD management.

The market for minimally invasive device-based solutions aimed at gastroesophageal reflux disease (GERD) has struggled to make headway over the past decade and a half, due to a combination of factors, including subpar safety, efficacy, and durability outcomes with many of the first-generation technologies, which limited acceptance among both physicians and payors, and widespread adoption of drug treatments, particularly acid-reducing proton pump inhibitors (PPIs), as a first-line therapy for GERD. However, after many years of effort, and a long list of company and device failures, the outlook for this market may finally be taking a positive turn.

Last year, the American Medical Association (AMA) issued a long sought Category I CPT code for transoral esophagogastric fundoplasty (incisionless reconstruction of the gastroesophageal valve using devices delivered orally through the esophagus), which went into effect on January 1. Moreover, in November, AMA created a second new Category I CPT code covering esophageal sphincter augmentation, which goes into effect on January 1, 2017. Those positive developments, coupled with new studies linking long-term PPI use to a variety of serious adverse health effects, are generating renewed interest in minimally invasive device-based treatments for GERD and could provide the impetus this market needs to finally gain significant traction with providers, payors, and patients. Indeed, recently there has been much public press about the long-term risks of PPIs, and GERD patients are increasingly looking for alternatives to drug therapies.
However, the tailwinds currently brewing in this space won’t necessarily boost all companies—only those with technologies that are proven safe, effective, and economically feasible in rigorous clinical studies are likely to fully benefit.

As the drawbacks of PPI use become more widely publicized, a growing number of GERD patients are seeking out alternative treatments, and many are turning their attention to device-based options.

A Brief History of the GERD Device Space

GERD affects an estimated 20% of the US population, according to the National Institutes of Health, and is responsible for nearly nine million US outpatient visits each year. Proton pump inhibitor drugs to treat GERD are among the most commonly prescribed medications; they account for nearly $8 billion in US healthcare expenditures annually, according to one estimate (Everhart JE, et al, Gastroenterology 2009;136:376-386). In fact, three well-known PPIs (Prilosec, Prevacid, and Nexium), as well as a number of other GERD drugs known as H2 receptor agonists, are now available over-the-counter in the US, making them easily accessible to patients who wish to bypass the doctor’s office altogether (Prilosec, was the first PPI to gain OTC approval in June 2003).

PPIs were never really intended for long-term, continuous use, although that is how they are often used by GERD patients today (the US Food and Drug Administration [FDA] recommends no more than three 14-day PPI treatment courses per year). However, a host of negative data has come to light linking long-term PPI use with a number of serious adverse side effects.

Over the past several years, FDA has issued a string of safety warnings on PPIs after studies linked their use to a variety of serious maladies, including *clostridium difficile*-associated diarrhea; low magnesium levels; and a possible increased risk of bone fractures of the hip, wrist, and spine. More recent studies suggest that long-term PPI use may also raise susceptibility to pneumonia and increase the risk of developing chronic kidney disease, end-stage renal disease, heart problems, and even dementia. As the drawbacks of PPI use become more widely publicized, a growing number of GERD patients are seeking out alternative treatments, and many are turning their attention to device-based options.

Further bolstering this trend is the fact that, in addition to their potential long-term adverse effects, PPIs simply are not an effective solution for many patients. In fact, as many as 40% of GERD sufferers fail to obtain sufficient symptom relief after an initial four to eight week course of PPI therapy, and only about 25% respond to twice-daily PPI dosing, according to published reports (Lipka S, et al, Clinical Gastroenterology and Hepatology 2015;13:1058-1067).

Patients with severe GERD who are refractory to PPIs, or who are concerned about the risks of long-term PPI use, are particularly challenging to treat since there are few widely accepted treatment alternatives outside of invasive surgical reconstruction. For many of these patients, the root cause of their GERD can be traced to improper functioning of the lower esophageal sphincter (LES), the valve-like muscle that is supposed to keep stomach contents from traveling backward into the esophagus. The LES can become lax due to age, obesity, or the presence of a hiatal hernia. In patients with this disorder, PPIs cannot address the underlying disease, but can only mask the symptoms, which is a primary reason why the drugs have such a high failure rate in patients with chronic, severe GERD.

The gold-standard surgical treatment for severe GERD due to LES dysfunction is Nissen fundoplication, which is most commonly performed laparoscopically. During a lap Nissen procedure, a portion of the upper stomach (the fundus) is wrapped around the lower esophagus to create a new, tighter “valve.” This procedure is effective in the majority of cases; however, it requires hospitalization and a seven to 10-day recovery period, and it is associated with a number of long-term, new-onset complications, including dysphagia (difficulty swallowing) and the inability to belch/vomit, as well as diarrhea, flatulence, and gas-bloat syndrome.

Device-based therapies for GERD were developed as a less-invasive alternative to surgical fundoplication and are aimed at filling the treatment gap between PPIs, which are more effective for patients with mild GERD, and lap Nissen surgery, which is typically reserved for patients with chronic, severe GERD who fail to respond to (or refuse to take) PPIs.

However, as is true of many nascent medical device markets, the initial clinical experience with many of the early GERD devices was less than stellar. In some cases, the benefits were minimal in terms of symptom relief and acid reduction and were not enough to outweigh the potential procedure-related risks for what is considered primarily a quality-of-life disease (i.e., a disease that is not immediately life-threatening). Other devices simply proved too unsafe and were abandoned or pulled from the market.

Moreover, there was a dearth of hard clinical evidence in those early days supporting device technologies that showed the potential to offer a safe and effective solution.
Although several devices received FDA 510(k) clearance and were launched in the US, manufacturers failed to provide users and payors with definitive evidence, from well-designed clinical trials, proving their safety and efficacy and determining exactly where they fit along the continuum of care.

As a result, a number of companies/technologies eventually fell by the wayside due to device performance/safety issues, a lack of reimbursement, or both. One of the most notable is the **EndoCinch** from **CR Bard**, a transoral device that placed stitches to tighten the LES (**EndoCinch**) was one of the first transesophageal GERD devices to obtain FDA approval—in 2000—but had disappointing long-term clinical results); the **Plicator** from **NDO Surgical Inc.**, a device that fixed a plication, or fold, to tighten the LES using a suture-based implant, but failed to gain traction with payors (J&J acquired the company, which ceased operations in 2008); the **Enterix** injectable bulking polymer from **Boston Scientific Corp.**, which was removed from the market in 2005 due to safety issues; and the **Gatekeeper Reflux Repair System**, a sphincter bulking implant from **Medtronic** that had performance issues during clinical trials.

In addition, **Curon Ltd.**, developer of the **Stretta**, a transoral device that delivers radiofrequency energy to shrink and tighten the LES, filed for bankruptcy in 2006, although that company's assets were subsequently purchased by **Mederi Therapeutics Inc.**, which brought **Stretta** back to the market in 2010. Clinical results with **Stretta** have been mixed; one systematic review and meta-analysis published last year that looked at four randomized, controlled **Stretta** trials (three of **Stretta** vs sham and one of **Stretta** vs PPIs) [Clinical Gastroenterology and Hepatology 2015;13:1058-1067], found no evidence that Stretta produced significant changes in objective measures such as pH normalization, LES pressure, ability of patients to discontinue PPI use, or health-related quality of life, compared with sham therapy. However, the device has consistently demonstrated patient-reported symptom improvement and appears to have an acceptable safety profile, according to John E. Pandolfino, MD, of Northwestern University, writing in the August/September 2015 issue of AGA Perspectives.

In addition to Mederi, a handful of other companies currently operate in the GERD device space, offering a number of next-generation and new and improved device-based solutions. These include **Endogastric Solutions Inc.** (EGS), which was founded in 2003, and **Medigus Ltd.**, founded in 2000 and publicly traded on the Tel-Aviv stock exchange. EGS offers the **EsophyX** device and **SerosaFuse** fasteners, which are used to perform Transoral Incisionless Fundoplication (TIF), a procedure that mimics a surgical Nissen by creating a partial fundoplication endoscopically through the esophagus (the EsophyX system is CE marked and FDA cleared); while Medigus offers the **Medigus Ultrasonic Surgical Endostapler (MUSE)**, a device that combines a miniaturized video camera, disposable surgical endostapler, and ultrasonic sight and range-finder to enable an incisionless, anterior partial fundoplication using standard surgical staples (MUSE is CE marked and was FDA cleared in 2014). Other GERD device competitors include **EndoStim**, founded in 2009, which has a laparoscopically implanted neurostimulation system for GERD; and **Torax Medical Inc.**, founded in 2002, which offers the **LINX Reflux Management System**, a multi-beaded band placed laparoscopically around the outside of the LES.

The latter two solutions from EndoStim and Torax are not incisionless, transoral therapies, but rather, involve devices that are implanted via multi-port laparoscopic surgery. Even though they require laparoscopy, they do not drastically alter the patient's anatomy, as lap Nissen does, and both are touted as having fewer side effects than Nissen and being reversible (although some question whether the LINX procedure will prove reversible over the long term). Conversely, both of these options are comparatively expensive and require the patient to have an implanted device (the LINX procedure is more expensive than a standard lap Nissen due to the cost of the device).

The EndoStim system consists of a pulse generator, implanted in a pocket in the upper abdomen, and a bipolar lead with two electrodes that are fastened to the LES. According to the company, electrical stimulation of the LES has been shown to strengthen the sphincter muscle, resulting in fewer GERD symptoms, less acid exposure, and reduced reliance on PPI drugs. Moreover, the firm claims there is no adverse effect on the patient’s ability to swallow. The EndoStim device is CE marked and available outside the US, and the company, which nixed its IPO plans in December, is preparing to conduct an IDE-approved multicenter, randomized, double-blind, sham-controlled trial aimed at US market approval.

Torax’s LINX is a unique GERD solution that consists of a ring of interlinked magnetic beads surrounding the LES (also known as magnetic sphincter augmentation). The beads are designed to expand when the patient swallows to allow the passage of food and liquids, and tighten together afterward to keep stomach contents from traveling back into the esophagus. According to the clinical study data released to date, the LINX procedure appears to be safe and effective, and it may result in fewer post-procedure complications than lap Nissen, although long-term data are limited. The company has nonrandomized follow-up data out to five years showing no device erosions, migrations, or malfunctions; significant reflux control; and minimal side effects (the most common side effect is dysphagia), and it is conducting a randomized trial (CALIBER) comparing LINX to PPIs.

The LINX device was FDA PMA approved in March 2012 and a new Category I CPT code that covers sphincter augmentation with LINX will take effect in January 2017 (LINX providers can also use existing laparoscopic codes). The device
appears to be gaining some traction among providers and payors—Health Care Service Corporation (HCSC), the fourth largest US private insurer (through its Blue Cross Blue Shield affiliates), recently issued a positive coverage policy for LINX that went into effect on April 1. The new policy endorses LINX as “medically necessary as a treatment alternative to surgical fundoplication when the patient has chronic GERD symptoms and is refractory to maximum medical therapy.”

Although clinical outcomes to date with the current generation of GERD devices appear to be considerably better than with earlier products, many physicians and payors continue to call for more rigorous, longer-term safety and efficacy data from large, randomized trials. Thus, it is likely that additional positive clinical evidence, along with continued momentum on the reimbursement front, will be required to spark significant, sustained growth in this market. In the meantime, widespread payor coverage remains difficult, although there are some encouraging signs in this area. The challenge now for GERD device companies is to successfully distance themselves from this market’s checkered past—which, in the end, can only be accomplished by investing in well-designed, long-term clinical studies that clearly demonstrate the safety, efficacy, and durability of their technology.

EndoGastric Solutions: A Study in Persistence

One company with a good perspective on both the past and present state of the nonsurgical GERD device market is long-time competitor EndoGastric Solutions, which managed to hang on through the market’s difficult early years while watching many of its competitors drop out. The aim of EGS’s TIF procedure is to produce results similar to a laparoscopic Nissen fundoplication while reducing the recovery time and avoiding or minimizing common complications associated with Nissen surgery, such as gas-bloat and dysphagia. Patients typically recover faster following TIF than lap Nissen, the firm says, with most able to return to non-weight-bearing activities within several days, versus a week or more following lap Nissen.

During a TIF procedure, which is performed under general anesthesia, the EsophyX device is inserted into the patient’s mouth over a standard endoscope and advanced down the esophagus to the gastroesophageal junction (the opening to the stomach). Under direct endoscopic visual guidance, the EsophyX device is then used to create a tissue fold, which is secured using the firm’s proprietary SerosaFuse nonresorbable, polypropylene tissue fasteners.

The Blessing and Curse of a 510(k) Device in Today’s Payor-Dominated World

EGS’s story is indicative of the significant change that has occurred in the medical device world over the past decade, notes Mike Carusi, General Partner at Advanced Technology Ventures, a long-time EGS investor, and Managing General Partner at Lightstone Ventures. The company’s experience also illustrates what Carusi now refers to as “the blessing and the curse of the 510(k) pathway.”

EGS started out at a time when FDA 510(k) clearance was the preferred US regulatory strategy for many device start-ups (and their investors), offering a lower-cost, expedited route to the US market compared with the more rigorous premarket approval (PMA) pathway. However, while devices that meet 510(k) requirements may enjoy a quicker path through the FDA, the abbreviated clinical evidence FDA requires of these devices often is no longer enough to satisfy payors and obtain the coverage and adoption necessary to establish and sustain a new technology in the marketplace. Interestingly, that important market shift is being driven not so much by government payors (i.e., Medicare) as by private payors, who in the past would often follow along with Medicare coverage decisions, but are now wielding new clout of their own.

As a result, EGS reached an important crossroads a few years back when the company realized it would need to conduct additional clinical studies to win payor and provider support. “If we had to do it all over again,” notes Carusi, “we would have done those bigger studies from the get go. Not because it was required by FDA, but because payors and [provider] societies required it [in order to obtain the Category I CPT code].”

It’s been a learning curve for all start-up investors, not only those in the GERD field, he explains, to realize that “we now have to run more trials, different trials, and multiple trials;” and whether it’s a 510(k) or a PMA is not that important anymore—“now the critical question is ‘what are the data needs?’”

“The data needs of all constituents have gone up,” Carusi continues. “And that means, unfortunately, that the
According to the company, the procedure reconstructs the gastroesophageal valve by creating a 270-degree, 2-3 cm long, partial wrap, thereby tightening the junction and reducing reflux.

Like many of its competitors in the GERD device space, EGS has faced both technology and business-related challenges over the years. In February 2014, the company agreed to pay $5.25 million to settle a US Department of Justice (DOJ) civil lawsuit over the firm’s marketing practices (EGS admitted no wrongdoing under the settlement agreement). The company also went through a couple of management shifts—the latest in May 2014, when medtech veteran Skip Baldino came on board as president and CEO.

EGS’s device technology, as well as the TIF procedure itself, also have evolved considerably as the company worked to improve and validate its GERD solution. The EsophyX system was first cleared by the FDA (via the 510(k) pathway) in 2007. In 2015, EGS received FDA clearance for a third-generation version of the device, the EsophyX Z, which has a trigger-like handle similar to common surgical stapler devices. Baldino says the EsophyX Z significantly reduces the number of steps required to perform TIF, making the procedure easier, faster, and more reproducible.

magnitude of the opportunity has to be that much bigger. So to justify that investment, you’ve got to be doing something big, you’ve got to be doing something meaningful, you’ve got to be doing something that’s clinically disruptive, and you’ve got to be taking into account cost-effectiveness. You’ve got to hit that trifecta of efficacy, safety, and cost-effectiveness, and you have to prove all three of those things with data—not just to FDA, but also to hospitals, physicians, payors, and patients.”

Carusi also points to something unique to the GERD market that he says EGS and its investors “underappreciated” at the beginning: the “overhang related to the [GERD device] failures that had come before us.” That lingering skepticism, he explains, “raised the [clinical evidence] bar even further. EGS has a very different approach and mechanism, but in the space as a whole, I think there was just doubt [that these devices would work] because of the failures of the past.”

So with all of these headwinds, why did EGS’s investors hold on for so long? Largely because they believed in the technology and in the magnitude of the opportunity, says Carusi, who now thinks their perseverance could soon be rewarded. The TIF procedure basically mimics a proven surgical Nissen, he notes, but it does so in a “more aggressive way” than earlier plicator devices. As a result, the investors believed it would work, he says, noting that the first-generation EGS device worked “pretty well,” but as both the device and surgeon technique evolved and improved, efficacy rates also improved. “I truly believe this is a cure for GERD,” he says.

He also notes that the safety profile of the TIF procedure is “much improved” compared with surgery, and the procedure is less expensive than a Nissen and some of the other emerging competitive device-based solutions. “This device and this procedure have the potential to evolve further and get quicker and easier to do, and that helps to improve the cost profile over time, so to me, it hits those three components [safety, efficacy, and cost effectiveness].”

Although Carusi acknowledges that EGS still needs to win over payors, he expects to see significant positive momentum in the GERD device market over the next three to five years, with private payor coverage beginning to ramp up this year and the next. “I think, for me, we can still see a reasonable outcome here, even though it’s taken far longer than any of us had hoped.”

Pausing to Gather Evidence

In addition to its product improvement efforts, EGS has been focused for the past several years on gaining the necessary clinical evidence required to achieve acceptance and coverage in today’s medtech market (see Box, “The Blessing and Curse of a 510(k) Device in Today’s Payor-Dominated World”). According to Baldino, the turning point for the company came several years ago when the firm made a pivotal decision to pull back on its commercialization efforts and instead focus on generating the type of rigorous clinical evidence sought by both payors and providers. Since then, EGS has conducted and published four randomized, controlled trials with TIF and the EsophyX, two of which were sham-controlled trials. Those include the 129-patient RESPECT study, the first randomized, blinded, sham-controlled trial to focus exclusively on regurgitation (the study was published last year in Gastroenterology [2015;148:324-333]), and the firm’s latest randomized study, TEMPO, which compared the TIF procedure to PPIs (six-month results were published in Surgical Innovation [2015 Feb;22(1):26-40]). Altogether, more than 17,000 patients worldwide have been treated with EsophyX since the device was first FDA-cleared.

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EGS has been one of the most active GERD device companies when it comes to investing in rigorous clinical trials; however, its studies (and those of its competitors) still rely heavily on subjective patient-reported symptom/quality-of-life (QOL) outcomes, and longer-term follow-up in these trials remains relatively limited.

The American Gastroenterological Association (AGA), in collaboration with EGS, is currently conducting a 500-patient, 20-center, three-year open registry study comparing QOL (health-related QOL is the primary outcome), safety, durability, and costs with the TIF procedure versus lap Nissen (the study’s primary completion date is July 2018).

In addition, EGS continues to follow patients in its randomized TEMPO trial, which is investigating patient-reported GERD symptoms as the primary endpoint and also is collecting data on acid exposure and other more objective parameters.

Six-month outcomes from TEMPO showed elimination of “troublesome regurgitation” (defined as mild symptoms for two or more days per week or moderate-to-severe symptoms for more than one day per week) in 97% of TIF patients, compared with 50% of PPI patients (relative risk: 1.9; p=0.006). In addition, 62% of TIF patients reported elimination of regurgitation and extraesophageal symptoms at six months versus only 5% of PPI patients (p=0.009); and 90% of TIF patients were able to discontinue PPI use. However, the groups were similar with respect to normalization of esophageal acid exposure, which was observed in 54% of TIF patients and 52% of PPI patients.

According to the TEMPO study authors, this was the first clinical trial, to their knowledge, where “an endoscopic anti-reflux procedure involving reconstruction of the gastroesophageal junction, was found to be more effective than PPIs” in controlling GERD symptoms. Based on these findings, they write, it appears that “the TIF procedure is ideally suited as a treatment alternative for GERD patients who fall in the so-called ‘therapy gap,’” which is used to describe the 30-40% of patients who fail to obtain adequate symptom relief by taking daily PPIs. Such patients, the authors point out, “are often unwilling to undergo a laparoscopic fundoplication for fear of its side effects.”

Three-year follow-up data from TEMPO, presented at this year’s SAGES (Society of American Gastrointestinal and Endoscopic Surgeons) meeting in Boston, found that the benefits of TIF were largely sustained, with 91% of TIF patients reporting elimination of “troublesome regurgitation” at 36 months, 70% of TIF patients off of PPI therapy, and 87% demonstrating healed reflux esophagitis. Two patients required laparoscopic revision procedures. (Note that the TEMPO study included 63 chronic GERD patients randomized to TIF [n=40] or PPIs [n=23]; all patients in the PPI group crossed over and received TIF at the six-month time point). A total of 52 patients were included in the three-year report.

Researchers also performed a two-year economic analysis using data on more than 13,000 patients contained in the Optum healthcare database. They found that the median per-patient costs at two years were similar when comparing the 73 patients who had undergone TIF and the 2,734 patients who had a Nissen fundoplication, while costs were substantially higher for the 10,486 patients on high-dose PPI therapy ($7,397 for the TIF procedure; $8,412 for Nissen; $9,697 for PPIs).

Although formal revised clinical guidelines on GERD have been slow to materialize, some societies have published limited updates covering device-based treatments, including the American Society for Gastrointestinal Endoscopy (ASGE), which issued a new guideline document last June. (And, Baldi says several others, including AGA, ACG, and SAGES, have taken tangible steps recently on key payor advocacy initiatives.) The ASGE’s publication, entitled “The Role of Endoscopy in the Management of GERD” (Gastrointestinal Endoscopy 2015;81(6):1305-1310), evaluated the clinical evidence to date for two endoluminal GERD technologies: EGS’s TIF procedure and the Stretta from Mederi Therapeutics. The authors suggest that physicians “consider” endoscopic antireflux therapy “for selected patients with uncomplicated GERD,” although they grade the quality of evidence as “low,” and they encourage more rigorous comparative studies. “Prospective trials,” they write, “comparing these therapies with existing medical and surgical options using objective measures of GERD as the primary endpoint could be useful in further defining the clinical role of these procedures.” (EGS points out that at the time these guidelines were written, its fourth randomized, controlled trial and the TEMPO 36-month data were not available for consideration.)

EGS still has a long road ahead of it before the TIF procedure is widely accepted as a standard therapy for GERD (most US private payors still consider TIF investigational). However, the company continues to benefit from a very supportive group of venture capital investors, several of whom have been with the firm from the start. Last December, EGS secured a $50 million debt and equity financing, led by new investor CRG, which joined with existing investors Advanced Technology Ventures, Canaan Partners, Chicago Growth Partners, Foundation Medical Partners, and Radius Ventures. The company plans to use the proceeds to begin broad-scale commercialization and make further investments in next-generation EsophyX products.

Like the other competitors in this arena, EGS’s biggest task going forward will be to overcome the skepticism and doubts that still linger in the marketplace and convince payors that its technology is safe, works well, and improves the economics of GERD treatment.
What’s Next for the GERD Device Market?

A Conversation with Skip Baldino of EndoGastric Solutions

To learn more about how current market dynamics might impact the GERD device arena going forward, and how EndoGastric Solutions plans to tackle the challenges ahead, The MedTech Strategist recently spoke at length with EGS CEO Skip Baldino. Although he has been with EGS for only two years, Baldino is far from a newcomer to the medtech space. Prior to joining EGS, he served for four years as President, Americas for Given Imaging (which was acquired by Covidien in 2014 and is now part of Medtronic plc), and before that, he spent 26 years with Abbott Laboratories in numerous medical device divisions.

In the following Q&A, Baldino points out that the existing GERD treatment gap is huge; Nissen fundoplication and drug therapies each have their own sets of risks, and many patients are seeking effective alternatives that don’t involve drugs or invasive surgery. Due to early GERD device company failures, he says, there’s been a hesitancy among providers and payors to fully endorse novel treatment approaches. However, once that hurdle is overcome, Baldino believes there will be room for a variety of proven, minimally invasive solutions in the GERD treatment armamentarium.

The MedTech Strategist: GERD has historically been a challenging market for device companies to penetrate—as you know, several companies/devices have come and gone over the years. Why has EGS been able to stay the course while others have failed in this space?

Baldino: It can be a challenge to find the right balance between short-term revenue-generating activities and being able to invest wisely in areas that are critical to long-term success. If you look at the GERD space, it represents a huge market opportunity with a significant unmet need. It’s possible some companies may not have focused on building the strong foundation that we’ve built—it takes time, perseverance, and a wise and patient healthcare-oriented investor base. And, if you look back on some of early product failures, there was a lack of clinical evidence with durable results. It is also possible that some companies didn’t truly understand the market dynamics and GERD pathology—whether that be referral patterns (the interplay between gastroenterologists and surgeons, because both specialty groups are treating GERD patients), hospital reimbursement, or changing payor expectations. Those areas have been problems for all of healthcare, but even more so in the GERD market because payors often perceive GERD as more of a quality-of-life disease, rather than a lifelong disease. The medical community understands that GERD cannot be cured; instead, it can be well managed. Additionally, as we’ve now learned, there are a lot of long-term consequences—like esophageal cancer—that can result from this disorder.
**MTS:** How has EGS’s strategy evolved to take all of this into account?

**Baldino:** Several years ago we made a very strategic decision to dramatically scale down our organization in terms of the revenue-generating activities—sales reps and marketing initiatives—so that we could redirect that money into building robust clinical evidence. We also worked more closely with physician specialty societies, payors, Key Opinion Leaders (KOLs), and the community physicians who see the majority of the GERD patients to ensure we understood what was important to them and to their patients. Ultimately, we needed to garner society support for our Category I CPT code and provide guidance to their membership about the benefits of adding this to their armamentarium of GERD management offerings.

I am convinced this was an incredibly important course correction for us, and frankly, one that differentiates us from a lot of the earlier players in this space. Building this strong foundation required significant buy-in and support from the Board as well as a total commitment from all of our employees.

**MTS:** What went into that decision? Can you talk a little bit more about that?

**Baldino:** Sure. Reaching out and gaining insights from all key stakeholders in the industry was a key area of focus. Our company got off to a really good start, and revenue was funding quite a bit of our operations. But I think our conversations with society members and leadership as well as other stakeholders indicated clearly that to really climb the mountain and get over the hurdles that others had not, we needed to give them greater confidence that our product worked, worked well, and that we understood not only the mechanism of action, but also what subset of patients are ideal for this therapy in order to get the best clinical outcomes and the highest quality of life. That only occurred with a deep investment into clinical studies further iterating our product offering to meet the needs of our surgeon and GI physicians.

Focusing on these key priorities enabled us to develop close relationships with the people who make the decisions on new technology and understand their requirements for support. I was at Given Imaging at the time this was all going on in the GERD space, and I was very impressed that EGS took the long view on this market opportunity. With 25% of the population in the US, or over 80 million people, suffering from pain or discomfort associated with GERD (see Figure 1), it is easy to understand why some pursued revenues without building a strong foundation of evidence. So, as mentioned earlier, it’s a matter of balancing the desire to capitalize on the significant GERD market potential and providing this novel treatment option to the GERD patient community—and doing it in a way that makes it sustainable and ultimately brings even greater value to the GERD patients we serve. Now that we have built a robust clinical foundation, we have gained strong endorsement from leading surgeon and GI societies, and we are clearly on the path to expanding our reach and scaling our business to enable a much larger portion of the population that suffers from GERD to utilize our TIF [Transoral Incisionless Fundoplication] procedure.

**MTS:** Obviously you couldn’t have done all that without ongoing support from your investors. And you have some very loyal investors who have supported the company from the beginning. What was it that set EGS apart for your investors? Was it your technology, your business plan, or both?

**Baldino:** First of all, the GERD market is quite large and there is a significant treatment gap that we believe our product can help fill in a precise and well defined segment. There are two opposite ends of the spectrum in terms of the continuum of care. At one end is PPIs [proton pump inhibitors]—drugs like Nexium that have been on the market for many, many years. Originally, those were FDA approved for acute use only; they were never meant to be used for more than a few weeks at a time. However, as we know, many people have stayed on PPIs consistently for many years. On the other side of the care continuum is laparoscopic Nissen fundoplication, a fairly invasive procedure that has been around since the 1950s. Lap Nissen is considered the gold-standard procedure for treating GERD. But, as more and more people have gotten Internet-savvy and become more educated on the procedure, there’s been a resistance to undergo lap Nissen surgery because of some of the side effects that occur, such as dysphagia [difficulty swallowing], gas bloat, flatulence, etc.

So, between those two treatment extremes, you have this whole middle section that we call the treatment gap: the real unmet clinical needs (see Figure 2). And that’s one reason why our investors are so steadfast in their support—they understand the size of this treatment gap and the real potential that exists for our TIF procedure to provide a great solution for a sizeable subset of these patients. Secondly,
our Board was very confident in our strategic plan, and understood the timeline. That’s a testament to our investors’ long-term view, their knowledge of the healthcare sector, and their belief that we will scale this business into a solid high-growth franchise. We’ve had a majority of our investor syndicate from the early years when EGS was founded, and several others who joined several years ago. And this past November, we added another solid investor to our syndicate. All of them, together with all of us, are very deeply committed to GERD patients and to what our procedure can do to help improve their lives.

**MTS: What attracted you to this field? Given the state of the GERD device market at the time, and the challenges the company had gone through, did you feel any trepidation about becoming EGS’s CEO?**

**Baldino:** At Given Imaging, we made two acquisitions in the GERD space that we integrated into our business. As a result, I understood and appreciated how pervasive GERD was and also knew that there was a significant treatment gap between PPIs and invasive lap Nissen surgery. At Given, prior to the Covidien acquisition, we were evaluating companies in the therapy side of this market, as we believed this was a natural acquisition opportunity for us since it was adjacent space that we felt our team could expand into without significant incremental SG&A resources. We certainly liked EGS’s minimally invasive treatment option, and I was personally impressed with their approach to building a strong foundation of clinical evidence, including their plans to further iterate the device to expand more broadly into the surgeon and GI community.

I discussed the EGS CEO opportunity with several key healthcare leaders I respected who had in-depth knowledge of the GERD market and the companies in this space. They provided great insights into the market, competing technologies, and what EGS needed to do to gain support from various stakeholders in the GERD arena.

Leading EGS at a time when the company’s multiple randomized, controlled clinical studies were being finalized presented a great opportunity to match my experiences with what the company needed to fully commercialize the business. After meeting with individual Board members, I was confident that they understood the market, EGS’s potential, and were highly committed to the timeline and resources required to bring this technology to the market. In fact, they agreed to make a sizeable additional investment into our company that would enable us to execute on our strategic plan.

**MTS: There have been a lot of news stories recently about the potential negative effects of long-term PPI use. As these studies become more widely publicized, is this opening up a new door of opportunity for the GERD device market?**

**Baldino:** Yes, absolutely. I think this will further educate caregivers and patients on the long-term adverse impact of PPI use. Many studies suggest these patients are at higher risk of a number of adverse effects, such as cardiac issues, osteoporosis, kidney problems, liver...
problems, and even dementia. As we do more direct-to-consumer awareness, we’re starting to see a lot of inbound interest from patients who want an alternative to invasive surgery. And they want to get off of PPIs. It’s a big percentage of the GERD population.

The amount of commentary online has really escalated recently. When we look at the chat rooms where a lot of these GERD patients go, there’s been a lot more activity this year and a lot more outreach from people who are trying to find an alternative. And we’ve seen it in our own sales, but more importantly, we’ve seen it in people asking their physicians about it when they go in and see them in the office. Now that patients and physicians know more about the potential adverse effects of long-term PPI use, I think it does create a tremendous opportunity for the entire GERD device industry.

**MTS: You mentioned the current GERD treatment gap. Is there a specific subset of patients in this gap that are the best candidates for your therapy? How are they being treated today?**

**Baldino:** Of the more than 80 million people in the US who experience GERD symptoms, the ones we are focused on are the 19 million patients who are dependent on PPIs either once or twice per day. Of these, 35% or close to seven million patients, actually do not achieve symptom relief—they are refractory to drug treatment. Until recently, those folks really had no long-term alternative other than to live with the problem and keep taking PPIs, or undergo invasive surgery. These were their only alternatives. But now we have a technology like ours that is minimally invasive, incisionless, and is proven to work very well with a well-defined subset of GERD patients. They can be in and out of the operating room very quickly and be back to living their lives in a much improved state.

**MTS: What’s the current standard-of-care for these drug refractory patients? Are they being offered lap Nissen surgery, and how do you get minimally invasive options like yours to be a part of that conversation?**

**Baldino:** Patients who are refractory to PPIs will be sent for additional diagnostic tests—usually an esophagogastroduodenoscopy (EGD). If this identifies an anatomical issue, which millions of these daily PPI patients have, PPIs won’t do anything but mask the symptoms (they don’t address underlying issues). Patients will then be tested for pH exposure and sometimes undergo manometry or impedance testing to further determine their anatomical condition and the potential root cause of their GERD. Many of these people will be offered a surgical procedure. But less than 25,000 Americans per year actually have lap Nissen—and this number continues to decline, primarily because it’s an invasive procedure with potential new side effects. When potential lap Nissen patients read about the side effects on the Internet from other patients who have had the procedure, many are not comfortable with those tradeoffs. So now, with the TIF procedure and the EsophyX device, they have an opportunity and an alternative to fix their anatomical defect by undergoing a procedure that has a near zero side-effect profile. I think that’s why, in markets where we have coverage and surgeons or GIs are offering the procedure, we’ve been extremely successful.

The other piece that’s interesting is that PPIs don’t work to reduce acid nearly as well as people think they do. In fact, significant reductions in stomach acid are observed in only about half of patients on PPIs [Milkes D, et al; *Am J Gastroenterol*. 2004;99(6)]. We’re finding now that many people on these drugs are still

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**Figure 2**

**Defining TIF’s Place in the GERD Treatment Continuum**

Lifestyle Changes | Pharmaceuticals | TIF Procedure | Conventional surgery
---|---|---|---
Early disease, no anatomic correction required | Anatomic correction warranted | Severe GERD
Mild

**TIF target market >$1.7B**

Source: EndoGastric Solutions
highly acidic. And if you think about what contributes to esophagitis and Barrett’s esophagus, a precursor to esophageal cancer, PPIs still may not get the pH to an appropriate level—so many patients are still exposing their esophagus to acid but their PPIs mask the pain that would normally be associated with acid exposure. Many people think if they’re taking PPIs that completely eradicates the issue, but it doesn’t. More than that, even alkaline gastric content is damaging to the esophageal mucosa and can lead to cancer because non-acid reflux contains enzymes, pepsin, or bile that is extremely harmful to the esophageal lining.

**MTS:** What does that translate to in terms of your annual potential patient pool?

**Baldino:** We don’t know the exact number because not all of these people have had a full work-up (EGD, etc.). But we do believe millions of these patients have anatomical problems that make them suitable candidates. As mentioned, 30% to 35% of GERD patients taking daily or twice-daily PPIs are refractory to the drugs, according to the published literature, which adds up to about 7 million people. About half of those patients will go on to have an EGD, and a significant number of those who do (millions) will be diagnosed with anatomical issues that require more than a PPI, or any chemical therapy, to remedy.

At that point, if there’s a large hiatal hernia or a large defect on EGD, then you have to consider which procedures in the physician’s armamentarium will be most appropriate and give the highest probability of success. This distinction goes back to your first question. I think, in retrospect, many of the early GERD device players didn’t do a good job of segmenting the patient population and understanding where their offering provided the greatest benefit. Many companies tried to address every patient or treat the entire market the same way. And what we now know from our experience in this arena, as well as the clinical research, is that there’s a certain patient profile that actually lends itself very nicely to the TIF procedure, and the success rates, as you can see from our clinical studies, are very, very good with these patients.

Patients with a small hiatal hernia (< 2 cm) and those that are earlier in the disease stage will obviously benefit significantly from our TIF procedure—that’s one thing we’ve learned over the years. After having performed more than 17,000 worldwide procedures, with the vast majority in the US, we have a significant body of evidence that confirms this. Although, ultimately, the physician is the one who determines which treatment option is best suited for each patient.

**MTS:** What percentage of those seven million US patients who are refractory to drugs have an anatomical problem that would make them suitable for your therapy? Is this your primary patient pool?

**Baldino:** It’s very hard to quantify exactly. But based on the two completed randomized trials, we believe that at least two-thirds of the refractory patient pool could be candidates for TIF. We know that up to one-third could be excluded because they have hernias greater than 2 cm or a BMI greater than 35 [another exclusion criteria for TIF and some of the other GERD treatment options]. That translates to up to four million patients in the US that fit into the refractory GERD category who could potentially benefit from a procedure like ours. It’s a very large opportunity for us to bring value to the marketplace.

**MTS:** What do those numbers look like outside the US?

**Baldino:** The US market is the largest. But outside the US represents a sizeable opportunity as well. If you just think of patient demographics and eating habits, there is significant interest from physicians and distributors overseas for us to go into markets in Europe, Latin America, and China. EGS previously marketed the Esophyx in Europe, before pulling back on its sales efforts to US only, in order to concentrate on clinical studies and further product development.) And we will eventually do that, possibly as early as 2017. But we will be very thoughtful and very measured in how we expand outside the US. Our primary goal is to scale the business in the US. But clearly, when we establish a strong commercial US business, as we plan to do, that really sets us up very nicely for an OUS expansion.

**MTS:** What would you say are the main market limiters remaining in this space? Is there still a need to get the word out to patients and physicians that these minimally invasive treatments are available? Is there a problem getting referrals from the primary care physicians who are prescribing PPIs?

**Baldino:** Number one, it’s overcoming the early history of failures with other companies’ medical device
offerings in the GERD space. EGS has robust clinical evidence, and we need to ensure that this information is clearly understood by the payor community in determining coverage policies with TIF 2 [TIF 2 is the latest version of the TIF procedure]. We work very closely with the major specialty societies—probably more in the past two years than we ever have—as well as KOLs to ensure they have the most up-to-date clinical information about our procedure and are aware of the new device enhancements with EsophyX. Because of early GERD device company failures, there’s a hesitancy to fully endorse new novel treatment approaches. And that’s why we continue to share our clinical evidence and ensure that this information is well understood. As a result, we now have stronger support from KOLs and society partners who are true believers in our endoluminal approach to treating a subset of GERD patients and have been active promoters of the TIF procedure with payors.

Number two, while we do very well in terms of communicating directly to the consumer, we have only just begun finalizing our plans for sizeable investments in our digital media campaigns. And, certainly, payors remain a key focus area for us.

MTS: Yes, that was my next question. The recently issued Category I CPT code is obviously a major milestone for the company—but what’s the state of EsophyX payor coverage in the US? As I understand it, most, if not all, of the private payors still consider TIF and other transesophageal GERD procedures to be investigational.

Baldino: We are very proud of the Category I code approval. If you look back, this is the first new Category I code for the GERD space in many years. We also were thrilled to have co-sponsorship and support by the leading GI and surgical societies—both sides of the aisle, from the two primary stakeholders who see GERD patient referrals. None of this would have happened without a very broad and significant body of clinical evidence on our TIF 2 procedure, which is the only TIF technique used in the US since early 2009 (representing 95% of the 17,000 cases to date).

When it comes to the payors, they at times still label a technology as investigational. So we’ve been working with the societies to make it very clear that it is not appropriate to call a procedure investigative when it has been utilized in over 17,000 patients, like our TIF procedure, and has strong clinical evidence that it works well. It takes the specialty societies, physician community, and patients to galvanize efforts behind the ability to change that investigational classification. And we’ve had some success with that from the industry leaders. I see tangible action by several key societies that underscore that they are listening to their members’ cries for more payor advocacy efforts. It’s hard work and a new leadership opportunity for societies, and it is really important to their members to have a treatment alternative, especially for the community doctor looking for an opportunity to offer patients a less-invasive solution. I am encouraged by the recent payor advocacy actions of several leading GI and surgical societies who are actively supporting their members’ needs in this critical area.

I personally know from over 30 years in the healthcare arena, the best probability for success with coverage, after you build strong clinical evidence, is to have the societies and KOLs directly or indirectly advocating the payors for coverage. I can also tell you having KOLs and users in the payors’ own geography who are staunch supporters and are willing to go in and present the merits of the procedure also significantly increases your probability for coverage success. We do that now and it certainly will help.

MTS: Is the procedure covered by CMS for Medicare patients?

Baldino: Yes, it is, as of January 1. There are eight administrators of Medicare across the country. In some of those, we received coverage approval prior to our CPT going live. Several more covered TIF effective this year, with the remainder being scheduled.
And we are confident that the others will come on board when we have the opportunity to present the robust data that we have on TIF 2.0 and they see other carriers covering TIF. We have over 60 peer-reviewed clinical papers from over 50 centers. We’ve got published documents demonstrating the consistent outcomes of 1,100 unique study patients that we’ve chronicled and in whom we’ve shown our procedure works, and works well. So a lot of times it’s just, again, overcoming the old history in the GERD device market where companies failed, and the fact that we need to get the message out about our clinical data and solid patient outcomes. Our most recent 36-month data from our TEMPO RCT offers another strong confirmation that our product works and is durable. When the payors see this new data and combine it with our other robust clinical evidence, I am confident they will agree to offer our minimally invasive transoral treatment option to their members.

**MTS:** Do you have any large private payors on board that you can talk about yet?

**Baldino:** We have a number of key policy reviews ongoing and I am optimistic about new coverage policies soon.

**MTS:** I also wanted to ask you about the CPT code because this is not specific to your procedure. This applies to competitive endoluminal procedures as well, right?

**Baldino:** Yes, most of the CPT codes that have been approved the last several years apply to a category of products. The workload on the societies and the AMA to review hundreds of individual products would significantly add to the timeline for review and approval. In the case of the new code, we are proud of the fact that the clinical data used for the CPT application was 100% EGS’s TIF procedure data. We have invested heavily in establishing robust clinical evidence; that investment gave the societies confidence to sponsor and submit our application, and for the AMA to approve the Category I code.

**MTS:** But won’t all of your heavy lifting benefit your competitors as well?

**Baldino:** Even though others will be able to use the same code, having a code doesn’t necessarily guarantee insurers will pay for those other technologies. Payors will evaluate each manufacturer’s clinical data when making policy coverage determinations. Our hurdle [with payors] should be much lower, given our high-quality body of clinical data. We don’t hide that fact, because we’re obviously quite proud of it. But we don’t try to make that a competitive issue versus anyone else in the market.

Given the GERD device market’s difficult past, and the history of device offerings that ultimately didn’t make it, our hope is that anyone entering this space will invest significantly in strong clinical evidence that proves their technology works and is durable. My belief is that there’s a lot of room for all of us and the more education and investment we all make in the GERD space to move the market forward, the better it is for everybody—for the GERD patients. I think there’s a tremendous amount of interest in other solutions besides PPIs and invasive surgery. And the patient benefits when physicians have a full armamentarium of procedure offerings from which to choose.

**MTS:** Have you quantified what kind of uptick in adoption and revenues you’re expecting going forward as a result of the new CPT code?

**Baldino:** Well, I will say that with the new CPT code, combined with the recent negative publicity on PPIs, we have seen a significant increase in interest among GIs and surgeons in our TIF 2 procedure as a treatment option. And, remember, our customers have performed over 17,000 procedures without a CPT code. So if you think about the hundreds of customers that consistently use our product—for them to do that is an amazing testimony to their belief in our procedure and their commitment to their patients. So, yes, CPT implementation January 1, 2016 changed the game considerably for EGS; as our customers know it’s an important tangible step in the pathway to payment. We’ve seen nice uptick already. And now that we have a new device—the EsophyX Z, or EZ for short—which was cleared by FDA last year, that adds to the momentum and interest. The EsophyX Z removed numerous steps in the TIF procedure, which is appealing to our current and future physician customer base. We initiated a limited launch of our new device recently and that will allow us to expand deeper into the GI and surgical communities.