Endoscopic Therapy For GERD: Does It Have a Future?

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Approximately 20% of patients with gastroesophageal reflux disease (GERD) have symptoms refractory to long-term proton pump inhibitor (PPI) therapy. Furthermore, PPI therapy is expensive. Fundoplication is considered the gold standard of GERD therapy in terms of normalization of esophageal acid exposure and symptom control; however, this exposes the patient to the risks of surgery and anesthesia. Therefore, an endoscopic approach to treating GERD that obviates the need for PPIs and avoids surgical morbidity is desirable. Several endoscopic methods have been used, including radiofrequency ablation, implantation of foreign substances as bulking agents, and various tissue apposition strategies. The emerging field of GERD endotherapy is promising, but more rigorous, sham-controlled, long-term studies are required to elucidate its exact role in clinical practice. This review discusses the evolution of these concepts, describes specific endoscopic devices that have been developed, and explores the future of endotherapies as viable treatment alternatives for GERD.

Introduction

Gastroesophageal reflux disease (GERD) is the most common disorder of the esophagus, affecting approximately 20% of the world's population and up to one third of the US adult population [1]. It typically presents as pyrosis and/or regurgitation and may lead to esophagitis, Barrett's metaplasia, and esophageal adenocarcinoma [2]. GERD also causes significant morbidity, affecting quality of life [3].

Mechanistically, GERD results from the loss of antireflux barrier (ARB) integrity [4••] (Table 1). The ARB comprises the intrinsic smooth muscle of the abdominal esophagus and proximal stomach (gastric "sling" fiber/"clasp" fiber complex) [5], the external skeletal muscles of the crural diaphragm, and the phrenoesophageal ligament that anchors the distal esophagus to the costal diaphragm. An impaired ARB may cause chronically low pressures of the gastroesophageal junction (GEJ) or more frequent transient lower esophageal sphincter relaxations (tLESRs) [6]. In the presence of a hiatal hernia, the crural diaphragm component of the ARB is physically separated from the esophageal components. Furthermore, hiatal hernia may also increase the frequency of tLESRs [7]. Current endoscopic treatments of GERD aim to mechanically alter the ARB and thus to increase basal pressure, decrease compliance of the GEJ, and/or decrease the frequency of tLESRs. Several additional mechanisms are thought to be responsible for the effects of laparoscopic fundoplication, including reconstruction of the angle of His, reduction of hiatal hernia, and increase in the length of the intra-abdominal segment of the ARB [8••].

Current medical and surgical therapies are adequate for many patients; however, this must be qualified. Medical treatment of GERD with proton pump inhibitors (PPIs) has emerged as an effective means of treating esophagitis, relieving symptoms, and maintaining symptomatic remission. Large series have shown PPIs to have a favorable side effect profile and excellent long-term safety, with the exception of possible bone demineralization that must be monitored and addressed if present [9]. Unfortunately, patients often require a lifetime commitment to PPIs, which can be expensive or, in some cases, cost-prohibitive. Furthermore, approximately 20% of GERD patients have refractory symptoms despite medical treatment [10]. The most commonly practiced surgical procedure for GERD is laparoscopic Nissen fundoplication with or without hiatal hernia repair. The procedure has excellent short-term outcomes; however, it is invasive, requires general anesthesia, and carries the risks associated with foregut surgery. In a recent database analysis of the surgical experiences of more than 3000 patients from all Veterans Administration medical centers nationwide [11], postoperative dysphagia was recorded in 19.4%, dilation was required in 6.4%, and repeat antireflux surgery was required in 2.3% of patients. The surgical mortality rate was 0.8%. Also, about 50% of patients received multiple prescriptions for antireflux medications a median of 5 years after surgery. Tertiary specialized centers are seeing

Table 1. Proposed mechanisms of action of GERD endotherapy and laparoscopic fundoplication

Increased lower esophageal sphincter pressure
Decreased compliance of the gastroesophageal junction
Decreased frequency of transient lower esophageal sphincter relaxations
Increased intra-abdominal segment of lower esophageal sphincter
Reduction of sliding hiatal hernia
Restoration of angle of His

GERD—gastroesophageal reflux disease.
(*Adapted from* Triadafilopoulos [8••].)

an increased rate of fundoplication "failures," estimated to be 5% of all surgeries and including herniation of the intact fundoplication into the chest, slipped fundoplication with a recurrent hiatal hernia, paraesophageal hernia through an intact fundoplication, excessively tight fundoplication, and malpositioned fundoplication, usually on the cardia of the stomach [12].

The desire to obviate a lifetime of PPI treatment and to avoid exposure to the risks of surgery raises appropriate interest in developing an endoscopic solution to GERD. The field is still evolving, and several strategies exist, including 1) radiofrequency ablation, 2) implantation/injection of foreign materials, 3) endoscopic tissue apposition techniques, and 4) endoscopic ultrasound–assisted endotherapies. This review discusses the evolution of these concepts, describes specific endoscopic devices that have been developed, and explores the future of endotherapies as viable treatment options for GERD. Each device description summarizes the basic technique of application, the mechanism of action, relevant clinical study results, safety profile, and current status of availability (Table 2).

Table 2. Categories of GERD endotherapies

Synthetic implants/injections at GEJ
Biopolymer (Enteryx*)
Prosthesis (Gatekeeper†)
Plexiglas microspheres‡
Polytef§
Radiofrequency ablation (Stretta)
Endoscopic tissue apposition strategies
Partial-thickness plications
EndoCinch¶
Endoscopic Suturing Device**
Full-thickness plications
NDO Plicator††
Syntheon Antireflux Device plicator‡‡
USGI g-Prox§§
EsophyX¶¶
Full-thickness strategies using endoscopic ultrasound assistance
Medigus SRS System***
Transgastric gastropexy (animal model only)

*Boston Scientific Corp., Natick, MA.
†Medtronic, Inc., Minneapolis, MN.
‡Artes Medical, Inc., San Diego, CA.
§Mentor O & O, Inc., Hingham, MA.
¶C.R. Bard, Inc., Billerica, MA.
**LSI Solutions, Rochester, NY.
††NDO Surgical, Inc., Mansfield, MA.
‡‡Miami, FL.
§§San Clemente, CA.
¶¶EndoGastric Solutions, Inc., Redmond, WA.
***Tel Aviv, Israel.
GEJ—gastroesophageal junction; GERD—gastroesophageal reflux disease.

Implantations and Injections

To date, four strategies for implantation or injection of a foreign substance into the lower esophageal sphincter have been described: a biopolymer of ethylene vinyl alcohol (Enteryx; Boston Scientific Corp., Natick, MA), a hydrogel prosthesis (Gatekeeper; Medtronic, Inc., Minneapolis, MN), Plexiglas (polymethylmethacrylate) microspheres (Artes Medical, Inc., San Diego, CA), and polytetrafluoroethylene (Polytef; Mentor O & O, Inc., Hingham, MA). These materials are hypothesized to serve as bulking agents that augment the natural mechanical barrier to reflux.

Only the first two devices have been commercially available in the United States or Europe and have been published in clinical trials. A randomized, sham-controlled, multicenter trial for Enteryx demonstrated a significant reduction in distal esophageal acid exposure and improvement in GERD symptoms at 3 months [13]. For Gatekeeper therapy, a report of the combined results of two European multicenter, prospective, open-label trials enrolling 68 patients showed significant symptom improvement at 6 months [14]. No sham-controlled data are available for Gatekeeper.

Serious adverse events have been reported for Enteryx and Gatekeeper. As of August 2005, there were 29 reports of adverse events related to Enteryx, including five deaths. One death was sudden in nature, occurring 3 days after the procedure with no intervening symptoms and therefore believed not to be device related. Another death occurred

from cardiovascular collapse after initiation of hemodialysis for chronic renal failure 1 month postprocedure. There were also two cases of aortoenteric fistulas postprocedure with exsanguinations and one case of mediastinitis with sudden death. These events led to the voluntary withdrawal of Enteryx by the manufacturer in September 2005. As for the Gatekeeper, the lone published trial reported a 15% complication rate at 1 month, including one patient requiring prosthesis removal for intractable nausea and another patient with pharyngeal perforation [14]. There have been no case reports or reports of adverse events in the US Food and Drug Administration (FDA) MAUDE (Manufacturer and User Facility Device Experience) database. The Gatekeeper clinical program was also suspended in late 2005 [15••].

Endoscopic Radiofrequency Ablation

The delivery of radiofrequency energy to the GEJ may be accomplished with endoscopic catheter-based systems, and the mechanism of action is thought to be due to scarring or neurolysis [16].

The Stretta system is specifically designed for this purpose. The catheter is composed of a soft, flexible bougie tip and a balloon–basket assembly with four nickel–titanium needle electrodes (22-gauge, 5.5 mm in length) arranged radially around the balloon. When the catheter is positioned and the needles deployed into the circular muscle of the distal esophagus and cardia, a four-channel generator delivers temperature-controlled radiofrequency energy to the smooth muscle of the GEJ via the needle electrodes (target temperature 85°C). Thermocouples at the base and tip of each needle allow for constant monitoring of temperature and impedance in the tissue. If the base of a needle (mucosal temperature) exceeds 50°C, the tip of a needle (muscle temperature) exceeds 100°C, or impedance exceeds 1000 Ω, the generator shuts off energy output to that particular needle. An integrated irrigation system delivers cooled sterile saline to help prevent mucosal injury. Radiofrequency energy is delivered to each electrode for 90 seconds. The catheter is then repositioned 45 degrees, and treatment is repeated to create a ring of eight lesions. The catheter is then repositioned in 0.5-cm increments to create a total of six rings. From start to finish, the procedure takes approximately 45 minutes [17].

Triadafilopoulos et al. [17] published the first US open-label results of radiofrequency ablation at 6-month follow-up. Significant improvement was found by intention-to-treat analysis in heartburn symptoms, GERD–health-related quality-of-life (HRQL) scores, and Short Form Health Survey-36 (SF-36; Rand Health Communications, Santa Monica, CA) scores. PPI therapy was completely eliminated in 87% of patients, and acid exposure time decreased significantly from 11.7% to 4.8%. However, there was no change in lower esophageal sphincter pressure to explain the results, suggesting an alternative mechanism [17]. This study was extended to 118 patients, with 12-month follow-up available in 94 patients. Significant improvements still existed in symptoms, HRQL, and SF-36 scores. Acid exposure time was still diminished, and PPI therapy remained discontinued in 70% of patients [18]. Results of a subsequent sham-controlled trial of radiofrequency ablation in 64 patients were not as favorable. This study demonstrated decreased heartburn symptoms and improved quality of life in the active therapy group at 6 months. However, no differences were seen in the critical areas of acid exposure, need for medications, or healing of esophagitis at 6 months [19].

Reported adverse events have ranged from minor and self-limited to death. The most common side effect is chest pain (1.7% to 100%) [19]. Review of the FDA's MAUDE database of voluntarily reported adverse events showed three deaths. One was related to conscious sedation in a morbidly obese patient, one to esophageal leak, and one to postprocedure aspiration pneumonia. The Stretta system is no longer on the market. Curon Medical, Inc. filed for bankruptcy in November 2006.

Endoscopic Tissue Apposition Strategies

Several endoscopic suturing and tissue apposition devices have been developed with the goal of creating plications of tissue just below the GEJ to mechanically bolster the lower esophageal sphincter. Two of these devices place superficial, mainly submucosal sutures and are therefore vulnerable to suture loss: the EndoCinch (C.R. Bard, Inc., Billerica, MA) and the Endoscopic Suturing Device (ESD; LSI Solutions, Rochester, NY; previously distributed by Wilson-Cook Medical, Inc., Winston-Salem, NC). Full-thickness plication devices also have emerged. The best-studied device in this category is the NDO Plicator (NDO Surgical, Inc., Mansfield, MA). Other devices currently undergoing evaluation include the EsophyX device (EndoGastric Solutions, Inc., Redmond, WA), the Syntheon Antireflux Device (Syntheon, LLC, Miami, FL), and the g-Prox (USGI, San Clemente, CA).

EndoCinch

The EndoCinch system is suction-based and uses T-tag sutures that are shuttled through the submucosal tissue. The current system requires two endoscopes, one for suturing and one for securing and cutting the suture. An esophageal overtube is also required due to the need for multiple passes and endoscope exchanges. A 9 × 32–mm capsule with attached suction is fixed to the tip of one endoscope, and a hollow needle runs through the endoscope channel and capsule, housing the T tag with attached suture at its distal tip. The second endoscope cinches the sutures via a catheter device that deploys a ceramic cylinder and plug through which the suture is threaded. Circular, linear, and helical orientations of the plications have been described, placed 1 to 2 cm apart

on the gastric side of the Z line. The ideal number and the optimal orientation of plications are unknown. Plications typically are made circumferentially, 1 cm below the Z line at 3-, 6-, and 9-o'clock positions or linearly at a 2-o'clock position 3, 2, and 1 cm below the Z line. The helical approach has been favored when a small hiatal hernia is present. It delivers four to six plications over a 3- to 4-cm stretch below the Z line. The entire procedure takes approximately 40 to 60 minutes under conscious sedation or, in some series, monitored anesthesia [20].

The first open, multicenter trial using EndoCinch, by Filipi et al. [21], randomized 64 patients to circumferential and linear plications. No difference was found between plication configuration groups at 6 months. There was a significant improvement in heartburn and regurgitation score but no improvement in lower esophageal sphincter pressure or grade of esophagitis. A second multicenter trial enrolling 85 patients also randomized to circumferential or linear plications found durable improvement in heartburn and regurgitation symptoms and a sustained reduction in PPI therapy at 2 years. PPIs were completely stopped in 41% of patients at 2 years. Also, there was a statistically significant reduction in duration and number of episodes of esophageal acid exposure 3 to 6 months postprocedure [22]. Three sham-controlled clinical trials have recently been reported in abstract form only. In their single-institution study of 34 patients, Rothstein et al. [23] showed significant differences in heartburn severity, acid exposure time, and discontinuation of PPIs at 3 months. However, there were no differences in heartburn severity, regurgitation, lower esophageal sphincter pressure, or quality-of-life scores [23]. Another single-center, sham-controlled study of 47 patients found no differences in acid exposure, medication use, or quality-of-life scores at 1 year [24]. Finally, the third randomized, sham-controlled trial of 45 patients showed a significant decrease in heartburn scores and PPI use at 3 months but no difference in regurgitation score, quality-of-life measures, or acid exposure time [25].

The comparatively larger body of literature with the EndoCinch has reported its use in certain intriguing cohorts that would have been excluded in other trials. Liu et al. [26] examined gastroplication in four patients with Barrett's esophagus, three patients with hiatal hernias greater than 3 cm, and four patients with prior antireflux surgery. Follow-up in this study ranged from 6 to 21 months. In the 24 patients available for follow-up, heartburn and regurgitation scores significantly decreased. Fifty percent of patients were completely off PPIs at 12 months. Again, there were no significant changes in acid exposure or lower esophageal sphincter pressure. Endoscopic follow-up in 10 patients revealed loose or missing plications in one half.

Several studies have also compared the EndoCinch to laparoscopic fundoplication. One study evaluating 54 patients found patient satisfaction to be higher in the surgery group (96%) compared with the gastroplication group (78%) at 3 months [27]. Another study of 87 patients revealed less medication use in the surgery group at a mean follow-up of 8 months [28]. Neither study reported any manometric or pH data.

The safety profile of the EndoCinch has been generally favorable. Rare adverse events have been reported, including one case of mediastinal air managed with supportive treatment, one case of aspiration pneumonia, and one case of perforation at the GEJ. In the initial US multicenter trial, adverse events included pharyngitis (31%), chest pain (16%), abdominal pain (14%), vomiting (14%), bleeding (3%), mucosal tear from the overtube (3%), and suture perforation (2%) [21]. The EndoCinch remains FDA approved for tissue apposition in the stomach and esophagus and for the endoscopic treatment of GERD.

ESD

The ESD operates on similar basic principles. It consists of a flexible plication device called the Sew-Right that is introduced via an externally fixed working channel. The Sew-Right is reloadable and consists of a dual-needle system that uses a single suture loop for tissue plication. A needle with suture is passed through tissue aspirated into a suction chamber. After removal of the Sew-Right, a separate Ti-Knot device that uses a malleable titanium plug to crimp and trap the suture secures the plicated tissue [29].

In a 2005 pilot study examining the feasibility of this device in 20 people, one to three vertical plications were successfully placed per patient. However, the clinical outcome was very limited due to the absence of full-thickness plications. At 3-month follow-up, only 12% (6/49) of plications remained in place [30]. The ESD is currently available through the original manufacturer, LSI Solutions.

For these devices that place submucosal sutures, stripping of the mucosa before suturing may lead to improved tissue healing such that the integrity of tissue appositions may not be dependent on the long-term retention of sutures. This phenomenon has been observed in limited animal experiments; however, long-term human studies have not been reported [31].

NDO Plicator

Compared with the predominantly submucosal sutures deployed by the EndoCinch and ESD, the NDO Plicator creates a single, full-thickness, serosa-to-serosa plication below the GEJ. The plication is created under direct retroflexed visualization provided by a pediatric gastroscope (5.9-mm outer diameter) that is inserted through a dedicated channel of the instrument. A pretied, suture-based pledget is delivered to create the plication, which is typically placed between the anterior gastric wall and the fundus, thereby avoiding major branches of the gastric arteries and vagus nerves. This procedure takes approximately 30 minutes to perform under conscious sedation [32].

In 2004, Pleskow et al. [33] reported the results of a North American, multicenter, open-label trial involving 64 patients. At 6 months GERD-HRQL scores and SF-36 scores improved significantly, and 74% of patients were completely off PPIs. However, acid exposure normalized in only 30% of patients, and lower esophageal sphincter pressures were unchanged. In the lone sham-controlled trial evaluating the use of the NDO Plicator in 78 patients, at 3 months, 56% of patients improved their GERD-HRQL score (vs 18.5% of the sham group), 50% were able to stop their PPIs (vs 24% of the sham group), and active therapy was better than sham in improving median percentage of time with pH less than 4. Lower esophageal sphincter pressures were not analyzed [34].

In the multicenter trial by Pleskow et al. [33], adverse events included pharyngitis (41%), abdominal pain (20%), chest pain (17%), dysphagia (11%), and nausea (6%). Serious adverse events were reported in six patients, including respiratory distress, pneumothorax, and pneumoperitoneum [34]. Review of the FDA's MAUDE database revealed reports of esophageal perforation requiring surgical repair and abdominal pain and leukocytosis that were managed conservatively. This device remains FDA approved for the endoscopic treatment of GERD with recent additional approval for the placement of two plications.

Syntheon Antireflux Device

The Syntheon device is another full-thickness plicator that simultaneously places two titanium pledgets in a manner similar to that of the NDO Plicator. Implantation is performed using a standard endoscope, and mean procedure time has been reported to be 21 minutes. Feasibility trials involving eight patients have shown 75% PPI discontinuation and 68% improved GERD-HRQL score at 6 months. However, there were no significant differences in acid exposure and lower esophageal sphincter pressure. Minor side effects included sore throat, epigastric/referred chest pain, and the gas bloat syndrome [35]. No sham-controlled trials are available. The Syntheon Antireflux Device was not FDA approved and not available for purchase at the time this review was submitted.

USGI g-Prox

The g-Prox is a full-thickness tissue grasper/approximation device with an integrated needle driver through which self-expanding nitinol tissue anchors are deployed. It is designed to work through the USGI endoscopic operating system. The device can be reloaded without removing it from the operating site, allowing for the placement of multiple plications. The system is FDA approved for tissue opposition in the upper gastrointestinal tract, among other indications. It is currently being evaluated in human trials for pouch and stoma reduction in gastric bypass patients, and preliminary work for endoluminal GERD therapy is also under way [36].

EsophyX

The EsophyX device attempts to more closely mimic the effects of antireflux surgery by elongating the angle of His and forming a one-way gastroesophageal valve. It uses an invaginator whereby the distal gastric cardia and fundus are captured and retracted into the plicating jaws. After the jaws are closed, the captured tissue is "molded" and secured using multiple full-thickness polypropylene fasteners in an attempt to create an omega-shaped valve 3 to 5 cm in length and 200 to 300 degrees in circumference. In a recent feasibility study of 13 patients, 81% of the patients demonstrated anatomic integrity of the gastroesophageal valve at 12 months, 62% of baseline hiatal hernias remained reduced, and 82% of the patients remained completely off PPIs. It was reported that 63% had normal pH (defined as $\leq 5.3\%$ of time with pH < 4); however, no preprocedure pH measurements are provided [37]. There have been no published sham studies to date. The device is currently available with FDA approval for tissue apposition.

Endoscopic Ultrasound-Assisted Endotherapies: A New Horizon

The SRS System (Medigus, Tel Aviv, Israel) combines a forward-viewing charge-coupled device chip endoscope, endoscopic ultrasound, and a surgical stapler in a single instrument with the goal of performing a partial anterior fundoplication. The SRS endoscope is advanced into the stomach so that the staple cartridge on the endoscope's shaft is at the selected stapling site 2.3 to 3.0 cm above the GEJ. The endoscope is further flexed to 270 degrees, and endoscopic ultrasound is used to confirm optimal alignment and distance between the anvil and stapler cartridge. The operator then cranks a flywheel that extrudes two screws that penetrate the tissue and lock the anvil and cartridge together. The staples are then fired to create the plication. The screws are subsequently withdrawn and the scope removed. The SRS system is then reloaded with a new cartridge, and the procedure is repeated. The goal is an anterolateral wrap designed to augment the angle of His. Small clinical trials (< 20 patients total at the time of publication) have been conducted in India and Australia, with results pending. No objective data on acid exposure or lower esophageal sphincter pressure are currently available, and the system is not yet FDA approved.

In another application of endoscopic ultrasound, Fritscher-Ravens and Swain [38] have demonstrated an endoluminal approach to the Hill procedure in a porcine model. The procedure entails using endoscopic ultrasound to place stitches in the median arcuate ligament and part of the right crus and ultimately anchoring them to the gastric wall to create a posterior gastropexy. Endoscopic ultrasound allowed for extension to anatomic structures outside the gastrointestinal tract. Preoperative manometry in 14 survival pigs showed a significant increase in

median lower esophageal sphincter pressure from 11 mm Hg to 21 mm Hg after stitch placement. Also, the lower esophageal sphincter's length increased from 2.8 cm preprocedure to 3.5 cm postprocedure [39]. No published reports of human clinical trials involving this technique are currently available.

Conclusions

Several endoscopic modalities have been introduced for treating GERD, including radiofrequency ablation, endoscopic implantation of foreign substances as bulking agents, and various endoscopic tissue apposition strategies (including use of endoscopic ultrasound). In general, the limited clinical trials performed with these devices have shown significant improvement in symptoms and reduction or elimination of antisecretory therapy. Furthermore, with the exception of the injection/implantation strategy, endotherapies in general have been shown to be safe. However, glaring areas of weakness exist in the literature to date. Most studies have been small (mostly cohort studies or small case series) and have featured short-term follow-up (< 2 years). More importantly, there has been a general failure to demonstrate objective physiologic changes, such as significant reduction in acid exposure time or increased lower esophageal sphincter pressures.

Moving forward, evaluating existing and not-yet-developed endoluminal solutions to GERD will require more scientific rigor. In particular, further sham-controlled trials and long-term outcome studies will be needed. It will also be important to modify current study designs to focus on the physiologic parameters of acid exposure and lower esophageal sphincter pressures as primary outcomes as opposed to subjective markers of improvement and PPI use. Another consideration is that some endoluminal GERD procedures may not be effective across the broad population but instead may yield optimal clinical effectiveness in subgroup populations that have not been widely studied. These may include patients with atypical reflux, patients who have failed PPI therapy, nonobese patients, and many other subsets. Future studies may consider varying inclusion and exclusion criteria and/or incorporating a robust subset analysis if patient numbers permit. Once the efficacy, durability, and target populations of endotherapies become more concrete, it may be possible to perform more rigorous comparisons of these modalities to medical and surgical therapies. After these outcomes are understood, economic analyses may then be appropriate to further elucidate the roles of all clinically available strategies.

Over the relatively short period of development of GERD endoluminal therapies, there has been a trend toward replicating the physiology of fundoplication—that is, increasing lower esophageal sphincter tone, lengthening the lower esophageal sphincter, augmenting the angle of His, and reducing hiatal hernias. As this field advances, it will be important to keep in mind the pathophysiologic mechanisms of GERD and the mechanisms of successful surgical therapy. Furthermore, the effects of endoluminal therapy must not hinder a patient's ability to undergo fundoplication, thereby serving as a bridge to surgery should it be ultimately required.

Although none of the available endoscopic modalities has been proven to be clinically appropriate, the desire to obviate a lifetime of antisecretory medication and avoid the complications of surgery suggests that an endoscopic solution to GERD is very much needed. With continually improving technology and an enhanced understanding of the mechanisms of disease and treatment earned over the past decade, the field marches ahead to heed this call.

Disclosures

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