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EndoGastric Solutions Ushers in a New Day for GERD Interventions

by
MARY STUART

Over the past two decades, many companies have tried and failed to develop safe and effective interventions for gastroesophageal reflux disease to the point where the field was practically unfinanceable. But EndoGastric Solutions has not only survived the journey, it's also gained FDA approval, reimbursement codes, and is now scaling up to serve a large patient population that previously had no good therapeutic options. Its recent $45 million venture capital round solidifies its lead.

At the end of May, **EndoGastric Solutions Inc.** announced that it successfully raised $45 million in venture capital, and that's no small feat because it's a device company with a treatment for gastroesophageal reflux disease (GERD). The interventional GERD space is littered by so many failures that for a time it became almost unfinanceable. Numerous start-ups have come and gone, and at least three strategics in the space have had to pull GERD interventions off the market. (We don't want to kill the buzz by talking about those failures, so for the checkered past of GERD devices, see our review of three years ago, *"The GERD Device Market: At the Crossroads,"* MedTech Strategist, *May 31, 2016*.)

Indeed, in three years, there have been many positive changes for EndoGastric Solutions and for the field of interventional (endoscopic) gastroenterology as a whole. Many of the diseases of the GI tract are yielding to minimally invasive solutions that offer the same benefits as they have for specialties like interventional cardiology—less tissue damage, the economics of shorter or no hospital stays, fewer complications from less invasive procedures, the potential to be more cost-effective than a lifetime of drugs for a chronic condition, and, perhaps most importantly, the ability to treat large numbers of patients who previously had no good therapeutic options.

In the US GERD market, approximately 19 million people take daily proton pump inhibitors (PPIs), the first line of drug therapy. Of these, 6.5 million aren't getting symptomatic relief from these drugs, but don't feel their condition warrants the risks of invasive surgery and the complications that come with GERD's gold standard, the Nissen fundoplication.

These are some of the reasons so many medical device companies have entered the space, not to mention that it's a global market potentially worth $1.7 billion (according to a recent investor presentation by **Apollo Endosurgery Inc.**). If you are at the dinner table with four people, one of them is likely to have GERD, since its prevalence is between 20-25% of the adult population in the US.

EndoGastric Solutions (EGS) is one of the very few companies that have been successful in the GERD segment, and is the leader, by far, in developing an endoluminal intervention (another leading GERD company, Torax, which is now owned by **Johnson & Johnson**, offers a minimally invasive treatment that requires laparoscopic surgery).

The Transoral Incisionless Fundoplication (*TIF 2.0*) platform from EGS is cleared in the US and Europe, and has been used in more than 22,000 procedures to date. *TIF*

2.0 gained a unique CPT code from the AMA in 2016, and an expanded label clearance from the FDA in 2017. The company has over 100 clinical studies demonstrating strong clinical evidence of the durability, safety, and efficacy of its procedure in a field that largely lacks such evidence. EGS also has several level-one randomized clinical trials that have demonstrated long term durability, including five-year follow-up from its US randomized controlled trial (RCT) TEMPO .

The *TIF 2.0* procedure is covered by Medicare in all 50 states, and by some private payors. With over 125 million covered lives, the company remains very focused on convincing private payors that the technology has moved well beyond investigational status and is a clinically validated and appropriate treatment.

It's by no means an overnight success—EGS has been at this for 17 years—but what the company has learned along the way has contributed to the accomplishments it's enjoying today.

The Secret to Success (So Far)

Founded in 2002, EndoGastric Solutions belonged to the first generation of minimally invasive GERD treatments, and it too, faced pressures that could have caused it to fail, namely the desire to run with an FDA 510(k) clearance to gain revenues as quickly as possible to support the next financing round.

In GERD, that turned out to be a risky proposition because there were still some unknowns in the space. The pathophysiology of GERD was not well understood, and GERD patients also have different types of anatomic alterations, which means that good outcomes depend on understanding appropriate patient selection. Finally, without a depth of solid, randomized controlled clinical trial data in a new area of therapy, clinicians and payors didn't embrace new technologies.

As noted, that strategy did not work for many companies, including, at first, EndoGastric Solutions. But in 2014, the company did some soul-searching, and so executed a strategy of investing in RCT level one clinical data and iterating its device multiple times until the procedure was easy to perform and consistently repeatable, while de-emphasizing revenue generation. The company is now focused on partnerships with physicians and practices that have GERD service lines where GERD is a substantial focus.

It is still very early in the adoption curve for interventional therapies for GERD, including that of EndoGastric Solutions. CEO Skip Baldino believes that between the three products available in the US market (the other two from private companies that don't publicly disclose revenues—the Torax *LINX* that J&J now sells, and *Stretta* from **Restech** [**Respiratory Technology Corp.**], US market penetration is probably less than 1%.

On the positive side, this market underpenetration is a strong driver for growth as are several other factors, including increased patient awareness, thanks to the Internet and social media, of the side effects of proton pump inhibitors and the Nissen fundoplication surgery. There is also increased awareness that unchecked GERD leads to Barrett's esophagus, a precursor to esophageal cancer. Winds of change in the gastroenterology specialty are also creating an impetus for the adoption of minimally-invasive technologies.

The American Foregut Society, which embraces both gastrointestinal clinicians and surgeons, is leading to a comprehensive multidisciplinary approach to treating diseases of the GI tract, one that takes down walls between surgeons and endoscopists.

The recent formation of the American Foregut Society, which embraces both gastrointestinal clinicians and surgeons, is leading to a comprehensive multidisciplinary approach to treating diseases of the GI tract, one that takes down walls between surgeons and endoscopists. This trend is pointing to a future of combined procedures for conditions that go hand-in hand to that ensure that patients get the least invasive therapy possible.

GERD is Not a Lifestyle Disease

GERD is a condition in which fluids from the stomach reflux into the esophagus and expose it to stomach acid. It's a mechanical disorder, caused by a failure of the lower esophageal valve, and the problem might be due to the valve itself, to alterations in the lower esophageal muscle just below it, or to a hiatal hernia, a condition where part of the stomach bulges into the chest through a natural defect in the diaphragm.

Patients with GERD experience heartburn, chest pain, regurgitation (the upflow of stomach fluid when patients bend over or they're supine), trouble sleeping, and many other symptoms. The first course of action, diet and lifestyle changes, is challenging to manage; patients must avoid certain foods and time their meals so they are several hours before bedtime.

However, it is medically important to control the symptoms of GERD because it is not a benign condition. When the esophagus is chronically exposed to stomach acid, tissue changes occur and a condition called Barrett's esophagus results. Barrett's is a precursor to cancer, and patients who develop the condition must be regularly monitored.

It's also economically important to get GERD patients under control because this disease can be expensive to manage. According to one US-based study about the cost of employees with GERD, because of physician visits, lab work, drug costs, and other direct and indirect costs, people with GERD cost $3,355 more per year than people without GERD (*see Figure 1).*

When diet and lifestyle modifications fail to control the disease, physicians prescribe proton pump inhibitors, which work by neutralizing stomach acid. They don't actually stop the reflux, which is due to an anatomical failure of the anti-reflux barrier. For that reason, and because they don't control symptoms for 30-40% of the people that take them every day, PPIs are only a partial solution.

For patients with severe GERD who don't respond to PPIs, there is a surgical solution, the Nissen fundoplication, which is performed laparoscopically. The goal of the surgery is to create a new, tighter valve by wrapping a portion of the upper stomach (the fundus) around the lower esophagus. This procedure is highly effective at preventing reflux in the majority of patients. However, there are now only about 30,000 such procedures each year (significantly fewer than previous years). Patients don't opt for Nissen fundoplication for several reasons; first, because it's surgery. It involves perhaps two nights in the hospital and a 7-10 day recovery period. But most impactful on the decision-making process is the new-onset of side effects that typically follow the procedure: discomfort when swallowing (dysphagia), an inability to belch, and increased gas bloat and flatulence.

This leaves a treatment gap for patients who aren't responding well to PPIs and who aren't eligible or don't want the Nissen fundoplication surgery (*see Figure 2*). And increasingly, patients don't want to be on PPIs for the long term either, because of highly publicized studies that find them associated with dementia, stroke, osteoporotic fractures, and a long list of other conditions that patients wouldn't want to experience (*see Figure 3*).

PPIs are not approved for long-term use; they're label allows for a 4-8 week course of treatment which may be repeated within a year. Since 2010, the FDA has issued several safety warnings about the potential effects of daily dependence on PPI therapy, and this has created a problem for gastroenterologists, as more and more patients demand alternatives to these drugs.

To address this ever widening gap, EndoGastric Solutions created an incisionless approach for rebuilding a physiologic lower esophageal sphincter. The *TIF 2.0* procedure results in a partial fundoplication that measures 270 degrees in circumference, and 3 cm in length. During the *TIF 2.0* procedure, a patient is placed under anesthesia. An endoscope is inserted into the *EsophyX Z+ device*, the device and endoscope enter through the patient's mouth and are advanced into the stomach. The stomach is inflated and the endoscope is retroflexed to provide direct visualization of the esophageal junction.

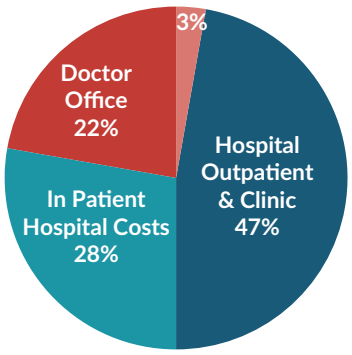
While lengthening the esophagus, the *EsophyX* Z+ device retracts a fold

Figure 1

Healthcare Economics: GERD Cost Drivers

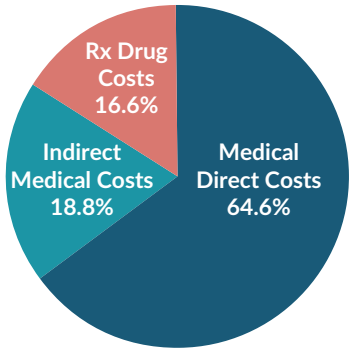
GERD sufferers had more physician office visits, hospital inpatient, outpatient and ER visits and more lab work[1]

ER Visits & Lab Work[2]



[2]Average payment for ER visits $560

The overall difference in direct and indirect health benefit costs was found to be $3,355 more per employee with GERD annually[1]



n=5878 employees with GERD out of 80,400 without GERD surveyed[1]

[1]Brooks, et al. Aliment Pharmacol. Ther; 2007; 26.
[2]Machlin, Medical Expenditure Panel Survey Stat. Brief #111, Jan. 2006.
Source: EndoGastric Solutions

of tissue into the device using suction, the tissue is folded up and around the distal esophagus, and suction is applied to reduce a small hiatal hernia. A trigger handle embeds a pair of nonabsorbable polypropylene H fasteners (called *SerosaFuse* fasteners) above the gastro-esophageal junction to oppose the fundus to the esophagus. This process is repeated in specific locations—approximately 20 *SerosaFuse* fasteners are used—to create a new valve.

In the weeks following the procedure, fibrosis at the serosa (the outermost layer of the stomach) causes full-thickness plication to occur. Because there are no incisions or dissection, *TIF 2.0* reduces the risk of adhesions and surgical complications. Other than the fasteners, *TIF 2.0* leaves no implant behind, another advantage that contributes to long-term durability.

Top Three Things on the "To Do" List

The *EsophyX* system was first cleared by the FDA via a 510(k) pathway in 2007, but the company wasn't sustaining traction in the marketplace, in part because it wasn't necessarily targeting the right clinical practices (because of the aforementioned pressures on start-ups to gain revenues to keep them afloat), and in part because there was scant clinical evidence to support the adoption of a brand new therapy, particularly in light of the skepticism created by failures of other endoscopic companies.

When Skip Baldino joined EGS in 2014 as its third CEO, he had his work cut out for him. He had an understanding of the GI space, as the former President, Americas, of Given Imaging for four years up to its acquisition by Covidien (now Medtronic plc) in 2014.

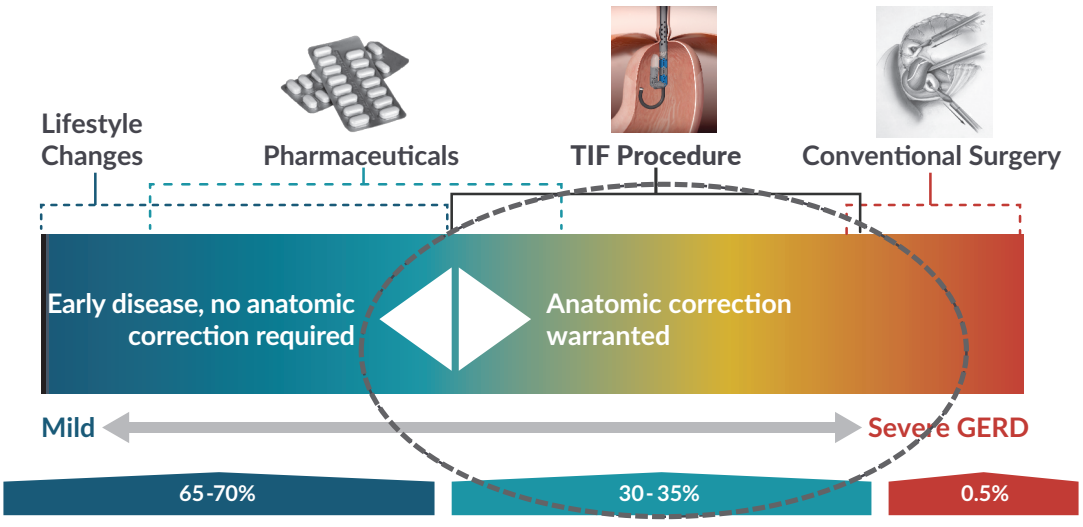
Before he joined, the board and he agreed that EndoGastric Solutions would need to focus on three things: investing in long-term clinical data, investing in device iterations so that, while maintaining its excellent safety profile, it would be easier to use for mainstream interventional GIs and surgeons, and establishing a pathway to payment so physicians and hospitals would be fairly compensated for doing the procedure. "We needed clinical evidence and support from both the GI and surgical societies in order to gain a dedicated pathway to payment," says Baldino.

As noted, the company was awarded a CPT code in 2016, a milestone that Baldino is especially proud of because "all five surgical and GI societies, together, co-sponsored the application, as their leadership saw the need to provide this solution for their clinician members to manage their GERD patients."

More than a hundred studies have been published that consistently demonstrate that *TIF 2.0* works, according to Baldino, and the company sponsored three randomized clinical trials generating level 1b data (two in the US and one in Europe). Five year results of the TEMPO (*TIF 2.0* vs Medical Proton Pump Inhibitor Management of Refractory Gastroesophageal Reflux Disease Symptoms) were published in February 2018. The study randomized 63 patients to either treatment with the *TIF 2.0* procedure, or PPI therapy.

The results were overwhelmingly positive. At five years post-procedure, 86% of patients reported the elimination of regurgitation and 80% of patients reported the elimination of all atypical symptoms. There was a low reoperation rate (5%). The report also included an economic analysis finding that at two years, total healthcare costs were substantially less in patients treated with *TIF 2.0* ($66,000) as

Figure 2
Intervening Earlier in the GERD Treatment Continuum of Care



TIF addresses a significant treatment gap between pharmaceutical and more invasive surgery options

Reference: Reavis KM, Perry KA. Expert Rev Med Devices. 2014 Jul.
Source: EndoGastric Solutions

compared to patients who undergo laparoscopic Nissen fundoplication ($124,000).

Kenneth Chang, MD, executive director of the multidisciplinary GI practice, the H.H. Chao Comprehensive Digestive Disease Center, which is part of the University of California Irvine's School of Medicine, has done well over a hundred *TIF 2.0* procedures to date (and is also an advisor to EGS). He says "Now a 35 minute noninvasive procedure gives my patients five years of relief from a chronic condition. I can get them off their PPIs and help improve their quality of life. And five years from now if things get loose, I can perform a simple *TIF 2.0* touch-up procedure, or they may need a surgery. But they have gained five years off of PPI therapy." That is the impact for patients, he says. "It gives them an alternative to surgery and reasonable durability of symptomatic control. And not only symptomatic control, but acid reflux can lead to Barrett's which can lead to cancers." (*See also "The Minimally-Invasive Revolution in Gastrointestinal Endoscopy: An Interview with Kenneth Chang," this issue.*)

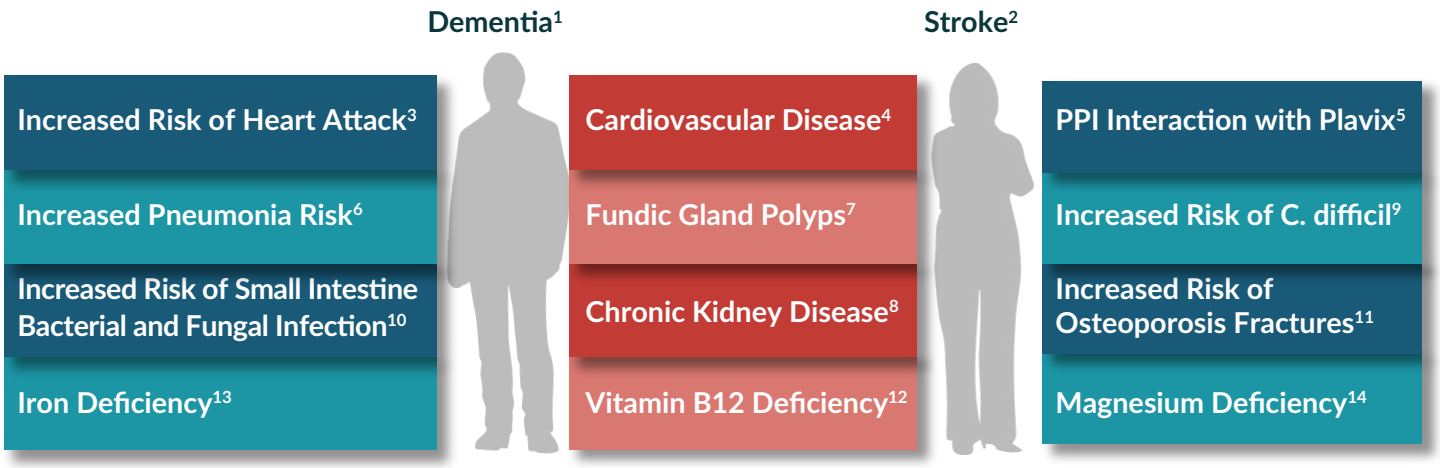
Combination procedures will become increasingly important, according to Kenneth Chang, MD, to appropriately give patients the least invasive procedure tailored to their need.

Baldino also notes that *TIF 2.0* has an exemplary patient safety profile, with a rate of serious adverse effects of less than half of one percent, and most of the events occurred before the device was iterated.

Indeed, EGS successfully accomplished Baldino's goal of creating a safe, easy, consistent procedure. Speaking of the current third generation device, the *EsophyX Z+*, which entered the market in January 2018, Baldino says "It's been a gamechanger. If you talk to people who used the older devices, they note how significantly easier it is to use the new device. When I joined EGS, the *TIF 2.0* procedure took between 60-90 minutes. Now, relatively early in the learning curve, you can do this procedure in less than 30 minutes."

Not that EGS is out to democratize the procedure, at least not at this stage. With significant long term data in hand and now that device iteration has made it much easier to use and more reproducible, Baldino wants to

Figure 3
Significant Long Term Published Risks Associated with PPI Use



References:
[1]JAMA Neurol. 2016 Apr; 73(4); [2]Shehested, TS, Circulation, 2016;134:A18462; [3]Shah NH, et al, PLOS One, 2015 June 10;10(6); [4]Shiraev TP, et al, Heart Lung Circ. 2017 Nov. 20; [5]Niu Q, et al, J Cardiovasc Pharmacol Ther., 2016, Aug. 10; [6]Lambert AA, et al, PLOS One, 2015, June,4;10(6); [7]Tran-Duy, An, et al, CGH Journal, Dec. 2016, Volume 14, Issue 12; [8]Lazarus B, et al, JAMA Intern. Med. 2016, Feb. 1;176(2); [9]Trifan, Anca, et al, World J Gastroenterol. 2017, Sept 21; [10]Jacobs C, et al, Aliment Pharmcol. Ther. 2013, June; 37(11); [11]Arj, A. et al, Int J Rheum Dis, 2016 19; [12]Lam, JR, et al, JAMA, 2013, 310(22), [13]Lam, JR, et al, Gastroenterology 2017, 152; [14]Danziger, William, JH, Danziger, J, Jour Clin Pharm. 2016, June 56(6).

Source: EndoGastric Solutions

ensure that the procedure is used on the right segment of the GERD patient population to maintain its safety profile as it becomes more mainstream. "Patient selection is important, and we work very closely with our physician partners to discuss where *TIF 2.0* fits into their overall treatment armamentarium."

He says the sales team is squarely focused on targeting practices that have full GERD service lines, and "are committed to performing the upfront diagnostic testing (EGDs, the *Bravo* 48 or 96-hour esophageal pH test, etc). Diagnostic information plays a critical role in determining appropriate treatment options for the patient. With *TIF 2.0*, we are confident that patients with early to moderate disease will benefit greatly."

To ensure that this disciplined strategy is consistently in place across the US, EGS has adopted a sales compensation model that focuses and rewards reps more for going deep into experienced accounts with strong GERD service lines and referral patterns than for signing up new, low-volume users. "We want to build a business with staying power. This strategy proved out last year, when we had great year-over-year growth."

Still on the list is the ongoing work of signing up private payors, although between Medicare coverage in all 50 states and current private payors that reimburse *TIF 2.0*, Baldino estimates that EGS has access to 125 million covered lives.

And finally, towards the goal of educating the market, EndoGastric Solutions began a direct-to-consumer marketing campaign late last year that spans multiple initiatives designed to grow awareness of *TIF 2.0* and the benefits to patients. "We have increased our DTC and co-marketing spend, as well as invested more in our website GERDHelp.com," Baldino says. "You might wonder why we didn't expand our DTC efforts sooner, but A) we needed to preserve capital and B) when you don't have a lot of reimbursement, the last thing you want to do is get patients and physicians excited about a procedure insurance companies won't consistently cover." Now, says Baldino, with the company's reimbursement success, physician commitment, and well developed partnerships in most key markets, "we are confident that investing more in patient education and co-marketing initiatives with our customers will result in qualified patients getting the *TIF 2.0* procedure."

As for penetration in ex-US markets, including Europe where the *EsophyX* system is cleared, Baldino says that "EGS has entered a few specific markets by targeting key opinion leaders who perform *TIF 2.0*."

The recent $45 million financing from a group of medical device VCs that includes Accelmed, will boost those marketing and commercialization efforts. Baldino lauds existing investors—Advanced Technology Ventures, Canaan Partners, Canepa Healthcare, Chicago Growth Partners, CRG and Radius Ventures—for their patience and continued investment in the company "knowing that there remains a significant unmet need that exists for patients suffering from GERD that *TIF 2.0* can meet." It appears that their patience is starting to pay off. "We are now ready for prime time," he says.

Enabling Minimally-Invasive Treatment on a Broader Scale

In 2016, the FDA granted EGS an expanded indication for the *EsophyX* device to include patients with a hiatal defect greater than 2cm when it is surgically corrected just prior to a *TIF 2.0* procedure. In March 2019, EGS announced the publication of positive clinical data from such concomitant procedures, analyzed retrospectively (see "pH Scores in Hiatal Repair with Transoral Incisionless Fundoplication," *The Journal of the Society of Laparoendoscopic Surgeons*, March 2019).

These types of procedure combinations will become increasingly important, according to Kenneth Chang, in "appropriately giving patients the least invasive procedure tailored to their need." Moreover, many GI conditions go hand-in-hand and are synergistically bad, he says, for example, obesity and GERD. Patients who are obese are more likely to have GERD; and obese patients are also less likely to respond well to GERD treatments and strategies. And GERD and obesity both increase the risk of cancer.

Concomitant laparo-endoscopic therapies can now be done to attack patients' health issues more precisely. "We have done combination procedures, where I have gone in and done a *TIF 2.0,* followed by an endoscopic sleeve gastroplasty [for obesity], trying to hit both of those risk factors," says Chang, who believes that is the wave of the future.

EndoGastric Solutions, for one, has an enabling platform for that vision. "There is a lot of white space adjacent to us, whether it be diabetes, obesity, or other conditions," Baldino says. He also notes that "We are really well positioned to go deep and broad with GIs and surgeons," as the only company addressing both groups, he says. "Right now sales are split 50-50 between GIs and surgeons. We can service both specialty groups, and patients will benefit because there are no walls that keep them from getting the procedure."

After 17 years, EndoGastric Solutions finds itself well positioned. It is operating in a market as large as the obesity market, in which, at present, there are very few players.