Check for updates

Devices for esophageal function testing

Rahul Pannala, MD, MPH, FASGE,[1] Kumar Krishnan, MD,[2] Rabindra R. Watson, MD,[3]
Marcelo F. Vela, MD, MS,[1] Barham K. Abu Dayyeh, MD, MPH, FASGE,[4] Amit Bhatt, MD,[5]
Manoop S. Bhutani, MD, FASGE,[6] Juan Carlos Bucobo, MD, FASGE,[7] Vinay Chandrasekhara, MD, FASGE,[4]
Andrew P. Copland, MD,[8] Pichamol Jirapinyo, MD, MPH,[9] Nikhil A. Kumta, MD, MS,[10] Ryan J. Law, DO,[4]
John T. Maple, DO, FASGE,[11] Joshua Melson, MD, MPH, FASGE,[12]
Mansour A. Parsi, MD, MPH, MBA, FASGE,[13] Erik F. Rahimi, MD,[14] Monica Saumoy, MD, MS,[15]
Amrita Sethi, MD, MASGE,[16] Guru Trikudanathan, MBBS,[17] Arvind J. Trindade, MD, FASGE,[18]
Julie Yang, MD, FASGE,[19] David R. Lichtenstein, MD, FASGE[20]

This document was reviewed and approved by the Governing Board of the American Society for Gastrointestinal Endoscopy.

Background and Aims: Esophageal function testing is an integral component of the evaluation of refractory GERD and esophageal motility disorders. This review summarizes the current technologies available for esophageal function testing, including the functional luminal imaging probe (FLIP), high-resolution esophageal manometry (HRM), and multichannel intraluminal impedance (MII) and pH monitoring.

Methods: We performed a MEDLINE, PubMed, and MAUDE database literature search to identify pertinent clinical studies through March 2021 using the following key words: esophageal manometry, HRM, esophageal impedance, FLIP, MII, and esophageal pH testing. Technical data were gathered from traditional and web-based publications, proprietary publications, and informal communications with pertinent vendors. The report was drafted, reviewed, and edited by the American Society for Gastrointestinal Endoscopy Technology Committee and approved by the Governing Board of the American Society for Gastrointestinal Endoscopy.

Results: FLIP is a high-resolution impedance planimetry system used for pressure and dimension measurement in the esophagus, pylorus, and anal sphincter. FLIP provides complementary information to HRM for esophageal motility disorders, especially achalasia. The Chicago classification, based on HRM data, is a widely adopted algorithmic scheme used to diagnose esophageal motility disorders. MII detects intraluminal bolus movement and, combined with pH measurement or manometry, provides information on acid and non-acid gastroesophageal reflux and bolus transit in patients with refractory GERD and for preoperative evaluation for anti-reflux procedures.

Conclusions: Esophageal function testing techniques (FLIP, HRM, and MII-pH) have diagnostic and prognostic value in the evaluation of esophageal motility disorders and refractory GERD. Newer technologies and classification systems have enabled an increased understanding of these diseases. (VideoGIE 2022;7:1-20.)

(footnotes appear on last page of article)

*The American Society for Gastrointestinal Endoscopy (ASGE) Technology Committee provides reviews of existing, new, or emerging endoscopic technologies that have an impact on the practice of GI endoscopy. Evidence-based methodology is used, performing a MEDLINE literature search to identify pertinent clinical studies on the topic and a Manufacturer and User Facility Device Experience (MAUDE) (U.S. Food and Drug Administration Center for Devices and Radiological Health) database search to identify the reported adverse events of a given technology. Both are supplemented by accessing the "related articles" feature of PubMed and by scru-*tinizing pertinent references cited by the identified studies. Controlled clinical trials are emphasized, but in many cases, data from randomized, controlled trials are lacking. In such cases, large case series, preliminary clinical studies, and expert opinions are used. Technical data are gathered from traditional and web-based publications, proprietary publications, and informal communications with pertinent vendors. Technology Status Evaluation Reports are drafted by a small group of members of the ASGE Technology Committee, reviewed and edited by the committee as a whole, and approved by the Governing Board of the ASGE. When financial

guidance is indicated, the most recent coding data and list prices at the time of publication are provided. For this review, the MEDLINE database was searched through March 2021 for relevant articles by using the key words *esophageal manometry, high resolution manometry, esophageal impedance, functional luminal imaging probe, MII,* and *esophageal pH testing.*

Technology Status Evaluation Reports are scientific reviews provided solely for educational and informational purposes. Technology Status Evaluation Reports are not rules and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment or payment for such treatment.

BACKGROUND

GERD is the most common GI diagnosis associated with outpatient visits in the United States, and approximately 20% of the U.S. population report at least weekly symptoms of GERD.[1,2] Esophageal function testing is an integral component of the evaluation of refractory GERD and esophageal motility disorders such as achalasia. Measurement of esophageal distensibility and compliance is also increasingly used for the evaluation of esophageal motility disorders, as well as other esophageal conditions such as eosinophilic esophagitis (EoE) and after endoscopic or surgical esophageal interventions.

In recent years, new technologies have expanded our understanding of esophageal motility and gastroesophageal reflux and are now rapidly being integrated into routine clinical practice. This review summarizes the current technologies available for esophageal function testing, including the functional luminal imaging probe (FLIP), high-resolution esophageal manometry (HRM), and multichannel intraluminal impedance (MII) and pH monitoring. This is an update of a previously published American Society for Gastrointestinal Endoscopy (ASGE) technology document on esophageal function testing.[3] Wireless pH testing has been addressed in a previous ASGE technology document[4] and is not reviewed here.

TECHNOLOGY UNDER REVIEW

Functional luminal imaging probe

FLIP uses high-resolution impedance planimetry during volume-controlled distension to quantify the relationship between luminal geometry and pressure in the assessment of the mechanical properties of the esophageal wall and esophagogastric junction (EGJ).[5] Specifically, FLIP analyzes the relationship between luminal cross-sectional area (CSA) and pressure, which provides a measure of luminal distensibility (CSA/pressure). The technology consists of a multielectrode probe and proprietary software

Figure 1. Image of an EndoFLIP system. ©2020 Medtronic. All rights reserved. Used with the permission of Medtronic.

that measures the dynamic geometrical changes of the EGJ and esophageal body during peristalsis.[6]

The EndoFLIP system (Medtronic Inc, Minneapolis, Minn, USA) is cleared by the U.S. Food and Drug Administration for pressure and dimension measurement in the esophagus, pylorus, and anal sphincter (Fig. 1). The system is intended for use as an adjunct to other diagnostic methods in the evaluation of patients with symptoms consistent with GI dysmotility. Additional applications include assessment of pylorus distensibility before or during gastric peroral endoscopic myotomy (POEM) or surgical pyloromyotomy, estimation of the size of the stoma after gastric band placement, intraoperative assessment for fundoplication tightness and lower esophageal sphincter myotomy adequacy, and as an adjunct to a bougie for measuring the size of the gastric sleeve during a sleeve gastrectomy.[7-9]

Main components. The FLIP system consists of a 240-cm-long, 3-mm-diameter catheter with a highly compliant balloon at the distal end that conforms to the esophageal lumen (Table 1). The balloon contains 16 paired impedance electrodes spaced at regular intervals and a

single solid-state pressure transducer at the distal end (Fig. 1). The electrodes are variably spaced from 5 mm to 1 cm apart, depending on the specific catheter model. The balloon device for standard esophageal evaluation is 16 cm in length; an 8-cm balloon device is also available for evaluation of sphincter anatomy and function or sizing of anastomoses. Devices with a balloon length of 8 and 16 cm are commercially available. Excitation electrodes located on the proximal and distal ends of the balloon generate a constant low electrical current through a conductive fluid that is instilled into the balloon through an 80-mL syringe housed in and controlled by the Endo-FLIP system. Voltage is measured by the paired sensors along the length of the balloon and based on the current and voltage; the electrical resistance of the fluid, or impedance, is calculated using Ohm's law ($V = I \times R$). When the constant of a defined fluid conductivity at a given temperature combined with the fixed distance between the electrodes is used, the CSA is derived from changes in impedance. The system also measures distensibility based on simultaneous measurement of pressure within the balloon by the solid-state transducer.

The EndoFLIP system also includes a touchscreen interface that displays a real-time colorized geometric image of the evaluated esophageal segment, numerical estimated luminal diameter (Dest) measurements along the electrodes, and the current balloon pressure (Fig. 2). The user may also toggle between display of the minimum diameter and CSA or distensibility and compliance. The distensibility index (DI) is used to measure sphincter distensibility and is calculated by dividing the median narrowest CSA by the median intraballoon pressure at a set timeframe or distension volume. Because CSA and pressure measurements are dynamic and influenced by respiration and spontaneous esophageal contractions, various statistical solutions are used to control for these variations, including FLIP Analytics software (Medtronic Inc) and MATLAB (The MathWorks, Natick, Mass, USA).[10-12] Data may be stored on the EndoFLIP system or uploaded to an electronic medical record.

The FLIP Topography module (available in EndoFLIP 2.0) is software that displays real-time diameter and distensibility estimates for each point along the measurement area. The data are expressed as a topographic plot with a color scale to display diameter values. A historical graph also displays diameter readings for a given period, allowing an assessment of diameter changes over time (Fig. 2A and B). The expression of diameter values in this fashion is analogous to data presentation with HRM. Thus, FLIP Topography enables evaluation of EGJ distensibility, along with assessment of esophageal body distensibility and contractile activity. The latter requires use of the 16-cm catheter to allow for a longer region of measurement in the esophageal body, and analysis based on FLIP topography, which relies on detection of distension-induced secondary peristalsis.[5]

TABLE 1. Technical specifications of the EndoFLIP system

Description	Part Number
EndoFLIP Catheter, 25 mm, 80 mm measurement length, with Pressure, Nasal Tip	EF-325N
EndoFLIP Catheter, 22 mm, 80 mm measurement length, with Pressure, Nasal Tip	EF-322N
EsoFLIP Catheter, 30 mm, 80mm measurement length	ES-330
EsoFLIP Catheter, 20 mm, 80mm measurement length	ES-320
EndoFLIP Localization Kit	LK-103
HD Image Box TEAC Unit	DD-971
EndoFLIP 1.0 System	EF-100
EndoFLIP 2.0 System	EF-200

Impedance-guided esophageal dilation catheters, which use the data acquired during impedance planimetry, are also available (EsoFLIP, Medtronic). These are available in 2 sizes (6 -20 mm, 3-30 mm), with the former indicated for dilation of benign esophageal strictures and the latter indicated for dilation of the EGJ in the setting of achalasia.

Technique. The procedure is usually performed with concomitant endoscopy. After catheter calibration and data entry, the catheter is advanced into the esophagus transorally, generally with patient sedation. The EGJ is identified by the waist-like constriction visible on the real-time 3-dimensional display at balloon fill volumes of around 20 to 30 mL. Catheter position is then adjusted, either under direct endoscopic visualization or based on measurements, depending on the clinical indication (eg, placement within the esophageal body for evaluation of EoE). Of note, if endoscopic visualization is used, the endoscope should be removed before initiating FLIP analysis; presence of the endoscope has been shown to significantly affect measurements.[13]

Once the catheter is positioned, volume-controlled distention of the balloon is performed. The balloon may be inflated to a particular pressure or volume; the rate of balloon inflation and maximal balloon inflation may also be configured. Stepwise volumetric distention performed at 5- to 10-mL increments may provide additional information, such as calculation of a distensibility plateau (DP),[14] and it enables evaluation of the esophageal body contractile pattern.[15] Sixteen sequential CSAs and a single intraballoon pressure measurement are made at a 10-Hz sampling rate, which may then be used to calculate an estimated luminal diameter (Dest) based on the assumption of a circular lumen (CSA = Πr^2). Various procedural protocols have been published, and a standardized testing algorithm has been recently proposed by an international consensus.[5]

Effectiveness and comparative data. *Asymptomatic healthy subjects.* Although the establishment of normative reference values in healthy individuals is critical to the appropriate interpretation of FLIP measurements in both
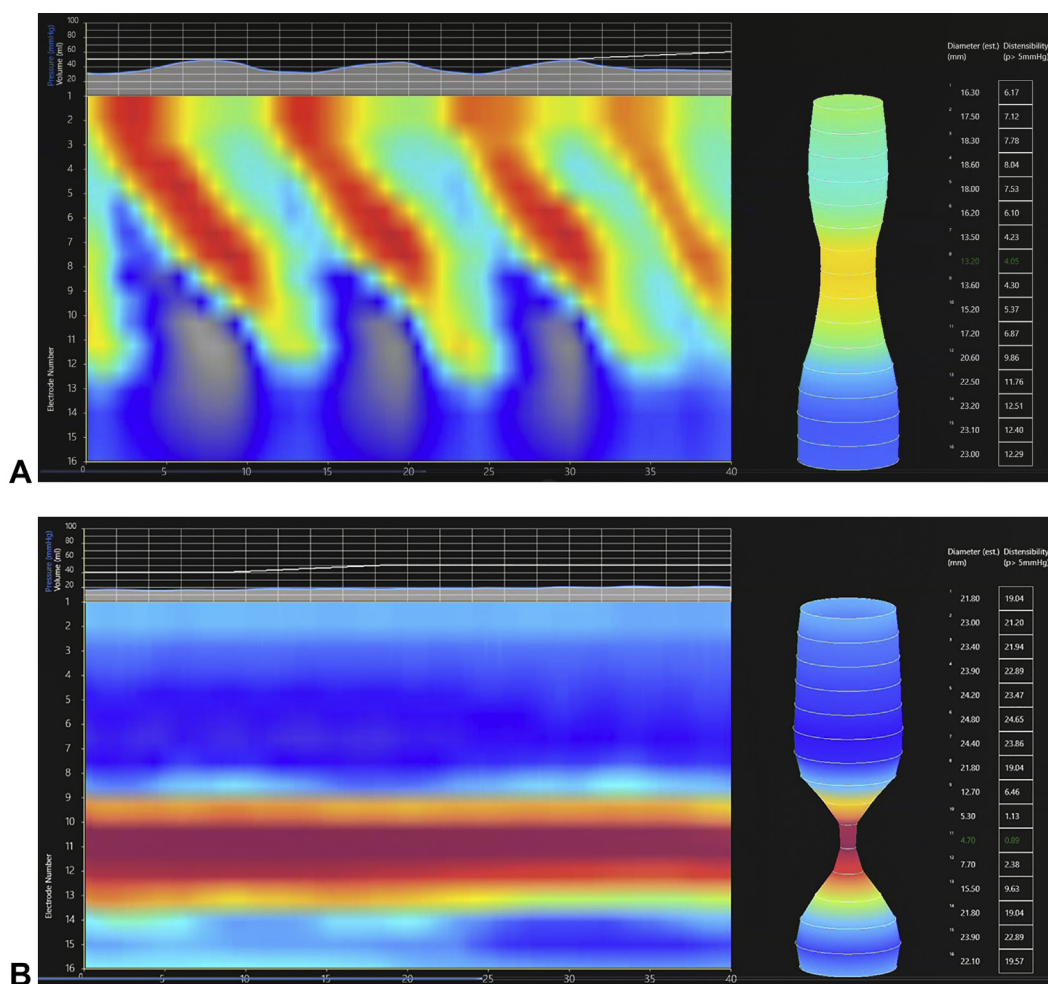
Figure 2. Examples of functional luminal imaging probe planimetry. **A,** Normal contraction pattern with repetitive antegrade contractions and normal distensibility index. **B,** Absent esophageal body contractility with reduced distensibility index in achalasia (courtesy of Dr Diana Snyder, Mayo Clinic Arizona).

research and clinical practice, the available data suggest a wide range of values. A systematic review of 5 studies including healthy subjects (n = 98) demonstrated a wide range of median EGJ distensibility (0.8-5.7 mm^2/mm Hg) at 30- to 40-mL balloon fill volumes, with a minimum observed EGJ distensibility of 2.4 mm^2/mm Hg at a 40-mL fill volume.[16] A subsequent prospective study of 20 healthy volunteers demonstrated a median distensibility of 5.8 mm^2/mm Hg (interquartile range, 4.9-6.7 mm^2/mm Hg) and a minimum observed distensibility of 2.8 mm^2/mm Hg.[17] The variability among studies may be explained by the use of differing FLIP protocols and balloon sizes and heterogeneity of patient populations.[16] Furthermore, body mass index (BMI) may also influence distensibility and CSA measurements.[18]

Achalasia and EGJ outflow obstruction. Achalasia is characterized by incomplete relaxation of the lower esophageal sphincter (LES) and abnormal esophageal peristalsis. Although HRM is integral to the diagnosis of achalasia, diagnostic uncertainty may persist in select cases of borderline pressure measurements or conflicting data.[19,20] Furthermore, although not a frequent issue, some patients do not tolerate the HRM procedure. By measuring EGJ distensibility, FLIP may provide complementary information to HRM to aid in the diagnosis of achalasia, definition of achalasia subtypes, and prediction of response to therapy.

Several studies have reported a characteristically low EGJ DI (EGJ-DI) in untreated patients with achalasia.[21-24] A single-center study that included 30 patients with achalasia and 15 healthy controls demonstrated a significantly lower EGJ-DI in the achalasia group as compared to controls (0.7 ± 0.9 vs 6.3 ± 0.7 mm^2/mm Hg; $P < .001$).[22] EGJ distensibility also correlated with esophageal emptying on timed barium esophagogram (r = –0.72; $P < .01$) and symptoms (r = 0.61; $P < .01$) in the achalasia group. Another study evaluated 20 healthy volunteers and 54 patients with achalasia, 31 of whom were treated with pneumatic dilation (n = 17), Heller myotomy with partial fundoplication (n = 10), or peroral esophageal myotomy (n = 4). The EGJ-DI was significantly

different between controls (8.2; 95% CI, 1.7-18.7 at 40 mL) and patients with achalasia before treatment. Furthermore, in the 31 treated patients, there was a significant difference in post-treatment EGJ-DI in the 17 patients with a good response (3.4; 95% CI, 2.2-4.9 at 40 mL) versus the 14 patients with a poor response (1.5; 95% CI, 0.6-2.8 at 40 mL; $P < .001$) as determined by Eckardt score. Significant correlations were also noted between EGJ-DI and integrated relaxation pressure (IRP) as measured by HRM.[24]

FLIP may also aid the diagnostic evaluation of the subset of patients who demonstrate characteristic symptoms of achalasia but have normal LES relaxation on HRM, seen especially in patients with type I achalasia. A single-center study included 13 patients with typical symptoms of achalasia (Eckardt score of 5-7) with HRM demonstrating absent peristalsis, a low mean basal EGJ pressure of 10 (5.8-12.9) mm Hg, and a normal mean IRP of 9.3 (6.1-12) mm Hg.[25] FLIP demonstrated a significant reduction in EGJ distensibility, as compared with previously acquired data from healthy controls (n = 15) (0.8 [0.7-1.2] mm^2/mm Hg vs 6.3 [3.8-8.7] mm^2/mm Hg; $P < .001$). Treatment resulted in significant improvement in Eckardt score as well as the EGJ-DI.

By simultaneously measuring esophageal contractility and EGJ function, FLIP also provides complementary information to HRM in the differentiation of achalasia subtypes. A study included 51 treatment-naïve patients with achalasia subclassified with HRM and 10 asymptomatic controls who underwent FLIP during endoscopy.[21] Contractility was observed in 27% of patients with type I achalasia, 65% of patients with type II, and 100% of patients with type III. In patients with type III achalasia, 8 of 10 demonstrated novel contractility (repetitive retrograde contractions), which was not observed in controls. The authors further noted that FLIP topography detected lumen-occluding and nonoccluding contractions as well as specific distention-related contractions that were not observed with HRM.

A second study from the same center included 145 patients with dysphagia who underwent HRM and FLIP with topography performed during sedated endoscopy.[15] FLIP topography was abnormal in 95% of patients who were diagnosed with achalasia or who had EGJ outflow obstruction by HRM. Furthermore, FLIP topography detected abnormalities in 17 of 34 (50%) symptomatic patients with normal or ineffective esophageal motility on HRM. Thirteen of these patients demonstrated abnormal EGJ-DI, whereas the remaining 4 patients demonstrated repetitive retrograde contractions and normal EGJ DI.

EGJ outflow obstruction (EGJOO) is a motility abnormality diagnosed by HRM characterized by impaired EGJ relaxation but with some preserved peristalsis such that criteria for achalasia are not met. According to the most recent Chicago classification (CC) of esophageal motility disorders version 4.0,[26] EGJOO diagnosed by HRM requires confirmation of true outflow obstruction

through additional testing, which can be accomplished by FLIP showing a reduced EGJ-DI. A study of 34 patients with EGJOO showed that FLIP was useful for identifying patients who are most likely to benefit from achalasia-type therapy.[27] Similarly, a recent study showed POEM to be a highly successful treatment for EGJOO confirmed by FLIP.[28]

Assessment of treatment. A growing body of literature supports the role of FLIP in the real-time assessment of EGJ function during endoscopic or operative therapy for achalasia. Several case series have demonstrated an increase in EGJ-DI measured intraoperatively immediately after laparoscopic Heller myotomy (LHM) and POEM.[29-36] In addition, FLIP may be used to inform intraoperative treatment decisions and predict postprocedure outcomes.

A multicenter retrospective study of 63 patients with achalasia treated with POEM examined the association of intraoperative FLIP measurements and short-term clinical outcomes (median follow-up of 122 days).[34] Patients were divided into 2 groups based on postprocedure Eckardt score (good response: <3, n = 50; or poor response: ≥3, n = 13). The intraoperative CSA after POEM was significantly higher in the good-response group (89.0 [78.5-106.7] mm^2 vs 72.4 [48.8-80.0] mm^2; $P = .01$). The final EGJ CSA was also significantly higher in those patients with postprocedure reflux esophagitis. EGJ-DI was lower in the poor-response group, although this did not reach statistical significance. However, 2 other studies (n = 56 and n = 52) evaluating the predictive value of intraoperative FLIP reported that the postmyotomy EGJ-DI was an independent predictor of response to treatment.[32,37]

Several studies have evaluated the role of intraprocedural FLIP during POEM and LHM to optimally guide the proximal and distal extent of myotomy, with variable results reported.

As with preoperative and intraoperative measurements, change in EGJ distensibility after treatment may provide complementary information to HRM. A prospective study compared the utility of FLIP EGJ-DI measurement and HRM in assessing posttreatment outcomes in achalasia. A total of 79 patients treated with pneumatic dilation, LHM, or POEM underwent timed barium esophagogram, HRM, and FLIP.[38] The area under the curve for EGJ metrics in association with barium retention was as follows: DI, 0.90; maximal EGJ diameter, 0.76; IRP, 0.64; and basal EGJ pressure, 0.53. When a 5-minute barium column area of >5 cm was used as the reference standard, only FLIP metrics were associated with retention given normal anatomy. Lower EJG-DI (2.4 vs 5.2 mm^2/mm Hg; $P < .0001$) and higher maximal EGJ diameter (13.1 vs 16.6 mm; $P = .002$) were associated with retention. Furthermore, 21 of 22 patients with retention had a low or borderline low DI (<2.8 mm^2/mm Hg). Additional cohort studies have demonstrated a significant association with post-myotomy EGJ-DI and symptom response as

measured by Eckardt scores, as well as associations between increased CSA with postmyotomy reflux.[7,22]

GERD. *Diagnosis.* EGJ incompetence and/or the presence of a hiatal hernia may contribute to GERD.[39] With the advent of FLIP, it has been hypothesized that increased EGJ distensibility may facilitate GERD diagnosis.[40,41] However, several case series evaluating FLIP in this context have demonstrated inconsistent results. An initial series of 20 patients with GERD without hiatal hernia and 20 healthy controls demonstrated a 2- to 3-fold increase in EGJ distensibility among patients with GERD, compared with controls.[42] However, a subsequent study including 18 patients with GERD and 21 healthy volunteers evaluated with FLIP followed by 48-hour wireless pH monitoring showed that EGJ metrics were similar between participants with and without pathologic acid exposure (CSA 98 mm^2 vs 107 mm^2; $P = .789$, distensibility; $P = .704$).[18] There was a correlation between BMI and CSA ($R^2 = 0.2758$; $P = .001$) and distensibility ($R^2 = 0.2005$; $P = .005$). Interpretation of these results is difficult because of the differences in BMI between the 2 groups.

The disparate findings of these studies imply that the association between GERD and esophageal function may be more complex than abnormalities in EGJ distensibility alone. A study of 25 patients who underwent ambulatory pH monitoring and FLIP during endoscopy examined the relationship between total percent acid exposure time (AET), symptoms as measured by a validated questionnaire (GERDQ), and response to esophageal distention.[43] A weak and insignificant correlation was found between AET and EGJ DI, GERDQ and AET, and GERDQ and EGJ-DI. Notably, AET was lower among patients with (6.1%, 3-7.8) than without (14.9%, 8.5-22.3) repetitive antegrade contractions induced with volumetric balloon distention ($P = .009$). This suggests that abnormal esophageal acid exposure may be associated with impaired esophageal clearance.

FLIP has also been shown to accurately identify the presence and quantify the effect of a hiatus hernia. A study including 30 patients with hiatus hernia and Barrett's esophagus and 14 healthy controls found the LES had a lower pressure (47.7 ± 13.0 vs 61.4 ± 19.2 mm Hg at 50-mL distension volume) in patients with hiatus hernia and was more distensible than the common EGJ in controls ($P < .001$).[38,44] In addition, in patients with hiatus hernia, the crural diaphragm had a lower pressure (eg, 29.6 ± 10.1 vs 47.7 ± 13.0 mm Hg at 50-mL distension volume) and was more distensible than the LES ($P < .001$).

Treatment. FLIP has been used to determine the impact of antireflux surgery on EGJ distensibility, although normative reference values have not been established. Several case series have demonstrated a significant reduction in distensibility immediately after intervention.[45-48] Pooled results from 4 expert centers demonstrated a mean EGJ distensibility of 2.82 ± 2.82 mm^2/mm Hg after

crural repair (n = 45) and a mean final DI of 1.60 ± 1.13 after creation of the fundoplication (n = 57).[45] However, clinical outcomes were not reported in these studies.

Reductions in EGJ-DI have also been reported in the early postprocedure period after transoral incisionless fundoplication in animal models and in small case reports and series.[49-51] However, a series including 25 patients who underwent preoperative FLIP demonstrated no significant difference in EGJ-DI values at 6 months postprocedure.[52] Furthermore, although low preoperative distensibility was associated with reduced AET after transoral incisionless fundoplication, it did not correlate with clinical outcomes.

Eosinophilic esophagitis. *Diagnosis.* EoE is associated with esophageal remodeling and fibrosis, resulting in a loss of compliance, development of symptomatic strictures, and recurrent food impactions.[53] Disease severity and stenosis are evaluated during upper endoscopy with biopsy, although this approach may be limited by biopsy sampling error and underrecognition of strictures.[54,55] FLIP allows for objective assessment of the CSA and biomechanical properties of the fibrotic esophageal body. Specifically, the DP, calculated as the maximum achievable CSA of the narrowest portion of the esophageal body during stepwise volumetric balloon distention, has emerged as a useful measure of disease severity in EoE. In a study of 33 patients with EoE and 15 healthy controls, the DP measured with FLIP was significantly lower in patients with EoE (median: CSA 267 mm^2 vs 438 mm^2; $P < .01$).[14] Mucosal eosinophil count, age, sex, and current proton pump inhibitor (PPI) treatment did not predict reduced distensibility of the esophagus ($P < .20$).

A subsequent study evaluated 72 patients with EoE, 90% of whom reported dysphagia. Higher ring scores on a validated scoring system (EoE Endoscopic Reference Score) were associated with lower DP ($r_s = –0.46$; $P < .0001$), whereas no association between eosinophil counts and ring severity or distensibility was noted. The authors suggest that decreased distensibility may be of use for food impaction risk stratification.[56]

Treatment. FLIP has also been shown to predict the need for treatment and response to therapy in the setting of EoE. A prospective study including 70 patients with EoE followed for a mean of 9.2 months demonstrated that those patients with a history of food impactions had significantly lower DP scores than those with dysphagia alone.[57] Additionally, a reduced DP (< 225 mm^2) was associated with future food impaction and need for dilation during the follow-up period. Notably, DP was the only significant predictor of future impaction, compared with age, sex, treatment type (including none), and mean esophageal eosinophil density.

A second study included 18 patients EoE who underwent medical and dietary FLIP performed at baseline

endoscopy and after therapy without interval dilation. Follow-up testing occurred at a mean (range) of 14.6 (8-28) weeks. Significant improvement in DP (13.9 [12.2-19.2] to 16.8 mm [15.8-19.2]; $P = .007$) and was noted with treatment. Six of 8 (75%) patients with a DP increase of ≥2 mm achieved at least a 30% improvement in a validated patient-reported outcome measure ($P = .077$), suggesting a possible role for FLIP DP as an outcome measure in EoE management.

Evaluation of esophageal motility with FLIP topography. The incorporation of the FLIP topography module into standard FLIP protocols has provided novel data in evaluation of the function of the esophageal body. It has been recognized that distention of the esophageal lumen by the balloon induces a contractile response that results in diameter changes that can be graphically represented over a space-time continuum using the FLIP topography module. The interpretation of such data has been used to identify characteristic distention-mediated anterograde and retrograde contractions of the esophageal body, which may provide an assessment of motor function analogous to HRM.[58] Normative data have been recorded in asymptomatic healthy subjects, and characteristic findings in various disease states such as achalasia have been described.[15,17] Furthermore, normal real-time FLIP topography results obtained during endoscopy reliably identify patients without major motility disorders and correlate with HRM findings.[59,60] Further studies are needed to determine how FLIP topography is best used in assessment algorithms as a complement to HRM, the role of real-time topography, and whether published results can be validated outside of expert centers.

Other applications. Limited data exist regarding additional applications of FLIP in esophageal diseases. Several series have explored the role of FLIP in the evaluation of upper esophageal sphincter (UES) function in healthy controls, in patients with upper esophageal strictures, and sleeve gastrectomy stenoses before and after treatment.[61]

The role of FLIP has also been explored in patients undergoing gastric POEM.[8,62] In a multicenter study of 37 patients, intraoperative postmyotomy CSA using 40-mL distention was shown to correlate with improvement in gastric emptying and clinical success.[8]

High-resolution manometry

Esophageal motor disorders characterize a heterogeneous group of conditions that may result in deglutitive dysfunction. These disorders primarily manifest as dysphagia or chest pain. Esophageal manometry involves functional assessment of esophageal pressure changes during awake swallows. Esophageal manometry systems convert intraluminal pressure differences in the esophagus to a tracing that can be recorded. These tracings correspond to a specific distance within the esophagus; hence, a pressure/time graph is created.[63] Our understanding of esophageal motor disorders has evolved substantially over the past 10 years, largely as a result of the transition from conventional line tracings derived from recordings in a handful of pressure sensors (usually 8) to esophageal pressure topography (EPT) plots derived from HRM catheters that incorporate a large number of pressure transducers (most often 36) closely spaced together. HRM catheters enable collection of more comprehensive pressure data during swallows. The EPT is what is used to view and analyze the output from the HRM catheters. The CC of esophageal motor disorders, currently in its fourth version, is an algorithmic scheme used to diagnose esophageal motility disorders.[26,64-66]

High-resolution esophageal manometry catheters. HRM catheters are made by several manufacturers and use either water-perfused or solid-state pressure transducers. Although both systems can convert intraluminal pressures into electrical signals that are used to develop pressure topography plots, substantial differences do exist in catheter design and pressure measurement technique.[67] Water perfusion systems are silicone catheters with channels along the length of the catheter. An external pump perfuses the system, and changes in intraluminal pressure are transmitted through the column of water to an external sensor. In general, water-perfused systems have the advantage of a lower cost and smaller, more durable catheter. They are also autoclavable and can be sterilized. These relative advantages are weighed against several disadvantages. Water-perfused systems require longer setup and are technically more challenging to use. For example, perfusion pressure and hydrostatic pressure must be corrected to obtain an accurate recording. Furthermore, because the sensor is external to the patient, position changes can result in artifact.[63] Solid-state catheters generally incorporate 36 pressure sensors along the length of the catheter. Compared to water-perfused systems, solid-state systems are easier to calibrate, and the output from the sensors is not affected by patient position, resulting in easier setup and use. Solid-state sensors can be affected by temperature, and as a result, a thermal correction is needed before analyzing EPTs obtained during HRM (this is very easily done through the available software analysis platforms). Because several sensors are embedded within the solid-state catheter, it is prone to damage; hence, longevity of the catheter is less than that of water-perfused systems. Furthermore, these catheters cannot be sterilized in an autoclave and thus require standard reprocessing.[63,67]

Technique of HRM. Regardless of catheter type, the technique of performing HRM is similar. Studies are performed in nonsedated patients, usually after 6 hours of fasting. The lubricated manometry catheter is advanced through the nares into the stomach, similar to standard nasogastric tube placement; topical anesthesia with lidocaine is used as necessary. Under real-time manometric guidance, the catheter position is adjusted such that placement allows for manometric visualization of the UES and
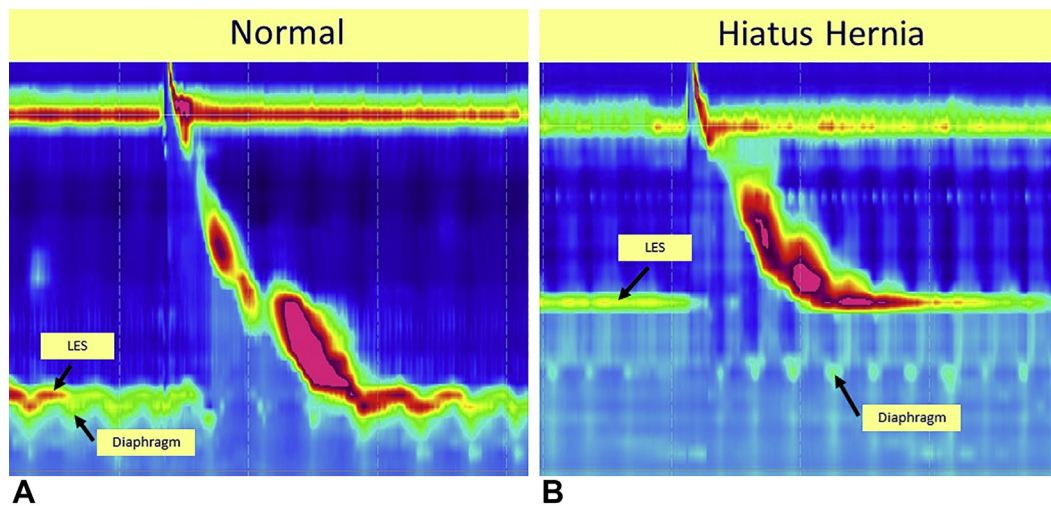
Figure 3. Hiatus hernia identified by high-resolution esophageal manometry. **A,** Normal esophagogastric junction without hiatus hernia; the lower esophageal sphincter and diaphragm are at the same position. **B,** Hiatus hernia, with displacement of the lower esophageal sphincter to a few centimeters above the diaphragm.

LES, and at least 5 sensors are positioned in the stomach. Once appropriate positioning is achieved, the catheter is secured at the nose with adhesive tape.[68] The study is performed with the patient in supine position. Standard manometric protocol involves a 5-minute period to assess basal LES pressures. This is followed by 10 wet swallows, each consisting of 5 mL of water. Although normative values have been developed with this protocol, seated or upright swallows are sometimes performed. Additional techniques including increasing bolus volume and altering bolus consistency (standardized test meals, solid swallows) have been suggested to improve the diagnosis of esophageal outflow obstruction syndromes.[69] It is important to note that peristaltic contractility and EGJ morphology are affected by positioning; as such, relative normative values obtained in the supine position may not be applicable to those values obtained in the seated or upright position.[70] In a study of 75 healthy volunteers, significant differences were noted in both esophageal contractility and EGJ relaxation when comparing supine and upright positioning.

In addition to the standard wet swallows, maneuvers such as multiple rapid swallows (MRS) have been suggested in specific clinical situations to reveal subtle pathology or evaluate peristaltic reserve. The MRS technique involves five 2-mL swallows every 2 to 3 seconds while in the upright position to reveal peristaltic reserve in patients with absent or ineffective esophageal motility. In one study, this technique was better able to demonstrate peristaltic augmentation and reserve in healthy controls compared to patients with scleroderma. This technique can be especially helpful in patients with ineffective esophageal motility (IEM) who are being considered for antireflux surgery because an abnormal response to MRS has been shown to be associated with increased risk of postfundoplication dysphagia.[71,72]

Although most esophageal motility studies are performed in unsedated patients, there are circumstances when sedation is needed. The primary factor is inability to pass the manometry catheter into the stomach, as in the case of tortuous esophagus. In this circumstance, endoscopy can be used to guide the manometry catheter. The impact of sedation before esophageal motility testing is not well studied; however, a small report suggests midazolam had a statistically significant impact on esophageal body function and EGJ relaxation.[73] Whether these changes affect the ultimate diagnosis is not clear. Of note, when endoscopic guidance is required, solid-state manometry catheters cannot be grasped using a snare or other tool because it will damage the sensors. The gastroscope tip can be used to guide the manometry catheter into the gastric lumen.

Interpretation of HRM. Interpretation of HRM studies involves an assessment of EGJ morphology, esophageal contractility, and coordination of esophageal peristalsis to formulate a diagnosis. This process has been simplified by the CC of esophageal motor disorders. Now in its fourth iteration, CC has developed a systematic process and algorithm based on HRM metrics.[26,64] There are 3 primary components to interpretation of an HRM study: (1) assessment of EGJ physiology and morphology, (2) esophageal body contractile vigor, and (3) assessment of peristaltic coordination.

EGJ. HRM allows for assessment of EGJ morphology, resting pressure, and deglutitive relaxation. Regarding morphology, HRM allows visualization of both the LES and crural diaphragm. Although normally overlapping and indistinguishable, separation between the LES and contractile deceleration (CD) is diagnostic of a hiatal hernia (Fig. 3). EGJ morphology functions as a surrogate for reflux barrier function. Three subtypes of barrier function have been

reported. LES/CD separation is measured as the distance between the intrinsic LES and respiratory pressure signals indicative of the CD. Although variability is expected, the CC has suggested a range be reported for the length of the study.[64] Although metrics have been proposed to characterize and define impaired EGJ relaxation, the only validated metric is the IRP. The IRP is median value of the maximum relaxation over a cumulative 4-seconds during a 10-second window starting at UES relaxation. A normal value is <15 mm Hg, and values >15 mm Hg are indicative of impaired relaxation, which may be seen in achalasia or EGJ outflow obstruction.[68,74]

Esophageal body function. Peristaltic contractile vigor and coordination are 2 other key elements of HRM interpretation. For analysis and interpretation of HRM studies, contractile vigor is summarized by the distal contractile integral, a measure that incorporates contraction amplitude in mm Hg, duration of the contraction in seconds, and length of the contracting segment in centimeters.[64] The upper limit of normal, based on evaluation of healthy controls, is 8000 mm Hg/s/cm.[75] Although initially developed to assess hypercontractility, absent or weak peristalsis can also be assessed. Values less than 450 mm Hg/s/cm are considered weak peristalsis, whereas values <100 mm HG/s/cm are considered failed peristalsis.[76]

In addition to contractile strength, peristaltic coordination can be assessed during analysis of HRM through calculation of the distal latency, measured as the time (in seconds) from onset of UES relaxation to the contractile deceleration point, the point of relative slowing of peristaltic propagation in the distal esophagus.[77] A reduced distal latency (<4.5 seconds) indicates premature contractions consistent with distal esophageal spasm.

Effectiveness and comparative data. *Achalasia.* The primary utility of HRM in the evaluation of dysphagia is to assess for the presence of achalasia. Furthermore, the utility of HRM in subtyping achalasia has been found in several studies to reliably predict outcome to treatments targeted at the EGJ.[22,65,78,79] These studies have confirmed that patients with type II achalasia have the most durable symptom improvement after treatments targeted to the LES, whereas patients with type III have the least durable symptom improvement.[80] A study that based treatment response on Eckardt scores <3 revealed a treatment success rate of 96% in type II achalasia compared to 81% and 66% in type 1 and III, respectively.[81] In a meta-analysis of 21 studies evaluating achalasia subtype, pneumatic dilation appeared to have an acceptable clinical success compared to both POEM and LHM in type II achalasia. The clinical success of LHM was 81%, 92%, and 75% for types I, II, and III, respectively. The success of POEM was 95%, 97%, and 93% in types I, II, and III.[79] The 2020 ASGE guideline on achalasia management states that laparoscopic Heller myotomy, pneumatic dilation, and POEM are comparable treatment options for achalasia types I and II but suggest POEM as the preferred treatment for type III achalasia.[82]

HRM also has clinical utility in the evaluation of recurrent symptoms after treatment of achalasia; however, the use of HRM metrics appears to be more nuanced than in the treatment naive patient. Prior studies have shown that an EGJ pressure of <10 mm Hg after pneumatic dilation correlated with improved symptoms. In a study of 75 patients after treatment (pneumatic dilation, Heller myotomy, or POEM), IRP values were not statistically significant between symptomatic and asymptomatic patients (12 vs 14).[83] Furthermore, the sensitivity of elevated IRP was only 65% for symptomatic outcome after treatment of achalasia.

GERD. HRM is not needed to make a diagnosis of GERD, but it does provide insight into faulty antireflux physiology in patients with pathologic reflux. Specifically, it can provide insight into the EGJ barrier function. In one study, prolonged separation of the crural diaphragm from the LES, pathognomonic for a hiatal hernia, was associated with prolonged reflux events, both acidic and weakly acidic[84] (Fig. 3). To this end, HRM has greater sensitivity and specificity compared to both endoscopy and radiography for the diagnosis of hiatal hernia, with one study revealing 92% sensitivity and 95% specificity.[85] EGJ pressures are intuitively associated with competence of the antireflux barrier. Recently, a new metric, the EGJ contractile integral, has been developed. This has been shown to correlate with the presence and severity of distal esophageal acid exposure.[86,87]

Esophageal manometry testing is a prerequisite for antireflux surgery. In one study of 1081 patients evaluated for fundoplication, preoperative manometry provided clinically relevant information that changed the surgical approach in 7% owing to impaired peristalsis or undiagnosed achalasia.[88] Furthermore, although exact values for ineffective esophageal clearance that are prohibitive to complete fundoplication do not exist, aperistalsis on preoperative manometry may lead some surgeons to opt for a partial fundoplication. Those patients with dysphagia and ineffective esophageal motility preoperatively are 3 times more likely to have postoperative dysphagia after fundoplication. Finally, abnormal response to MRS has been shown to be associated with increased risk of postfundoplication dysphagia.[72]

Multichannel intraluminal impedance

MII is a catheter-based technique that enables detection of intraluminal bolus movement in the esophagus and can be combined with pH measurement or manometry to respectively provide information about both acid and nonacid gastroesophageal reflux and bolus transit.[3,89,90] Because MII-pH detects all reflux regardless of acidity (acid or nonacid) or composition (liquid, gas, or mixed), it is considered the criterion standard for reflux monitoring.[91] The addition of impedance to HRM provides further information not only on bolus transit but also

clearing velocity, correlation between LES relaxation and bolus transit, and esophageal bolus retention.[92]

The catheters used for impedance measurement have multiple sets of impedance electrodes distributed through the length of the esophagus. The change in resistance (in Ohms) between the rings is measured to calculate the impedance. At baseline, current is conducted between the rings by ions on the mucosa; passage of a liquid bolus with increased ion conductivity decreases impedance, and conversely an air bolus with poor conductivity increases impedance. By measuring the direction of the impedance changes, bolus movement from proximal to distal or vice versa can be detected, and antegrade or retrograde flow of esophageal contents can be determined.

Several MII systems are available commercially. Systems usually consist of a selection of single- or multiple-use catheters, data recorders, and dedicated computers and/or proprietary software for data analysis and reporting. Separate catheters are required for MII and pH or MII and HRM. Catheters are usually made of biocompatible polyurethane, are latex-free, and have radiopaque markers. MII-pH catheters have a diameter around 6F and have 6 impedance channels (made of tin-plated copper) and 1 to 2 (esophageal or esophageal and gastric) pH channels (made of antimony or an ion-sensitive field-effect transistor).[3,93] Probes are available in varying lengths for pediatric and adult use. Separate probes that are designed to measure pharyngeal and esophageal pH and impedance are also available. The data recorder is usually a small, lightweight ambulatory device that is carried by patients and has multiple event buttons that are used by patients to document body position, meals, and specific symptoms. At the end of the test, data are downloaded from a memory card in the data recorder. Catheters are only compatible with the individual manufacturer's data recorders. Patients are also usually given a diary with instructions to record body position, meals, and symptoms manually in addition to documenting them electronically on the recorder.

MII high-resolution manometry requires the use of different catheters, which combine esophageal solid-state or water-perfused pressure sensors for esophageal motor function assessment, with impedance electrodes to evaluate bolus transit. These probes are usually 8F to 12F in diameter and have up to 36 pressure channels and 16 impedance channels.

Both MII and pH or manometry also include a proprietary software program that is part of the system and is designed to perform automated analysis of the recording and patient-reported events and provide a reporting interface for review and creation of a customized final report that incorporates salient data. The automated analysis may facilitate but should not replace interpretation by a clinician, and manual review of the tracings is mandatory to avoid false-positive or false-negative results. The impedance

with manometry system includes a dedicated computer system or software program that provides topographic pressure graphs and 3-dimensional representation of the measured manometry and bolus transit. These systems also integrate reporting based on the CC of esophageal dysmotility.[64]

Patient preparation, test procedure, analysis, and interpretation. *MII-HRM.* Patients are usually asked to fast for at least 4 to 6 hours before the procedure.[94] Patients are instructed to take their regular medications. After catheter calibration and application of a topical anesthetic to the patient's nose and/or posterior pharynx, the MII-HRM catheter is introduced intranasally and advanced so that the pressure sensors span a length extending from the hypopharynx through the esophagus and 3 to 5 cm into the stomach.[95] Correct catheter placement can be ascertained by visualization of both UES and EGJ on the EPT plot and further confirmed by recognizing the pressure inversion point (the point at which the inspiration-associated negative intrathoracic pressure inverts to positive intra-abdominal pressure).[95,96] After appropriate positioning of the catheter and an acclimatization period of 5 minutes, 10 liquid swallows of 5 mL each are given 30 seconds apart with the patient in supine position. Normal saline solution is preferred over water for liquid swallows because it has standard ionic concentration and provides more predictable impedance changes. Newer testing protocols[66] call for the addition of five 5-mL swallows in upright position, along with provocative maneuvers such as administration of multiple rapid swallows, a rapid drink challenge, or solid bolus swallows.[69] During MII-HRM, manometric data is interpreted and reported using the CC as outlined, and MII measurements are used to assess whether bolus transit is normal.

MII-pH. Patient preparation is similar to the MII-EM. Usually a 24-hour study is performed. An a priori decision is made whether to perform the procedure on or off PPI therapy. The catheter is calibrated with buffer solution as per manufacturer recommendations. The location of the LES is usually identified previously by manometry; endoscopic assessment of LES location is thought to be less reliable.[97] The probe is passed transnasally with the esophageal pH sensor positioned 5 cm above the proximal border of the LES, leaving the gastric pH channel (when present), 10 cm beyond the LES. Once the catheter is positioned at the desired level, it is secured in place by taping to the skin, ensuring there is no pressure on the catheter or the nostril. The patient is then advised to continue all daily activities and consume a regular diet, including foods and activities that typically induce symptoms. However, patients are advised to limit food to mealtimes and to avoid carbonated beverages between meals. Patients are also instructed to record diet, position (upright or supine), and specific symptoms

Gastric Acid Control: Gastric pH was normal during the recording period off acid suppression.

Upright Esophageal Acid Exposure: Normal

Supine Esophageal Acid Exposure: Normal

DeMeester Score: Normal

Total Number Reflux Episodes: Combined acid/weakly acid/ non-acid reflux frequency was normal.

Symptom Association: Symptom association was minimal, but few symptoms were reported during the study.

FINDINGS: Impedance/pH Reflux Monitoring

Analysis Duration Upright:	9	Hrs
Analysis Duration Supine:	8	Hrs
Analysis Duration Total:	17	Hrs

GASTRIC Ph (% TIME THAT GASTRIC Ph < 4.0)

Fractional Time Upright:	84.9
Fractional Time Supine:	97.5
Fractional Time Total:	91

ESOPHAGEAL ACID EXPOSURE PATIENT VALUES (NORMAL VALUES)

Total Acid Exposure:	1.3	%	(< 6.00 %)
Upright Acid Exposure:	0.4	%	(< 8.20%)
Supine Acid Exposure:	2.2	%	(< 3.40%)
DeMeester Score:	7.6		(< 14.72%)

REFLUX EPISODE ACTIVITY (NUMBER OF IMPEDANCE REFLUX EPISODES)

	Upright	Supine	Total	
Acid:	0	3	3	
Nonacid:	13	3	16	
All Reflux:	13	6	19	(< 60 Events)

TOTAL NUMBER SYMPTOM EPISODES REPORTED

Regurgitation	10
	0
	0

SYMPTOM INDEX FOR TOTAL REFLUX EPISODES

Regurgitation	10 %
	0 %
	0 %

** The SI was calculated according to Wiener et al. as the percentage of symptoms that was reflux related. The Symptom Index (SI). This means that > 50% of the symptoms were associated with reflux events. Chance associations are more common using the SI. (The Symptom Index: a clinically important parameter of ambulatory 24-hour esophageal pH monitoring. GJ Wiener, JE Richter, JB Copper et al., Am J Gastro 1988; 83: 358-361) monitoring. GJ Wiener, JE Richter, JB Copper et al., Am J Gastro 1988; 83: 358-361.

Figure 4. Example of an impedance-pH report detailing reflux-related data and symptom association (courtesy of Dr Michael Crowell, Mayo Clinic Arizona).

using the electronic recorder and/or diary for subsequent symptom correlation with acid exposure.

Once the study period is completed, patients return the recorder and the data are downloaded and analyzed using the proprietary software. For pH studies, AET is considered the primary outcome (Fig. 4); this measure is easily extracted from automated analysis and is predictive of response to medical or surgical therapy.[91,94,98] An AET value of >6% is considered abnormal, whereas <4% is considered normal, and 4% to 6% is considered inconclusive.[91] Total, upright, and supine AET are reported separately. A composite score (DeMeester score) is also calculated and reported combining total, upright, and supine AET; total number of reflux episodes; number of reflux episodes >5 minutes long; and longest reflux episode.[92] For MII-pH studies, the number of reflux episodes (total, acid, and nonacid) is reported based on the impedance measurements.

Symptom reflux association is also an important part of the analysis. Symptom index (SI) and symptom association probability (SAP) are other measures that are complementary to each other. SI is defined as the percentage of symptom events that are related to reflux episodes; a cutoff of >50% is considered positive. SAP is a statistical parameter that assesses the relationship between symptom events and reflux episodes during the measurement; SAP >95% is considered positive.[99] SI and SAP are independent predictors of response to therapy.[100] An abnormal AET with a positive SI and SAP is considered the strongest evidence for GERD.[91,94] MII also enables calculation of other parameters that may be useful as markers of GERD, including reflux bolus exposure, baseline impedance, postreflux swallow-induced peristaltic waves, and mean nocturnal baseline impedance; these MII-derived measures are adjunctive parameters that are variably used and are currently being validated.[91,94,101] Of note, the number of reflux episodes determined by impedance has been recently shown to predict the need for and response to surgical augmentation of the LES in patients with PPI-refractory regurgitation.[102] Finally, a modified MII-HRM protocol that includes a test meal can provide objective documentation of rumination.[103]

Effectiveness and comparative data. _MII-pH._ Ambulatory pH testing off PPI is recommended in patients with persistent symptoms of GERD who have failed an empiric treatment trial with PPIs and do not have confirmatory evidence of GERD on upper endoscopy (grade C or D esophagitis, peptic stricture, or Barrett's mucosa), patients with atypical symptoms, preoperative testing when antireflux surgery/transoral endoscopic fundoplication is being considered, or persistent symptoms despite antireflux surgery.[91,94] For confirmation or exclusion of GERD while off PPIs, pH testing alone is sufficient. Twenty-four-hour MII-pH monitoring is considered superior to pH monitoring alone because it detects the type of refluxate, direction, and the nature of the refluxate (acidic pH <4, weakly acidic pH 4-7, weakly alkaline >7, gaseous and re-reflux episodes). MII-pH is also useful for detection of supragastric belching and evaluation of atypical symptoms such as cough, and it may suggest rumination as a mechanism for regurgitation (the latter can be confirmed by MII-HRM, as mentioned).[94] Pharyngeal reflux monitoring is available, but consensus statements note that there is limited data currently for routine clinical use of this test.[91,94]

Testing on antisecretory therapy. The merits of performing testing while the patient is on or off antisecretory therapy remain to be conclusively established in prospective studies, but recommendations are provided in consensus statements. Testing off PPI therapy provides information on basal AET and a higher yield of symptom-reflux association. The Lyon consensus recommends testing off PPI therapy as a means of confirming or excluding GERD in patients with no prior positive pH testing, absence of either grade C or D esophagitis, or when testing is being done to evaluate patients for antireflux surgery.[91] The recommendations of the Porto consensus conference are also similar: Testing off PPI therapy is recommended when the question is whether

the patient has GERD or when testing is being done before antireflux surgery. Testing off PPI is also recommended for absence of response or incomplete response to PPI therapy, atypical symptoms, and recurrent or persistent symptoms after antireflux surgery.[94] Testing on PPI therapy is recommended when there is unequivocal evidence of GERD (prior positive pH study, higher grades of esophagitis, peptic stricture or Barrett's esophagus >1 cm in length) but there is incomplete or absence of response to treatment. In these instances, impedance-pH testing is recommended over pH monitoring alone to identify patients with nonacid reflux. In a study of 168 patients who were symptomatic despite being on twice-daily PPI therapy, MII-pH testing on therapy was performed; 48% had a positive symptom index for at least 1 symptom, and among these 77% were associated with nonacid reflux.[104] In patients who had atypical symptoms (131, 43%), the majority (78%) had a negative symptom index; 25 (19%) had a positive symptom index for nonacid reflux. In another multicenter study of 150 patients with GERD-type symptoms where impedance and pH measurements were performed, a positive symptom association probability was noted in only 55%; for patients on PPI (n = 71), nonacid reflux accounted for nearly 17% of symptoms. These studies demonstrate the relatively high prevalence of symptoms secondary to nonacid reflux and the importance of performing impedance along with pH monitoring to evaluate symptoms refractory to PPI therapy. As mentioned earlier, number of reflux episodes measured by MII-pH has been recently shown to predict the need for and response to surgical augmentation of the LES in patients with PPI-refractory regurgitation.[102] The performance of MII-pH testing on and off medications also provides information on GERD phenotypes and can help differentiate between GERD, reflux hypersensitivity, and alternate diagnoses such as rumination syndrome.

Atypical symptoms. Atypical symptoms such as cough are often attributed to GERD, and patients receive empiric PPI therapy. MII-pH testing may be a useful diagnostic modality to evaluate the association between cough and gastroesophageal reflux. In a multicenter study of 192 patients with chronic cough, 24-hour pH impedance pressure monitoring was performed with measurement of acid and weakly acid reflux.[105] Only 25% of patients had reflux-induced cough; among them, acid reflux episodes accounted for only 22% of patients. Conversely, 24% of patients had cough-induced reflux. Also, patients with acid reflux-induced cough were significantly more likely to have typical reflux symptoms compared to patients without the diagnosis. In patients with chronic cough undergoing esophageal function testing, MII-pH is preferred compared to pH monitoring alone to detect symptoms triggered by weakly acid reflux. An acoustic cough detector or esophageal manometry (EM) testing can be beneficial to differentiate reflux-cough from cough-reflux se-

quences,[94] but this is not routinely used in clinical practice.

Belching is also a common symptom that is seen both in GERD and in other functional disorders such as supragastric belching, functional dyspepsia, and rumination syndrome.[106] MII-pH is a reliable test to differentiate gastric belching episodes due to reflux from supragastric belching, a behavioral disorder that can be managed by cognitive behavioral therapy. As mentioned earlier, rumination can be confirmed by a modified MII-HRM protocol that includes a meal challenge.[103,107]

Testing before antireflux surgery. Esophageal function testing by manometry and pH off PPI are recommended before antireflux surgery, to rule out esophageal motility disorders, and to confirm the presence of GERD because symptoms alone are not a reliable indicator of GERD.[94,108] The benefit of adding MII to pH testing for preoperative assessment is not clear but may be considered in patients with atypical symptoms or laryngeal symptoms. In a retrospective study of 237 patients with extraesophageal reflux symptoms who underwent pH and impedance testing before fundoplication, heartburn and regurgitation symptoms and abnormal acid exposure were the only predictors of response; impedance parameters did not predict response to fundoplication.[109] In a recent retrospective study of 71 patients who underwent MII-pH testing on PPI, 42 (59%) had GERD as defined by >48 reflux episodes. When these patients were tested off medications, 31% did not have GERD based on pH testing (abnormal Demeester score).[110] A recent randomized controlled trial that compared magnetic sphincter augmentation (MSA) and twice-daily PPI in patients with regurgitation refractory to once-daily PPI showed a significantly higher rate of response for MSA (89% vs 10%).[111] Subsequent analysis of the MII-pH studies used in that trial revealed that the presence of >80 reflux episodes detected by MII-pH on PPI predicted satisfaction with MSA, and reduction of reflux episodes to <35 was associated with improvement of regurgitation after MSA.[102] Therefore, 24-hour pH testing with or without MII off medications is recommended for preoperative evaluation before antireflux surgery.[94]

MII-EM. As with standard HRM, MII-EM is also used for the evaluation of dysphagia, odynophagia, chest pain, and regurgitation after a structural cause is excluded. Impedance adds assessment of whether bolus transit is complete or incomplete for each swallow, along with other measurements such as bolus clearance velocity and esophageal bolus retention, to the information obtained during conventional manometry. Normative data for MII-EM (conventional line tracing manometry rather than HRM) were established in which impedance changes correlated with radiographic bolus movement in 97% of

swallows.[89] In a prospective study of MII-EM (also based on conventional manometry) in 350 patients with various esophageal manometric abnormalities, all patients with achalasia (n = 24) and scleroderma (n = 4) had abnormal bolus transit.[112] Dysphagia was noted most often in patients with abnormal bolus transit. Of the patients with diffuse esophageal spasm and IEM, 55% and 51%, respectively, had normal bolus transit, and patients with isolated LES abnormalities (hypo- or hypertensive LES), nutcracker esophagus, or normal manometry almost always (>95%) had normal bolus transit. This study suggested a role for MII-EM in assessment of the functional abnormalities associated with manometric diagnoses noted on conventional manometry. In a subsequent study focusing on the IEM group of patients (n = 70), the authors noted that 33% had normal bolus transit for both liquid and viscous swallows, and manometrically normal contractions were almost always associated with normal bolus transit.[113] Abnormalities in viscous impedance were further evaluated in a prospective study of 240 patients (129 with nonobstructive dysphagia [NOD], 111 GERD patient controls) with normal liquid manometry. Patients with NOD were more likely to have abnormal viscous impedance compared to the control group (29% vs 16%; $P = .02$), but a statistically significant difference was not noted in liquid impedance abnormalities.[114] In a study evaluating the role of MII-EM in patients with achalasia and scleroderma, compared with normal controls, it was noted that patients with achalasia had impaired bolus transit across all sites in the esophagus, and pressures were also similar.[115] In contrast, in patients with scleroderma, bolus clearance rates and contraction amplitudes decreased from proximal to distal; in normal controls, the majority of swallows were associated with normal bolus transit. Several other studies have evaluated the role of MII-EM in patients with NOD and other esophageal motility abnormalities, establishing the additional advantage of evaluating bolus transit, specifically viscous bolus transit in the functional evaluation of the esophagus in these diseases.[115-119] That said, whether the impedance findings in MII-EM or MII-HRM alter clinical management has not been clearly proven.

Testing before and after antireflux surgery. Esophageal manometry is recommended before antireflux surgery to exclude achalasia and other esophageal motor abnormalities, which may predispose to postoperative dysphagia.[108] The role of MII-EM to identify manometric abnormalities and guide patient selection before fundoplication has been evaluated in several studies,[120-122] but although there are no direct comparative studies evaluating these 2 modalities, there does not appear to be an additional benefit to MII-EM over conventional HRM in guiding patient selection. In a prospective study of 74 patients undergoing Nissen fundoplication who were evaluated with MII-EM preoperatively and at a median of 18 months postoperatively, neither MII-EM nor manometry predicted postoperative dysphagia, and preoperative dysphagia was the only predictor of postoperative dysphagia.[120] However, in this study, 43% of patients self-reported preoperative dysphagia without any difference in pH, manometric, or MII-EM parameters between those with and without dysphagia. There was a significant improvement in the severity of dysphagia symptom score postoperatively (6.8 ± 2 to 2.6 ± 3.4; $P < .01$). The high prevalence of preoperative dysphagia and the improvement postoperatively suggest that this study population may not be comparable to the majority of patients undergoing fundoplication.

In another study, novel metrics were derived on MII-EM data before and after fundoplication through an automated iterative process, and 3 of these variables were combined to create a dysphagia risk index (DRI); a DRI >14 was noted to be optimally predictive of postoperative dysphagia.[117,122] DRI was applied in the evaluation of 25 children who underwent fundoplication, and in addition to postoperative delayed gastric emptying, DRI values were significantly higher in patients who developed postoperative dysphagia compared to those who did not (56, 15-105 vs 2, 2-6; $P = .016$).[122]

MII-EM has also been used to evaluate bolus transit and manometric abnormalities after fundoplication.[123,124] In a prospective study of 25 patients, MII-EM was performed before and after laparoscopic Nissen fundoplication; postoperatively, an increase was noted in the LES pressure, but there was no significant difference in the number of complete esophageal bolus transits and transit time for liquid swallows.[123] Transit time was more rapid for viscous swallows after surgery. The authors attribute the absence of postoperative manometric abnormalities to careful patient selection by preoperative evaluation of manometric abnormalities and surgical technique. In a separate study comparing Nissen with Toupet fundoplication, no differences were noted in MII parameters between the 2 operations.[125]

SAFETY AND TOLERABILITY

HRM and impedance monitoring are safe, and there are no reported serious adverse events. Epistaxis can occur with the transnasal catheter passage but is usually self-limited. Passage of transnasal catheters may be relatively contraindicated in patients on anticoagulants, recent gastric surgery, and previous nasopharyngeal surgeries or trauma.[126] There are no reported data on the safety of the use of MII in patients with cardiac defibrillators or pacemakers, but the voltage generated is below the threshold for cardiac stimulation.[127] There have been no reported adverse events associated with FLIP.

EASE OF USE

HRM

Placement of a transnasal manometry catheter requires basic understanding of pharyngeal and esophageal anatomy. In most centers, this is performed by a trained technician or nurse. HRM usually takes 30 to 40 minutes to complete and requires a 6-hour fast before the procedure. Sufficient understanding of HRM and EPT plots is required to ensure proper placement of the catheter and a study without artifacts. Occasionally, patients may be intolerant to passage of a catheter and may require sedation with endoscopic placement. FLIP topography can be considered as a means to assess esophageal motor function in patients who do not tolerate manometry.

EndoFLIP

The FLIP is usually placed transorally during sedated endoscopy or in the operating room with the patient under general anesthesia for patients who are undergoing fundoplication or Heller myotomy. Transnasal placement of FLIP is problematic because of the size of the probe, as is a study in an awake patient because of discomfort. Direct visualization during endoscopy may be used to assist with catheter placement, although the endoscope must be removed before taking measurements. Familiarity with the proprietary software and published measurement algorithms is needed for appropriate positioning of the catheter across the EGJ and reliable data acquisition. If the FLIP topography module is used, the software must be installed on a computer with an ethernet cable connection to the FLIP system. Analysis of the data may be aided by commercially available software, although the relative dearth of normative data and standardized protocols requires an experienced operator for final interpretation.

MII-pH

Placement of a transnasal catheter may be associated with transient discomfort despite the use of lubricant or topical anesthetic. Some patients may not tolerate a transnasal catheter and may require wireless pH monitoring.[94] The presence of a transnasal catheter may also affect some daily activities and dietary patterns, but most patients are able to complete the examination. Facilities offering MII pH or MII-HRM should have a dedicated area where catheter placement and testing can be performed and should have access to workstations or computers with the required proprietary software programs for analysis and reporting. Analysis and interpretation of the data collected during either of these tests requires an experienced operator. Automated analysis and interpretation of the data by the software programs included with these systems is helpful, but manual review and evaluation of this information by an experienced provider is mandatory before final reporting to avoid falsely negative or falsely positive results, which may affect treatment decisions.

FINANCIAL CONSIDERATIONS

EndoFLIP

FLIP requires both a capital investment in the hardware and software, as well as purchase of single-use catheters. The list price for the EndoFLIP System 1.0 is $25,962. The EndoFLIP System 2.0 includes the Topography Display Terminal, Topography Cart, and EndoFLIP System 1.0 and costs $81,000. The 16-cm (EF-322N) and 8-cm (EF 325N) single-use catheters cost $1973 each, whereas the Esoflip 20-mm dilation catheter (ES-320) and 30-mm dilation catheter (ES-330) cost $1550 and $1863, respectively.

FLIP may be reported using the Current Procedure Terminology code 91040 (Esophageal balloon distension study, diagnostic, with provocation when performed). Of note, this code is not included in the Medicare Ambulatory Surgical Center fee schedule. When performed in outpatient hospital facilities, 91040-26 is appropriate.

HRM

Performing high-resolution manometry involves an investment in both equipment and trained personnel to help perform the examination. Capital and per-case expenditures are needed, in addition to indirect costs related to equipment upkeep, reprocessing, and software upgrades. As indicated previously, water-perfusion systems require less upfront capital cost, but require more highly trained staff to perform the examination. Water-perfusion systems can cost $25,000, with the cost of each catheter being $500. The water-perfusion catheter has less overall durability. The most common HRM system is the Manoscan system (Medtronic Inc,). The system retails for $70,000, with each catheter costing $12,000. Reprocessing of catheters is required and incurs indirect processing costs.

MII-pH

MII-pH testing requires a similar set-up as HRM with dedicated personnel and initial purchase and continued upkeep of catheters and recorder devices. A dedicated laptop or desktop computer with the proprietary software program is also required for analysis and reporting of the results. Commercially available MII-pH systems include the Digitrapper system (Medtronic Inc), the ZepHr impedance/pH monitoring system (Diversatek Healthcare, Milwaukee, Wisc, USA), and the Ohmega system (Laborie, Portsmouth, NH, USA).

Esophageal MII-pH testing may be reported using the Current Procedure Terminology code 91038 (esophageal function test, gastroesophageal reflux test 91038 with nasal catheter intraluminal impedance electrode(s) placement, recording analysis and interpretation).

AREAS OF FUTURE RESEARCH

EndoFLIP

Impedance planimetry has ushered in a new era of esophageal function testing, providing novel information regarding the function of the esophageal body and sphincters of the GI tract. Despite a growing body of literature supporting its use in the evaluation and treatment of esophageal motility disorders, normative data remain lacking and expansion of this data pool is needed. The role of the FLIP topography module is also yet to be defined. Distention-mediated contractility may also represent a novel measure in distinguishing normal esophageal function from disease states and merits further investigation. Finally, investigations into the role of FLIP in evaluation of the pyloric and anal sphincters have been limited and further study is warranted.

HRM

High-resolution manometry has been the primary tool for diagnosing esophageal motor disorders. One limitation has been the "snapshot in time" assessment of esophageal physiology. The nature of the catheter has made prolonged ambulatory esophageal motility studies challenging owing to patient tolerance; however, 24-hour studies have been reported. These studies may be helpful in identifying intermittent physiologic events that result in symptom generation (ie, esophageal spasm). They can aid in the identification of meal- or sleep-associated events such as transient LES relaxations. The primary limitation is patient tolerance. Smaller catheters or a wireless system may be able to overcome this. The clinical usefulness of prolonged, ambulatory manometry has not been clearly proven.

Reflux monitoring with MII-pH

GERD is a complex disease with diverse phenotypic presentations. There are several novel techniques and methods being studied to diagnose and characterize GERD to guide treatment strategies. The optimal testing strategy (on or off antisecretory therapy) and the sequence of testing needs further prospective evaluation. The reliability and validity of newer metrics such as postreflux swallow-induced peristaltic waves, baseline impedance, mean nocturnal baseline impedance, and so on, should also be further investigated. The characterization of manometric abnormalities in GERD and incorporation of these measures into the diagnosis and treatment of GERD is an area of active study. Furthermore, the role of EM in evaluating pharyngeal motor function and supraglottic symptoms needs further study. MII-pH and EM testing also has an emerging role in patients undergoing lung transplantation and bariatric surgery.

SUMMARY

In the past few years, there have been substantial developments in the understanding and assessment of esophageal function, some of this owing to the introduction of newer technologies, which have led to a paradigm shift in disease classification, understanding of pathophysiology, and treatment. Impedance planimetry using the EndoFLIP system has been studied extensively in achalasia to diagnose and guide treatment. It also has a role in eosinophilic esophagitis and several other applications. The availability of HRM has enabled a greater understanding of swallow physiology and the manometric correlates of pathology related to non-obstructive dysphagia. Furthermore, the development of clinically relevant phenotypes has not only provided a better understanding of clinical outcomes related to therapy but has further helped define subgroups who may benefit from one therapy over another. MII combined with pH or high-resolution manometry assesses bolus transit and several other measures, which provide a functional assessment of esophageal motility and enable identification of nonacid reflux. HRM and pH monitoring are recommended before antireflux surgery for optimal patient selection with regard to postoperative outcomes such as symptom resolution and dysphagia. Refinements in automated analysis of the vast amounts of data generated during these studies can help facilitate clinician analysis and reporting. Prospective, randomized studies are needed to further evaluate the role of these technologies in clinical practice.

REFERENCES

1. El-Serag HB, Sweet S, Winchester CC, et al. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut 2014;63:871-80.
2. Richter JE, Rubenstein JH. Presentation and epidemiology of gastroesophageal reflux disease. Gastroenterology 2018;154:267-76.
3. Wang A, Pleskow DK, Banerjee S, et al. Esophageal function testing. Gastrointest Endosc 2012;76:231-43.
4. Chotiprashidi P, Liu J, Carpenter S, et al. ASGE technology status evaluation report: wireless esophageal pH monitoring system. Gastrointest Endosc 2005;62:485-7.
5. Savarino E, di Pietro M, Bredenoord AJ, et al. Use of the functional lumen imaging probe in clinical esophagology. Am J Gastroenterol 2020;115:1786-96.
6. McMahon BP, Frøkjær JB, Drewes AM, et al. A new measurement of oesophago-gastric junction competence. Neurogastroenterol Motil 2004;16:543-6.

7. Su B, Callahan ZM, Novak S, et al. Using impedance planimetry (Endo-FLIP) to evaluate myotomy and predict outcomes after surgery for achalasia. J Gastrointest Surg 2020;24:964-71.

8. Vosoughi K, Ichkhanian Y, Jacques J, et al. Role of endoscopic functional luminal imaging probe in predicting the outcome of gastric peroral endoscopic pyloromyotomy (with video). Gastrointest Endosc 2020;91:1289-99.

9. Conchillo JM, Straathof JWA, Mujagic Z, et al. Gastric peroral endoscopic pyloromyotomy for decompensated gastroparesis: comprehensive motility analysis in relation to treatment outcomes. Endosc Int Open 2021;9:E137-44.

10. Lin Z, Nicodème F, Boris L, et al. Regional variation in distal esophagus distensibility assessed using the functional luminal imaging probe (FLIP). Neurogastroenterol Motil 2013;25:e765-71.

11. Lin Z, Kahrilas PJ, Xiao Y, et al. Functional luminal imaging probe topography: an improved method for characterizing esophageal distensibility in eosinophilic esophagitis. Therap Adv Gastroenterol 2013;6:97-107.

12. Carlson DA, Lin Z, Hirano I, et al. Evaluation of esophageal distensibility in eosinophilic esophagitis: an update and comparison of functional lumen imaging probe analytic methods. Neurogastroenterol Motil 2016;28:1844-53.

13. Bianca A, Schindler V, Schnurre L, et al. Endoscope presence during endoluminal functional lumen imaging probe (FLIP) influences FLIP metrics in the evaluation of esophageal dysmotility. Neurogastroenterol Motil 2020;32:e13823.

14. Kwiatek MA, Hirano I, Kahrilas PJ, et al. Mechanical properties of the esophagus in eosinophilic esophagitis. Gastroenterology 2011;140:82-90.

15. Carlson DA, Kahrilas PJ, Lin Z, et al. Evaluation of esophageal motility utilizing the functional lumen imaging probe. Am J Gastroenterol 2016;111:1726-35.

16. Chen JW, Rubenstein JH. Esophagogastric junction distensibility assessed using the functional lumen imaging probe. World J Gastroenterol 2017;23:1289-97.

17. Carlson DA, Kou W, Lin Z, et al. Normal values of esophageal distensibility and distension-induced contractility measured by functional luminal imaging probe panometry. Clin Gastroenterol Hepatol 2019;17:674-81.

18. Tucker E, Sweis R, Anggiansah A, et al. Measurement of esophagogastric junction cross-sectional area and distensibility by an endoluminal functional lumen imaging probe for the diagnosis of gastro-esophageal reflux disease. Neurogastroenterol Motil 2013;25:904-10.

19. Amaravadi R, Levine MS, Rubesin SE, et al. Achalasia with complete relaxation of lower esophageal sphincter: radiographic-manometric correlation. Radiology 2005;235:886-91.

20. Mearin F, Malagelada JR. Complete lower esophageal sphincter relaxation observed in some achalasia patients is functionally inadequate. Am J Physiol Gastrointest Liver Physiol 2000;278:G376-83.

21. Carlson DA, Lin Z, Kahrilas PJ, et al. The functional lumen imaging probe detects esophageal contractility not observed with manometry in patients with achalasia. Gastroenterology 2015;149:1742-51.

22. Rohof WO, Hirsch DP, Kessing BF, et al. Efficacy of treatment for patients with achalasia depends on the distensibility of the esophagogastric junction. Gastroenterology 2012;143:328-35.

23. Rieder E, Swanström LL, Perretta S, et al. Intraoperative assessment of esophagogastric junction distensibility during per oral endoscopic myotomy (POEM) for esophageal motility disorders. Surg Endosc 2013;27:400-5.

24. Pandolfino JE, de Ruigh A, Nicodème F, et al. Distensibility of the esophagogastric junction assessed with the functional lumen imaging probe (FLIP™) in achalasia patients. Neurogastroenterol Motil 2013;25:496-501.

25. Ponds FA, Bredenoord AJ, Kessing BF, et al. Esophagogastric junction distensibility identifies achalasia subgroup with manometrically normal esophagogastric junction relaxation. Neurogastroenterol Motil. Epub 2016 Jul 25.

26. Yadlapati R, Kahrilas PJ, Fox MR, et al. Esophageal motility disorders on high-resolution manometry: Chicago classification version 4.0©. Neurogastroenterol Motil 2021;33:e14058.

27. Triggs JR, Carlson DA, Beveridge C, et al. Functional luminal imaging probe panometry identifies achalasia-type esophagogastric junction outflow obstruction. Clin Gastroenterol Hepatol 2020;18:2209-17.

28. Ichkhanian Y, Sanaei O, Canakis A, et al. Esophageal peroral endoscopic myotomy (POEM) for treatment of esophagogastric junction outflow obstruction: results from the first prospective trial. Endosc Int Open 2020;8:E1137-43.

29. Teitelbaum EN, Boris L, Arafat FO, et al. Comparison of esophagogastric junction distensibility changes during POEM and Heller myotomy using intraoperative FLIP. Surg Endosc 2013;27:4547-55.

30. Teitelbaum EN, Soper NJ, Boris L, et al. Predictors of intraoperative esophagogastric junction distensibility and physiologic improvement during heller myotomy and poem. Surg Endosc 2014;28:3359-65.

31. Teitelbaum EN, Soper NJ, Pandolfino JE, et al. An extended proximal esophageal myotomy is necessary to normalize EGJ distensibility during Heller myotomy for achalasia, but not POEM. Surg Endosc 2014;28:2840-7.

32. Teitelbaum EN, Soper NJ, Pandolfino JE, et al. Esophagogastric junction distensibility measurements during Heller myotomy and POEM for achalasia predict postoperative symptomatic outcomes. Surg Endosc 2015;29:522-8.

33. Teitelbaum EN, Sternbach JM, El Khoury R, et al. The effect of incremental distal gastric myotomy lengths on EGJ distensibility during POEM for achalasia. Surg Endosc 2016;30:745-50.

34. Ngamruengphong S, von Rahden BHA, Filser J, et al. Intraoperative measurement of esophagogastric junction cross-sectional area by impedance planimetry correlates with clinical outcomes of peroral endoscopic myotomy for achalasia: a multicenter study. Surg Endosc 2016;30:2886-94.

35. Familiari P, Gigante G, Marchese M, et al. EndoFLIP system for the intraoperative evaluation of peroral endoscopic myotomy. United European Gastroenterol J 2014;2:77-83.

36. Ilczyszyn A, Hamaoui K, Cartwright J, et al. Intraoperative distensibility measurement during laparoscopic Heller's myotomy for achalasia may reduce the myotomy length without compromising patient outcome. Dis Esophagus 2016;29:455-62.

37. Yoo IK, Choi SA, Kim WH, et al. Assessment of clinical outcomes after peroral endoscopic myotomy via esophageal distensibility measurements with the endoluminal functional lumen imaging probe. Gut Liver 2019;13:32-9.

38. Jain AS, Carlson DA, Triggs J, et al. Esophagogastric junction distensibility on functional lumen imaging probe topography predicts treatment response in achalasia - anatomy matters! Am J Gastroenterol 2019;114:1455-63.

39. Barham CP, Gotley DC, Mills A, et al. Precipitating causes of acid reflux episodes in ambulant patients with gastro-oesophageal reflux disease. Gut 1995;36:505-10.

40. Pandolfino JE, Shi G, Curry J, et al. Esophagogastric junction distensibility: a factor contributing to sphincter incompetence. Am J Physiol Gastrointest Liver Physiol 2002;282:G1052-8.

41. Jenkinson AD, Scott SM, Yazaki E, et al. Compliance measurement of lower esophageal sphincter and esophageal body in achalasia and gastroesophageal reflux disease. Dig Dis Sci 2001;46:1937-42.

42. Kwiatek MA, Pandolfino JE, Hirano I, et al. Esophagogastric junction distensibility assessed with an endoscopic functional luminal imaging probe (EndoFLIP). Gastrointest Endosc 2010;72:272-8.

43. Carlson DA, Kathpalia P, Craft J, et al. The relationship between esophageal acid exposure and the esophageal response to volumetric distention. Neurogastroenterol Motil. Epub 2018 Nov 2.

44. Lottrup C, McMahon BP, Ejstrud P, et al. Esophagogastric junction distensibility in hiatus hernia. Dis Esophagus 2016;29:463-71.

45. Perretta S, McAnena O, Botha A, et al. Acta from the EndoFLIP® symposium. Surg Innov 2013;20:545-52.

46. Ilczyszyn A, Botha AJ. Feasibility of esophagogastric junction distensibility measurement during Nissen fundoplication. Dis Esophagus 2014;27:637-44.

47. Kwiatek MA, Kahrilas PJ, Soper NJ, et al. Esophagogastric junction distensibility after fundoplication assessed with a novel functional luminal imaging probe. J Gastrointest Surg 2010;14:268-76.

48. DeHaan RK, Davila D, Frelich MJ, et al. Esophagogastric junction distensibility is greater following Toupet compared to Nissen fundoplication. Surg Endosc 2017;31:193-8.

49. Hoppo T, McMahon BP, Witteman BPL, et al. Functional lumen imaging probe to assess geometric changes in the esophagogastric junction following endolumenal fundoplication. J Gastrointest Surg 2011;15:1112-20.

50. Rinsma NF, Smeets FG, Bruls DW, et al. Effect of transoral incisionless fundoplication on reflux mechanisms. Surg Endosc 2014;28:941-9.

51. Haito Chavez Y, Ngamruengphong S, Bukhari M, et al. Transoral incisionless endoscopic fundoplication guided by impedance planimetry to treat severe GERD symptoms after per-oral endoscopic myotomy. Gastrointest Endosc 2017;85:254-5.

52. Smeets FGM, Keszthelyi D, Bouvy ND, et al. Does measurement of esophagogastric junction distensibility by EndoFLIP predict therapyresponsiveness to endoluminal fundoplication in patients with gastroesophageal reflux disease? Neurogastroenterol Motil 2015;21:255-64.

53. Dellon ES, Liacouras CA. Advances in clinical management of eosinophilic esophagitis. Gastroenterology 2014;147:1238-54.

54. Dellon ES, Speck O, Woodward K, et al. Distribution and variability of esophageal eosinophilia in patients undergoing upper endoscopy. Mod Pathol 2015;28:383-90.

55. Gentile N, Katzka D, Ravi K, et al. Oesophageal narrowing is common and frequently under-appreciated at endoscopy in patients with oesophageal eosinophilia. Aliment Pharmacol Ther 2014;40:1333-40.

56. Chen JW, Pandolfino JE, Lin Z, et al. Severity of endoscopically identified esophageal rings correlates with reduced esophageal distensibility in eosinophilic esophagitis. Endoscopy 2016;48:794-801.

57. Nicodème F, Hirano I, Chen J, et al. Esophageal distensibility as a measure of disease severity in eosinophilic esophagitis. Clin Gastroenterol Hepatol 2013;11:1101-11007.e1.

58. Carlson DA, Lin Z, Rogers MC, et al. Utilizing functional lumen imaging probe topography to evaluate esophageal contractility during volumetric distention: a pilot study. Neurogastroenterol Motil 2015;27:981-9.

59. Baumann AJ, Donnan EN, Triggs JR, et al. Normal functional luminal imaging probe panometry findings associate with lack of major esophageal motility disorder on high-resolution manometry. Clin Gastroenterol Hepatol 2021;19:259-68.e1.

60. Carlson DA, Gyawali CP, Kahrilas PJ, et al. Esophageal motility classification can be established at the time of endoscopy: a study evaluating real-time functional luminal imaging probe panometry. Gastrointest Endosc 2019;90:915-23.e1.

61. Yu JX, Baker JR, Watts L, et al. Functional lumen imaging probe is useful for the quantification of gastric sleeve stenosis and prediction of response to endoscopic dilation: a pilot study. Obes Surg 2020;30:786-9.

62. Hedberg HM, Carbray J, Ujiki MB. Initial experience with endoscopic pyloromyotomy, with description and video of technique. J Gastrointest Surg 2019;23:1706-10.

63. Gyawali CP, Patel A. Esophageal motor function: technical aspects of manometry. Gastrointest Endosc Clin N Am 2014;24:527-43.

64. Kahrilas PJ, Bredenoord AJ, Fox M, et al. The Chicago Classification of esophageal motility disorders, v3.0. Neurogastroenterol Motil 2015;27:160-74.

65. Pandolfino JE, Ghosh SK, Rice J, et al. Classifying esophageal motility by pressure topography characteristics: a study of 400 patients and 75 controls. Am J Gastroenterol 2008;103:27-37.

66. Yadlapati R, Pandolfino JE, Fox MR, et al. What is new in Chicago Classification version 4.0? Neurogastroenterol Motil 2021;33:e14053.

67. Bredenoord AJ, Hebbard GS. Technical aspects of clinical high-resolution manometry studies. Neurogastroenterol Motil 2012;24:5-10.

68. Ghosh SK, Pandolfino JE, Zhang Q, et al. Quantifying esophageal peristalsis with high-resolution manometry: a study of 75 asymptomatic volunteers. Am J Physiol Gastrointest Liver Physiol 2006;290:G988-97.

69. Rogers BD, Gyawali CP. Enhancing high-resolution esophageal manometry: use of ancillary techniques and maneuvers. Gastroenterol Clin North Am 2020;49:411-26.

70. Xiao Y, Read A, Nicodeme F, et al. The effect of a sitting vs supine posture on normative esophageal pressure topography metrics and Chicago Classification diagnosis of esophageal motility disorders. Neurogastroenterol Motil 2012;24:e509-16.

71. Carlson DA, Crowell MD, Kimmel JN, et al. Loss of peristaltic reserve, determined by multiple rapid swallows, is the most frequent esophageal motility abnormality in patients with systemic sclerosis. Clin Gastroenterol Hepatol 2016;14:1502-6.

72. Stoikes N, Drapekin J, Kushnir V, et al. The value of multiple rapid swallows during preoperative esophageal manometry before laparoscopic antireflux surgery. Surg Endosc 2012;26:3401-7.

73. Marsh JK, Hoffman SM, Dmuchowski CF. Effect of intravenous midazolam on esophageal motility testing in normal human volunteers. Am J Gastroenterol 1993;88:860-3.

74. Pandolfino JE, Ghosh SK, Zhang Q, et al. Quantifying EGJ morphology and relaxation with high-resolution manometry: a study of 75 asymptomatic volunteers. Am J Physiol Gastrointest Liver Physiol 2006;290:G1033-40.

75. Roman S, Pandolfino JE, Chen J, et al. Phenotypes and clinical context of hypercontractility in high-resolution esophageal pressure topography (EPT). Am J Gastroenterol 2012;107:37-45.

76. Xiao Y, Kahrilas PJ, Kwasny MJ, et al. High-resolution manometry correlates of ineffective esophageal motility. Am J Gastroenterol 2012;107:1647-54.

77. Pandolfino JE, Leslie E, Luger D, et al. The contractile deceleration point: an important physiologic landmark on oesophageal pressure topography. Neurogastroenterol Motil 2010;22:395-400.

78. Pratap N, Kalapala R, Darisetty S, et al. Achalasia cardia subtyping by high-resolution manometry predicts the therapeutic outcome of pneumatic balloon dilatation. J Neurogastroenterol Motil 2011;17:48-53.

79. Andolfi C, Fisichella PM. Meta-analysis of clinical outcome after treatment for achalasia based on manometric subtypes. Br J Surg 2019;106:332-41.

80. Ou YH, Nie XM, Li LF, et al. High-resolution manometric subtypes as a predictive factor for the treatment of achalasia: a meta-analysis and systematic review. J Dig Dis 2016;17:222-35.

81. Rohof WO, Salvador R, Annese V, et al. Outcomes of treatment for achalasia depend on manometric subtype. Gastroenterology 2013;144:718-25.

82. Khashab MA, Vela MF, Thosani N, et al. ASGE guideline on the management of achalasia. Gastrointest Endosc 2020;91:213-27.e6.

83. Carlson DA, Lin Z, Kahrilas PJ, et al. High-resolution impedance manometry metrics of the esophagogastric junction for the assessment of treatment response in achalasia. Am J Gastroenterol 2016;111:1702-10.

84. Bredenoord AJ, Weusten BL, Timmer R, et al. Intermittent spatial separation of diaphragm and lower esophageal sphincter favors acidic and weakly acidic reflux. Gastroenterology 2006;130:334-40.

85. Weijenborg PW, van Hoeij FB, Smout AJ, et al. Accuracy of hiatal hernia detection with esophageal high-resolution manometry. Neurogastroenterol Motil 2015;27:293-9.

86. Nicodeme F, Pipa-Muniz M, Khanna K, et al. Quantifying esophagogastric junction contractility with a novel HRM topographic metric, the EGJ-Contractile Integral: normative values and preliminary

evaluation in PPI non-responders. Neurogastroenterol Motil 2014;26: 353-60.

87. Rengarajan A, Bolkhir A, Gor P, et al. Esophagogastric junction and esophageal body contraction metrics on high-resolution manometry predict esophageal acid burden. Neurogastroenterol Motil 2018;30: e13267.

88. Chan WW, Haroian LR, Gyawali CP. Value of preoperative esophageal function studies before laparoscopic antireflux surgery. Surg Endosc 2011;25:2943-9.

89. Tutuian R, Vela MF, Balaji NS, et al. Esophageal function testing with combined multichannel intraluminal impedance and manometry: multicenter study in healthy volunteers. Clin Gastroenterol Hepatol 2003;1:174-82.

90. Hirano I, Richter JE. ACG practice guidelines: esophageal reflux testing. Am J Gastroenterol 2007;102:668-85.

91. Gyawali CP, Kahrilas PJ, Savarino E, et al. Modern diagnosis of GERD: the Lyon Consensus. Gut 2018;67:1351-62.

92. Gyawali CP, de Bortoli N, Clarke J, et al. Indications and interpretation of esophageal function testing. Ann N Y Acad Sci 2018;1434: 239-53.

93. Wenzl TG, Benninga MA, Loots CM, et al. Indications, methodology, and interpretation of combined esophageal impedance-pH monitoring in children: ESPGHAN EURO-PIG standard protocol. J Pediatr Gastroenterol Nutr 2012;55:230-4.

94. Roman S, Gyawali CP, Savarino E, et al. Ambulatory reflux monitoring for diagnosis of gastro-esophageal reflux disease: update of the Porto consensus and recommendations from an international consensus group. Neurogastroenterol Motil 2017;29:1-15.

95. Carlson DA, Pandolfino JE. High-resolution manometry in clinical practice. Gastroenterol Hepatol (N Y) 2015;11:374-84.

96. Conklin JL. Evaluation of esophageal motor function with high-resolution manometry. J Neurogastroenterol Motil 2013;19: 281-94.

97. Kahrilas PJ, Quigley EM. Clinical esophageal pH recording: a technical review for practice guideline development. Gastroenterology 1996;110:1982-96.

98. Savarino E, Bredenoord AJ, Fox M, et al. Expert consensus document: advances in the physiological assessment and diagnosis of GERD. Nat Rev Gastroenterol Hepatol 2017;14:665-76.

99. Weusten BL, Roelofs JM, Akkermans LM, et al. The symptom-association probability: an improved method for symptom analysis of 24-hour esophageal pH data. Gastroenterology 1994;107:1741-5.

100. Patel A, Sayuk GS, Gyawali CP. Parameters on esophageal pH-impedance monitoring that predict outcomes of patients with gastroesophageal reflux disease. Clin Gastroenterol Hepatol 2015;13:884-91.

101. Ravi K, Geno DM, Vela MF, et al. Baseline impedance measured during high-resolution esophageal impedance manometry reliably discriminates GERD patients. Neurogastroenterol Motil. Epub 2016 Oct 24.

102. Rogers BD, Valdovinos LR, Crowell MD, et al. Number of reflux episodes on pH-impedance monitoring associates with improved symptom outcome and treatment satisfaction in gastro-oesophageal reflux disease (GERD) patients with regurgitation. Gut 2021;70:450-5.

103. Halland M, Pandolfino J, Barba E. Diagnosis and treatment of rumination syndrome. Clin Gastroenterol Hepatol 2018;16:1549-55.

104. Mainie I, Tutuian R, Shay S, et al. Acid and non-acid reflux in patients with persistent symptoms despite acid suppressive therapy: a multicentre study using combined ambulatory impedance-pH monitoring. Gut 2006;55:1398-402.

105. Herregods TVK, Pauwels A, Jafari J, et al. Ambulatory pH-impedance-pressure monitoring as a diagnostic tool for the reflux-cough syndrome. Dis Esophagus 2018;31:1-7.

106. Kessing BF, Bredenoord AJ, Smout AJ. The pathophysiology, diagnosis and treatment of excessive belching symptoms. Am J Gastroenterol 2014;109:1196-203.

107. Kessing BF, Bredenoord AJ, Smout AJ. Objective manometric criteria for the rumination syndrome. Am J Gastroenterol 2014;109:52-9.

108. Jobe BA, Richter JE, Hoppo T, et al. Preoperative diagnostic workup before antireflux surgery: an evidence and experience-based consensus of the Esophageal Diagnostic Advisory Panel. J Am Coll Surg 2013;217:586-97.

109. Francis DO, Goutte M, Slaughter JC, et al. Traditional reflux parameters and not impedance monitoring predict outcome after fundoplication in extraesophageal reflux. Laryngoscope 2011;121:1902-9.

110. Ward MA, Dunst CM, Glasgow ME, et al. Can impedance-pH testing on medications reliably identify patients with GERD as defined by pathologic esophageal acid exposure off medications? J Gastrointest Surg 2019;23:1301-8.

111. Bell R, Lipham J, Louie B, et al. Laparoscopic magnetic sphincter augmentation versus double-dose proton pump inhibitors for management of moderate-to-severe regurgitation in GERD: a randomized controlled trial. Gastrointest Endosc 2019;89:14-22.e1.

112. Tutuian R, Castell DO. Combined multichannel intraluminal impedance and manometry clarifies esophageal function abnormalities: study in 350 patients. Am J Gastroenterol 2004;99:1011-9.

113. Tutuian R, Castell DO. Clarification of the esophageal function defect in patients with manometric ineffective esophageal motility: studies using combined impedance-manometry. Clin Gastroenterol Hepatol 2004;2:230-6.

114. Clayton SB, Rife C, Kalbfleisch JH, et al. Viscous impedance is an important indicator of abnormal esophageal motility. Neurogastroenterol Motil 2013;25:563-e455.

115. Mainie I, Tutuian R, Patel A, et al. Regional esophageal dysfunction in scleroderma and achalasia using multichannel intraluminal impedance and manometry. Dig Dis Sci 2008;53:210-6.

116. Blonski W, Hila A, Vela MF, et al. An analysis of distal esophageal impedance in individuals with and without esophageal motility abnormalities. J Clin Gastroenterol 2008;42:776-81.

117. Conchillo JM, Nguyen NQ, Samsom M, et al. Multichannel intraluminal impedance monitoring in the evaluation of patients with non-obstructive Dysphagia. Am J Gastroenterol 2005;100:2624-32.

118. Cho YK, Choi MG, Park JM, et al. Evaluation of esophageal function in patients with esophageal motor abnormalities using multichannel intraluminal impedance esophageal manometry. World J Gastroenterol 2006;12:6349-54.

119. Blonski W, Hila A, Jain V, et al. Impedance manometry with viscous test solution increases detection of esophageal function defects compared to liquid swallows. Scand J Gastroenterol 2007;42: 917-22.

120. Montenovo M, Tatum RP, Figueredo E, et al. Does combined multichannel intraluminal esophageal impedance and manometry predict postoperative dysphagia after laparoscopic Nissen fundoplication? Dis Esophagus 2009;22:656-63.

121. del Genio G, Tolone S, del Genio F, et al. Prospective assessment of patient selection for antireflux surgery by combined multichannel intraluminal impedance pH monitoring. J Gastrointest Surg 2008;12: 1491-6.

122. Myers JC, Nguyen NQ, Jamieson GG, et al. Susceptibility to dysphagia after fundoplication revealed by novel automated impedance manometry analysis. Neurogastroenterol Motil 2012;24:812-e393.

123. Del Genio G, Tolone S, Del Genio F, et al. Impact of total fundoplication on esophageal transit: analysis by combined multichannel intraluminal impedance and manometry. J Clin Gastroenterol 2012;46:e1-5.

124. Yigit T, Quiroga E, Oelschlager B. Multichannel intraluminal impedance for the assessment of post-fundoplication dysphagia. Dis Esophagus 2006;19:382-8.

125. Koch OO, Kaindlstorfer A, Antoniou SA, et al. Comparison of results from a randomized trial 1 year after laparoscopic Nissen and Toupet fundoplications. Surg Endosc 2013;27:2383-90.

126. Rodriguez SA, Banerjee S, Desilets D, et al. Ultrathin endoscopes. Gastrointest Endosc 2010;71:893-8.

127. Vaezi MF, Shay SS. New techniques in measuring nonacidic esopha-geal reflux. Semin Thorac Cardiovasc Surg 2001;13:255-64.

Abbreviations: AET, acid exposure time; ASGE, American Society for Gastrointestinal Endoscopy; BMI, body mass index; CC, Chicago classification; CD, contractile deceleration; CSA, cross-sectional area; DI, distensibility index; DP, distensibility plateau; DRI, dysphagia risk index; EGJ, esophagogastric junction; EGJOO, esophagogastric junction outflow obstruction; EoE, eosinophilic esophagitis; EM, esophageal manometry; EPT, esophageal pressure topography plots; FLIP, functional luminal imaging probe; HRM, high-resolution esophageal manometry; IEM, ineffective esophageal motility; IRP, integrated relaxation pressure; LES, lower esophageal sphincter; LHM, laparoscopic Heller myotomy; MII, multichannel intraluminal impedance; MRS, multiple rapid swallows; MSA, magnetic sphincter augmentation; NOD, nonobstructive dysphagia; POEM, peroral endoscopic myotomy; PPI, proton pump inhibitors; SAP, symptom association probability; SI, Symptom index; UES, upper esophageal sphincter.

Disclosure: *Dr Pannala is a consultant for HCL Technologies; has received travel compensation and food and beverage from Boston Scientific Corporation; has received food and beverage from Apollo Endosurgery US, Inc.; and is on the scientific advisory board for Nestle Health Sciences. Dr Krishnan is a consultant for Olympus Corporation of the Americas and Medtronic; has received travel compensation and food and beverage from Olympus Corporation of the Americas; and has received food and beverage from Boston Scientific Corporation. Dr Watson is a consultant and speaker for and has received travel compensation and food and beverage from Apollo Endosurgery US Inc and Boston Scientific Corporation; is a consultant for Neptune Medical Inc.; and has received food and beverage from Covidien LP, ERBE USA Inc, and Braintree Laboratories, Inc. Dr Vela is a consultant for Medtronic USA, Inc. Dr Abu Dayyeh is a consultant for Metamodix, BFKW, Endogenex, Hemostasis, and Boston Scientific Corporation; is a consultant and has received research support from Medtronic; has received research support from Apollo Endosurgery, USGI, Spatz Medical, GI Dynamics, Cairn Diagnostics, Endogastric Solutions Inc., and Aspire Bariatrics.; is a speaker for Johnson and Johnson, Endogastric Solutions Inc., and Olympus Corporation of the Americas; has received travel compensation and food and beverage from Olympus Corporation of the Americas and Endogastric Solutions, Inc.; and has received food and beverage from Boston Scientific Corporation, Covidien LP, Apollo Endosurgery US Inc, and Medrobotics Inc. Dr Bhatt is a consultant and speaker for Boston Scientific Corporation, Eleview, and Olympus Corporation of the Americas; is a consultant and speaker for and receives royalties from Medtronics; is a consultant for and has received food and beverage from Lumendi LLC; has a patent for a commercial device licensed to Medtronic; and has received food and beverage from Covidien LP, Boston Scientific Corporation, Olympus America Inc., and Shionogi Inc. Dr Bhutani has received research grants from Silenseed Inc., Galera Inc, Oncosil Inc., Nanobiotix, and Augmenix Inc.; has received food and beverage from Augmenix Inc., Conmed Corporation, Boston Scientific Corporation, and Olympus Corporation of the Americas; and has received travel compensation from Augmenix Inc. Dr Bucobo is a consultant for and has received travel compensation and food and beverage from Cook Medical LLC; has received travel compensation and food and beverage from Olympus Corporation of the Americas; and has received food and beverage from Boston Scientific Corporation, AbbVie, Inc., Janssen Biotech, Inc., STERIS CORPORATION, Ferring Pharmaceuticals Inc., Takeda Pharmaceuticals U.S.A., Inc., Endogastric Solutions, Inc., Merck Sharp & Dohme Corporation, Dova Pharmaceuticals, PFIZER INC., and Allergan Inc. Dr Chandrasekhara is a consultant for Covidien LP; is on the advisory board for Interpace Diagnostics; is a shareholder in Nevakar, Inc.; and has received food and beverage from Olympus*

America Inc. and Boston Scientific Corporation. Dr Copland has received education compensation from Salix Pharmaceauticals, Ltd. Dr Jirapinyo is a consultant for Endogastric Solutions, and Lumendi; is a consultant for and has received research support from GI Dynamics; has received research support from Apollo Endosurgery and Fractyl; has received travel compensation and food and beverage from Boston Scientific Corporation; and has received travel compensation from Olympus Corporation of the Americas. Dr Kumta is a consultant for and has received travel compensation and food and beverage from Boston Scientific Corporation, Gyrus ACMI, Inc., Olympus Corporation of the Americas, and Apollo Endosurgery US Inc.; and has received food and beverage from FIJUFILM Medical Systems USA, Inc., STERIS CORPORATION, ERBE USA Inc., Endogastric Solutions, and CONMED Corporation. Dr Law is a consultant for and has received travel compensation and food and beverage from Olympus America Inc.; is a consultant for Medtronic; and has received food and beverage from Boston Scientific Corporation. Dr Maple has received food and beverage from Covidien LP, Olympus America Inc., and Boston Scientific Corporation. Dr Melson received an investigator-initiated grant from and has received food and beverage from Boston Scientific Corporation; has received food and beverage from Cook Medical LLC; is a consultant for Geneoscopy; and has stock options with Virgo Imaging. Dr Parsi has received travel compensation and food and beverage from Olympus Corporation of the Americas; and has received food and beverage from CONMED Corporation, Salix Pharmaceuticals, AbbVie, Inc., Shionogi Inc., Shire North American Group Inc., and Boston Scientific Corporation. Dr Rahimi has received food and beverage from AbbVie, Inc., Boston Scientific Corporation, and Covidien LP. Dr Saumoy has received food and beverage from Boston Scientific Corporation, Ethicon US, LLC, Allergan Inc., and AbbVie, Inc. Dr Sethi is a consultant for Boston Scientific Corporation, Fujifilm, Medtronic, Micro-Tech, Intuitive Surgical, and Olympus Corporation of the Americas; has received travel compensation and food and beverage from ERBE USA, Inc., Covidien LP, and Cook Medical LLC; and has received food and beverage from Lumendi. Dr Trikudanathan is a consultant for and has received travel compensation and food and beverage from Boston Scientific Corporation; and has received food and beverage from Cook Medical LLC. Dr Trindade is a consultant for and has received food and beverage from Olympus Corporation of the Americas; is a consultant for and has received travel compensation and food and beverage from PENTAX of America, Inc.; has consulted for and received travel compensation and food and beverage from Gyrus ACMI, Inc.; has received food and beverage from Boston Scientific Corporation; and has a research grant from NinePoint Medical, Inc. Dr Yang is a consultant for and has received travel compensation and food and beverage from Olympus Corporation of the Americas; is a consultant for and has received food and beverage from Cook Medical LLC; and has received food and beverage from US Endoscopy, Boston Scientific Corporation, CONMED Corporation, Salix Pharmaceuticals, and AbbVie, Inc. Dr Lichtenstein is a consultant for and has received education compensation, travel compensation, and food and beverage from Olympus Corporation of the Americas; is a consultant for Iterative Scopes, CONMED Corporation, AMBU; and is a consultant and has received food and beverage from Boston Scientific Corporation.

Department of Gastroenterology and Hepatology, Mayo Clinic, Scottsdale, Arizona (1), Division of Gastroenterology, Department of Internal Medicine, Harvard Medical School and Massachusetts General Hospital, Boston,

Massachusetts (2), Department of Gastroenterology, Interventional Endoscopy Services, California Pacific Medical Center, San Francisco, California (3), Department of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota (4), Department of Gastroenterology, Hepatology & Nutrition, Cleveland Clinic, Cleveland, Ohio (5), Department of Gastroenterology Hepatology and Nutrition, Division of Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas (6), Division of Gastroenterology and Hepatology, Stony Brook Medicine, Stony Brook, New York (7), Division of Gastroenterology and Hepatology, University of Virginia Health Systems, Charlottesville, Virginia (8), Division of Gastroenterology, Hepatology and Endoscopy, Brigham and Women's Hospital, Boston, Massachusetts (9), Division of Gastroenterology, Mount Sinai Hospital, New York, New York (10), Division of Digestive Diseases and Nutrition, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma (11), Division of Digestive Diseases, Department of Internal Medicine, Rush University Medical Center, Chicago, Illinois (12), Division of Gastroenterology and Hepatology, University of Tennessee Health Sciences Center, Memphis, Tennessee (13), Department of Gastroenterology, Baylor Scott & White Health, Lakeway, Texas (14), Department of Gastroenterology, University of Pennsylvania, Philadelphia, Pennsylvania (15), Department of Digestive and Liver Diseases, New York-Presbyterian Medical Center/Columbia University Medical Center, New York, New York (16), Division of Gastroenterology, Hepatology and Nutrition, University of Minnesota, Minneapolis, Minnesota (17), Department of Gastroenterology, Zucker School of Medicine at Hofstra/Northwell, Long Island Jewish Medical Center, New Hyde Park, New York (18), Division of Gastroenterology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York (19), Division of Gastroenterology, Boston Medical Center, Boston University School of Medicine, Boston, Massachusetts (20).