

The Arrival of Intestinal Ultrasound for Inflammatory Bowel Disease Care in the United States

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Abstract: Intestinal ultrasound (IUS) is a noninvasive and highly reliable point-of-care tool to evaluate inflammation of the bowel. It offers comparable accuracy to endoscopy and magnetic resonance enterography. Although IUS has been incorporated into the management of inflammatory bowel disease (IBD) in other parts of the world, it has only recently arrived in the United States. However, barriers to integration of IUS into IBD care in the United States have included a lack of adoption by leading centers, lack of educational opportunities, and an unclear path for remuneration. This article provides information about the use of IUS in IBD, reviews the data comparing existing modalities of assessment of IBD with IUS, and summarizes strategies to overcome existing barriers to IUS implementation, including the newly available US-based training pathway and appropriate billing practice.

Inflammatory bowel disease (IBD) consists of chronic, progressive, and relapsing and remitting diseases characterized by intestinal inflammation. Symptoms of IBD and objective measures of disease activity do not always correlate. Therefore, treating to composite endpoints of symptoms and objective targets as well as proactive disease monitoring have been incorporated into an updated approach to the treatment of IBD.¹⁻³ There are numerous tools for assessment of disease activity, ranging from the gold standard of endoscopy (also the most invasive) to biomarker tests such as C-reactive protein (CRP) and fecal calprotectin (FCP). Proactive disease monitoring allows for earlier interventions for optimization of treatments and prevention of clinical consequences.^{1,4} However, limitations involving test characteristics, invasiveness, inconvenience, and delay in obtaining results render these monitoring strategies to have limited utility in various clinical scenarios, and none of the strategies currently include point-of-care (POC) assessment of disease activity.

Intestinal ultrasound (IUS) is an evolving tool for disease monitoring of IBD. IUS has been used for several decades as the standard of care

Keywords

Inflammatory bowel disease, ulcerative colitis, Crohn's disease, intestinal ultrasound, disease activity, disease monitoring

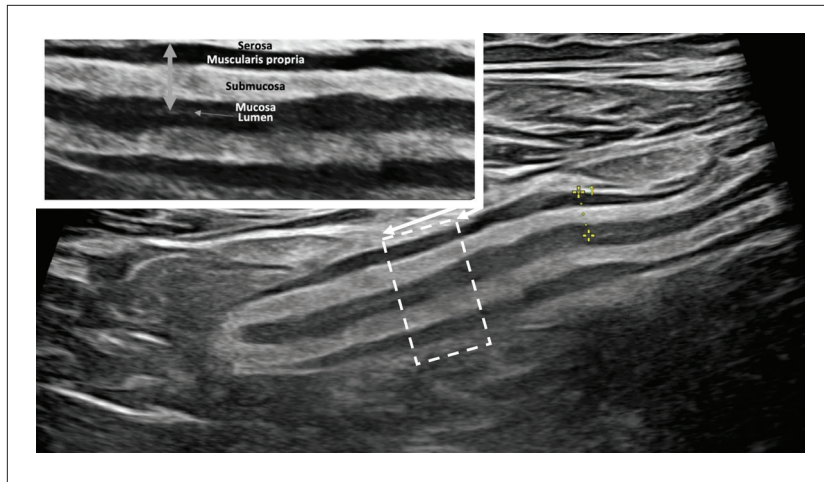


Figure 1. Intestinal ultrasound (IUS) image showing a longitudinal view of the sigmoid colon. Magnified depiction of labeled bowel wall layers with transabdominal IUS examination: lumen-mucosal interface, mucosa, submucosa, muscularis propria, and serosa. Gray double-headed arrow shows the borders of the measured bowel wall from the lumen-mucosal interface to the muscularis propria–serosal interface (also depicted by the yellow caliper).

in expert IBD centers throughout parts of Europe, Australia, Asia, and Canada for disease monitoring of IBD. It arrived in the United States several years ago and only a few US IBD centers (including the authors³) currently offer it as an integrated part of IBD care. The increasing adoption of IUS into IBD care is attributed to its accuracy,^{5,6} reproducibility, repeatability, well-tolerated⁷ and relatively inexpensive nature,⁸ and convenience and efficiency as a POC test. This article reviews the state of the art of IUS by describing the fundamentals and benefits of using this tool, its comparison with other modalities of disease assessment in IBD, barriers to its integration in the United States, and unique considerations for this tool in the United States.

What Is Intestinal Ultrasound?

IUS is an imaging modality that uses sonographic technology to visualize the small and large bowel and quantify inflammation and disease-related complications. IUS is accurate and noninvasive, and requires no preparation, fasting, radiation, or contrast. It provides real-time measures of disease activity in IBD, and has been shown to be repeatable and reproducible and both cost- and time-effective.⁹ IUS also improves patients' knowledge about their disease as well as their understanding of the origin of their symptoms, and this has been shown to help patients make more-informed decisions about their IBD management.¹⁰

How Is Intestinal Ultrasound Performed?

The first component of IUS is having an appropriate ultrasound machine. The machine should have Doppler capability and at least 2 transducers with low and high frequency. The second essential component is having a

trained sonographer. The requirements and approaches for training are described later in this article.

The ultrasound examination begins by having the patient lie in a semi-darkened room in a supine position and exposing the entire abdomen from the xiphoid process to the anterior superior iliac spine bilaterally. Next, the patient's waist is draped to protect clothing; an ultrasound gel is applied across the patient's abdomen and on the ultrasound transducer itself. The transducer is held with the right hand and maintains constant contact with the abdominal wall while the left hand is used to manage the ultrasound machine keys. The sonographer starts the examination with an overall scan of the colon and small bowel using a low-frequency curved probe (<5 MHz), which allows for visualization of the gross structures and anatomy with greater depth but limited resolution. This is followed by scanning with a high-frequency linear probe (>5 MHz) to visualize the bowel with higher resolution and to obtain measurements.

The examination starts by placing the transducer parallel to the iliac spine and visualizing 3 landmarks: the iliac vessels medially (the common iliac artery and vein), the iliopsoas muscle inferolaterally, and the hyperechoic iliac crest inferiorly to that.¹¹ When these landmarks are identified in the right lower abdomen of the patient, the terminal ileum will lie superiorly, and on the left lower abdomen, the sigmoid colon will lie superior to these landmarks. Visualization of the ileocecal valve or ileocolonic anastomosis can ensure that the terminal or neo-terminal ileum is indeed the small bowel loop identified and not a more proximal small bowel loop, among other characteristics unique to the large and small bowel that are assessed as part of the examination. Once the sigmoid colon or terminal ileum is identified, the examiner should follow the bowel in a systematic fashion and attempt to visualize all bowel segments. It should be noted that the

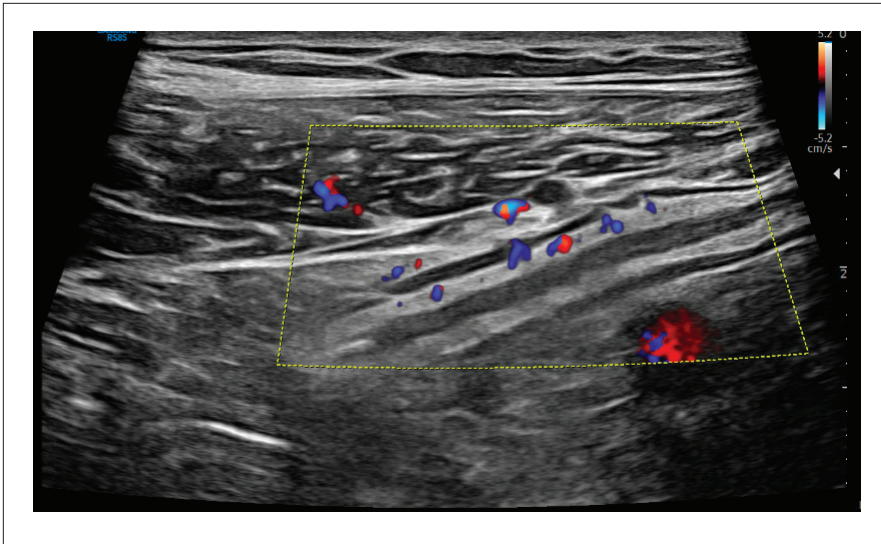


Figure 2. Color Doppler showing hyperemia (Limberg score = 2) in the bowel wall of a patient with active ulcerative colitis.

rectum cannot be reliably visualized and measured using the transabdominal technique. Although low-frequency curved probes may improve visualization, transperineal ultrasound is a more accurate technique to visualize the rectum.¹² Subsequently, a systematic scanning of the small bowel should be performed either by identifying the terminal ileum and following the small bowel proximally or by sweeping up and down the abdomen from one side to the other (as in a lawn mowing fashion). Further details of IUS scanning technique will not be reviewed in this article, as they are beyond its scope.

What Are the Standard Ultrasound Parameters?

To quantify inflammation in patients with IBD, several established IUS parameters are assessed during an IUS examination. These include bowel wall thickness (BWT); assessment of the stratification of the bowel wall layers, blood flow, luminal diameters, and motility; and assessment for fistulas and abscesses.^{5,13,14} Additional extraintestinal surrogates to bowel inflammation to assess for include mesenteric fat proliferation and lymphadenopathy.

The bowel wall has 5 layers that are visualized using IUS owing to their alternating hyperechoic and hypoechoic sonographic appearances. The first layer, starting from the luminal side of the bowel wall, is the hyperechoic mucosal-lumen interface, which is not part of the true bowel wall; the second is the hypoechoic deep mucosa; the third is the hyperechoic submucosa; the fourth is the hypoechoic muscularis propria; and the fifth is the hyperechoic serosa (Figure 1). The thickness of the bowel wall is measured from the top of the hyperechoic mucosal-lumen interface to the top of the muscularis

propria (2 hypoechoic layers with a bright hyperechoic layer in between).¹⁵

The most prominent and sensitive parameter of IUS in detecting active inflammation is BWT.¹⁶ A BWT of greater than 3 mm in the terminal ileum and colon is considered abnormal and consistent with active inflammation. For transperineal ultrasound, a BWT of less than 4 mm predicts endoscopic and histologic remission in the rectum.^{14,16-18}

Vascularization assessment using color Doppler imaging is another standard parameter of IUS. Hyperemia is associated with increased inflammation and is usually seen in the submucosal layer or, in severely active inflammation, by blood vessels penetrating the muscularis propria into the mesentery (Figure 2). There are several hyperemia scores that quantify the degree of inflammation, with the most widely accepted being the Limberg score,^{19,20} which ranges from 0 to 4.²¹ A score of 0 signifies normal BWT, preservation of wall layer stratification, and no signal on color Doppler; 1 signifies wall thickening and absent color Doppler signal; 2 signifies wall thickening with spot-like focal increases in vascularity; 3 signifies wall thickening and diffuse stretches of increased mural vascularity; and 4 signifies wall thickening with increased color Doppler signal in the bowel wall with extension into the mesentery. A score of 2 or above is considered abnormal and consistent with active inflammation.¹⁹ This scoring system has been validated in Crohn's disease (CD) but not yet in ulcerative colitis (UC).²²

Additional parameters associated with bowel inflammation include loss of the bowel wall stratification (loss of delineation of the various bowel wall layers) and increase in fibrofatty proliferation (appearing as hyperechoic surrounding the bowel).^{5,23,24} Lymphadenopathy, especially

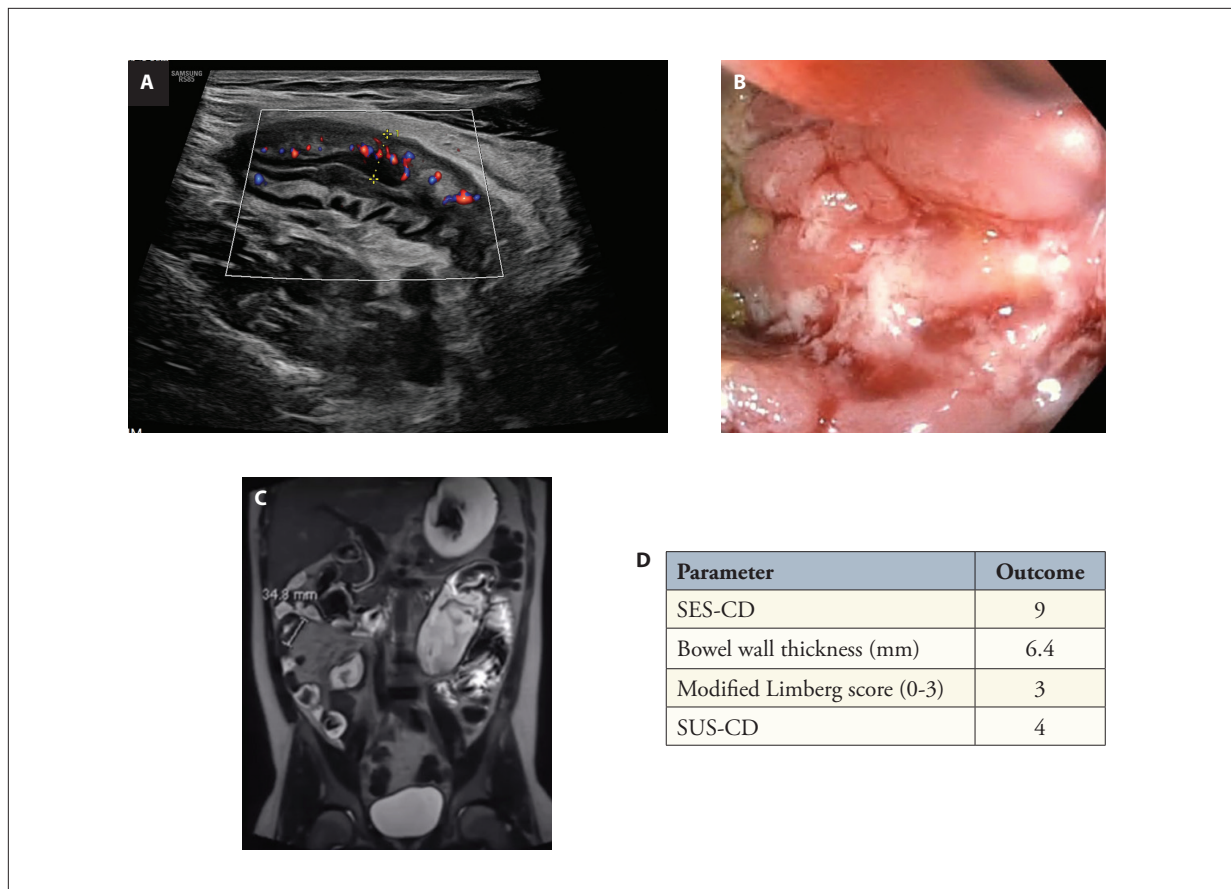


Figure 3. Moderate to severe Crohn's disease activity seen in the terminal ileum in a patient who underwent intestinal ultrasound (A), endoscopy (B), and magnetic resonance enterography (C) within 48 hours. Calculations for the Simple Endoscopic Score for Crohn's Disease (SES-CD) and Simple Ultrasound Score for Crohn's Disease (SUS-CD), as well as measurements for bowel wall thickness and modified Limberg score, are shown in the corresponding table (D).

in CD, can frequently be seen with active inflammation and at the time of disease complications such as fistula or abscess formation, which can be very well visualized using IUS.²⁴

Small bowel strictures can also be identified and characterized by IUS. Generally, luminal dilation beyond 25 mm should be considered abnormal and concerning for a proximal stricture.²⁵ However, a stricture can also be diagnosed with the identification of a thickened bowel wall with a narrowed lumen in the absence of proximal bowel dilation.²⁴ Unique to IUS is the ability to visualize and assess peristaltic activity and lumen compressibility, which may be altered by inflammation or fibrosis and can be seen with small bowel strictures. Furthermore, contrast-enhanced ultrasound by use of oral or intravenous contrast agents improves the sensitivity of detection of small bowel strictures.^{26,27}

Certain ultrasound machines have the functionality of elastography (strain or shear wave), which allows for

the assessment of the elasticity of the bowel and assists in the differentiation between fibrosis and inflammation.²⁸

How Was Intestinal Ultrasound Validated as a Monitoring Tool for Disease and Therapeutic Response?

Through the development of scoring systems, IUS has been validated as an accurate tool for the assessment of disease activity benchmarked to the gold standard of endoscopy in both UC and CD.

Ulcerative Colitis

In UC, 2 scoring systems have been prospectively validated with the endoscopic Mayo subscore: the Milan Ultrasound Criteria (MUC; $1.4 \times \text{BWT [mm]} + 2 \times \text{colonic wall flow [0 = absence, 1 = presence]}$) and the UC-Ultrasound index (UC-IUS index; 0-7 points = $\text{BWT [}>2 \text{ mm} = 1, >3 \text{ mm} = 2, >4 \text{ mm} = 3]} + \text{Doppler}$

signal [0 = none, 1 = spots, 2 = stretches] + abnormal haustrations [0 = normal, 1 = abnormal] + fat wrapping [0 = absent, 1 = present]). A MUC score greater than 6.2 accurately detects UC activity (Mayo score of 2 or 3) with an area under the receiver operating characteristic curve (AUROC) equal to 0.891, sensitivity of 71%, and specificity of 100%, and this was subsequently externally validated in 43 patients. In addition, the UC-IUS index demonstrates a strong correlation with the Mayo score ($r=.83$).^{5,23} In a follow-up study of 98 UC patients, a MUC score greater than 6.2 was the only UC activity index shown to be predictive of a negative disease course (need for treatment escalation, corticosteroids, or hospitalization) over a median follow-up of 1.6 years.²⁹

To date, the lack of studies utilizing UC activity indices to monitor treatment responsiveness remains a significant limitation to utility of these indices in clinical practice. The timing of IUS reassessment after initiating a new therapy, responsiveness of validated scores, and ability to predict treat-to-target outcomes remain unknown. However, several studies demonstrate the ability of IUS to monitor treatment response in UC, albeit without endoscopic validation. The TRUST-UC study was a prospective, observational, 42-center, German study of 224 adults with UC experiencing a clinical flare who underwent treatment with corticosteroids, mesalamine, immunomodulators, and biologics. The study demonstrated that changes in IUS parameters of BWT and color Doppler signal can be seen within 2 weeks and followed to normalization over the course of 12 weeks of treatment.³⁰ A smaller single-center study of 27 adults with moderate to severe UC initiating treatment with tofacitinib (Xeljanz, Pfizer) demonstrated that changes in BWT on IUS were accurate to monitor and predict endoscopic response after 8 weeks. A decrease of 32% in BWT from baseline to week 8 predicted endoscopic response with an AUROC of 0.87, with a significantly more pronounced decrease in BWT (-58.1%) in endoscopic responders compared with nonresponders (-13.4%).³¹ Finally, early changes on IUS in patients with acute severe ulcerative colitis (ASUC) can predict response to therapy. In a single-center study of 56 patients hospitalized with ASUC, change in both absolute and relative BWT in the first 48 hours predicted response to intravenous corticosteroids with an odds ratio of 22.6 (95% CI, 4.2-201.2) for patients with a greater-than-20% reduction in BWT.³² These findings may have a large impact on the treatment course and management of hospitalized patients with ASUC, as using IUS may facilitate faster decision-making and prevent surgery in certain patients. IUS has been shown to have strong interobserver agreement in UC, perhaps even stronger than in CD; thus, IUS can be reliably performed by different providers to monitor

treatment response.³³ Given its potential role in the management of ASUC, as well as its flexibility, noninvasive nature, and real-time results, IUS can be a beneficial tool for inpatient IBD management.

Crohn's Disease

Similar to UC, 2 scoring systems have been developed and validated with endoscopy in CD (Figure 3). A multicenter Spanish study of 72 adults with CD from 3 hospitals developed and validated a simple ultrasound score. This score was based on only BWT and color Doppler grade, which were accurate in detecting endoscopic activity, based on a Simple Endoscopic Score for CD (SES-CD) greater than 3 with an AUROC of 0.923, 90% sensitivity, and 86.4% specificity using a cutoff score of 5.5.³⁴ Furthermore, this score correlated well with SES-CD grade ($r=.72$; $P=.001$). A single-center study of 40 adults with CD developed and externally validated a similar ultrasound score, aptly named the Simple Ultrasound Score for CD (SUS-CD), from 0 to 5 points, based on BWT and color Doppler grade as well. Likewise, SUS-CD greater than 1 was accurate to detect any endoscopic activity (SES-CD >2) and SUS-CD greater than 3 was accurate to detect moderate endoscopic activity (SES-CD >7) with an AUROC of 0.92 and 0.88, respectively. In both the development and validation phases, SUS-CD correlated well with SES-CD ($\rho=.83$ and $\rho=.78$, respectively), better than CRP ($\rho=.46$) and FCP ($\rho=.51$), the current standard-of-care biomarkers for disease activity monitoring. As with the interobserver agreement for individual IUS parameters previously shown, interobserver agreement for SUS-CD was excellent (weighted kappa=.82, intraclass correlation=.95).^{6,35} Lapses in interobserver agreement not owing to common differences in perception could be improved through standardized training and comparison of IUS images across institutions.³⁵

Evidence from the TRUST Study Group for treatment responsiveness was also examined in CD, wherein IUS examination demonstrated improvement in ultrasound parameters that correlated with improvements in both Harvey-Bradshaw index scores and CRP across short-term and long-term periods of 3 and 12 months, respectively.³⁶ Improved ultrasound parameters included a reduction in BWT, decreased mesenteric fat proliferation, and improved hyperemia. Similarly, a multicenter Italian study from 16 sites and 188 CD patients treated with biologic therapy demonstrated that there was an improvement in BWT from baseline at 3 and 12 months and that colonic lesions were more likely to demonstrate sonographic transmural healing at 3 months compared with ileal lesions.³⁷ Although neither of these studies were validated with treat-to-target endoscopic outcomes,

results are similar to a previous single-center study of 51 CD patients that demonstrated that ultrasound response (decrease in BWT and color Doppler flow) by 3 months is predictive of clinical outcomes and sonographic transmural healing at 1 year.³⁸ More recently, a small single-center study of 31 adults with active CD (SES-CD >3 in at least 1 bowel segment) starting treatment with anti-tumor necrosis factor therapy demonstrated that a reduction in BWT 4 to 8 weeks after induction predicted endoscopic response and remission.³⁹

How Does Intestinal Ultrasound Compare With Other Imaging Modalities?

Long-standing cross-sectional imaging modalities such as magnetic resonance enterography (MRE) serve as the current gold standard tool by which to evaluate the accuracy of IUS in assessing transmural activity.

In a large, prospective, multicenter, comparison trial involving 284 patients, MRE and IUS were determined to be comparable. For example, the sensitivity of MRE for detection of disease activity within the terminal ileum was 97%, whereas the sensitivity for IUS was 92%.⁴⁰ The study determined that MRE is preferable to IUS in large hospital settings. This decision was made owing to a higher sensitivity of MRE to IUS and superior assessment of small bowel disease extent on MRE. The same study also demonstrated higher specificity in identifying colonic disease (67% and 47% for IUS and MRE, respectively), and consistent with other studies, found that IUS was more acceptable by patients than MRE.

Another study examined the comparison between IUS and the combined assessment of MRE with endoscopy. This study of 60 ileocolonic CD patients determined that IUS was comparably accurate to the combination of MRE and endoscopy in analyzing IBD. IUS was found to be accurate across several ultrasound parameters, including enhancement and activity, as well as for visualizing complications such as fistulas, strictures, and abscesses. Furthermore, IUS has been shown to be superior to MRE in analysis of certain bowel criteria in CD. IUS demonstrated higher specificity in the detection and visualization of ascites, bowel wall thickening, loss of stratification, and stenosis in comparison with MRE.⁴¹ In the same study, however, MRE showed higher sensitivity in detecting the same criteria of BWT, loss of stratification, and stenosis in the analysis of mural wall lesions.⁴¹

It is also imperative to evaluate the accuracy and feasibility of IUS in comparison with magnetic resonance imaging (MRI) to evaluate chronic bowel damage. In a study of 71 CD patients undergoing MRE, IUS, and endoscopy within 1 month, an IUS-based Lemann index performed similarly to the MRI-based Lemann index

with excellent correlation ($\rho=0.90$).⁴² In the future, handheld ultrasound probes, guided by artificial intelligence programs, may facilitate remote IUS monitoring, as handheld ultrasound has already been shown to be comparable with MRE for the diagnosis of CD.⁴³

In summary, the relatively comparable sensitivity and accuracy of IUS to MRE,^{24,40-45} its better tolerance by patients,⁷ and POC nature suggest advantages of IUS in IBD care. Furthermore, outside of the United States, MRE has been shown to be a cheaper alternative,⁹ although a cost-effectiveness analysis in IBD has yet to be performed in the United States.

How Can Barriers of Intestinal Ultrasound Be Overcome in the United States?

There are several reasons that IUS has not been previously integrated into IBD clinical care in the United States. First, ultrasound technique and interpretation are not taught as standard skills in medical school and postgraduate training. Second, and possibly related to the aforementioned limitation regarding training, there has not been adoption of this technology by leading centers and voices of authority in the United States. Third, the appropriate manner for remuneration for performing this procedure on patients with IBD was not defined. With addressing some of these barriers, the incorporation of IUS into management of IBD has become more accessible. Recognition of the positive impact that IUS may have on patients with IBD is starting to lead IBD experts in the United States to endorse and incorporate IUS into their programs. This includes participating in the existing 3-stage training pathways that are promoted and available through the International Bowel Ultrasound Group (IBUS-group.org). The IBUS program has recently been expanded to include US-based hands-on training, first at Mount Sinai Hospital in New York City in 2022 and now, with support of a grant from the Helmsley Charitable Trust, the University of Chicago in 2023 and subsequently in 2 other locations in the United States in 2024 and 2025. The same grant provides support for the second and third steps of training for US clinicians and supports a North American alliance (Intestinal Ultrasound Group of the United States and Canada [iUSCAN]) for shared research and clinical operation approaches. The credentialing and direct cost recovery of IUS have been described using available Current Procedural Terminology codes (limited abdominal ultrasound, 76705; Doppler ultrasound of the abdomen, 93975).⁸ Indirect cost benefits of improved disease management, reduction in costs and invasiveness of traditional endoscopy and cross-sectional imaging (nongastroenterology cost centers), and reduction in expensive adverse

outcomes (eg, emergency department visits, hospitalization, and surgery) support the widespread investment and incorporation of IUS into standard care for patients with IBD.⁴⁶ Ongoing US-based studies of relevant outcomes may result in further adoption and successful dissemination. It remains unclear, however, what threshold will be required in order for the momentum of this movement to become self-sustaining as a standard-of-care approach in the field. More work is clearly needed.

Conclusions

IUS offers a noninvasive, highly reliable, and sensitive POC method for assessment of disease activity and response to therapy in IBD. A variety of studies have demonstrated its comparability with established measures of endoscopy and cross-sectional imaging. More recent work and emphasis on the transmural nature of IBD suggest that this technology is not only preferable to current approaches of invasive and asynchronous evaluation, but also may be superior in predicting disease outcomes. Although this technology has only recently been introduced, training courses are available, and research is ongoing to examine its utility in the management of patients with IBD in the United States.

Disclosures

Dr Krugliak Cleveland serves as a consultant to Takeda; a consultant for NeuroLogica, a subsidiary of Samsung Electronics; and a speaker for Bristol Myers Squibb. Ms Picker has no relevant conflicts of interest to disclose. Dr Dolinger is a consultant for NeuroLogica, a subsidiary of Samsung Electronics. Dr Rubin has received grant support from Takeda and has served as a consultant for AbbVie, AbGenomics, Bellatrix Pharmaceuticals, Boehringer Ingelheim, Bristol Myers Squibb, Celgene/Syneos, Dizal Pharmaceuticals, Genentech/Roche, Gilead Sciences, Ichnos Sciences, InDex Pharmaceuticals, Iterative Scopes, Janssen Pharmaceuticals, Lilly, Pfizer, Prometheus Laboratories, Prometheus Biosciences, Reistone, Takeda, and Techlab.

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