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Small bowel imaging in inflammatory bowel disease: updates for 2023

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ABSTRACT

Introduction: Cross-sectional imaging techniques including MR and CT enterography and ultrasound are integral to Crohn's disease management, accurate, responsive, and well tolerated. They assess the full thickness of the bowel wall, perienteric environment, and distant complications. As we strive toward tighter disease control, imaging's role will expand further with transmural healing becoming an increasingly important therapeutic target.

Areas covered: MEDLINE and Web of Science were searched from 2012 to 2023 inclusive. We review the evidence for cross-sectional imaging in assessing disease activity, phenotyping, and therapeutic response assessment. Emerging novel imaging applications such as quantifying enteric motility and fibrosis, prognostication, and potential utility of artificial intelligence will be covered. Recent international consensus statements highlight the need for standardized imaging reporting and definitions of transmural healing and remission. We will discuss how recent advances may be best integrated into patient care and highlight key outstanding research questions.

Expert opinion: Cross-sectional imaging is established in Crohn's disease management. Research emphasis should be placed on optimal integration of imaging modalities in clinical care pathways, workforce training, definitions, and evidence for use of imaging based therapeutic targets such as transmural healing, better phenotyping of stricturing disease, and developing novel techniques, including integration of artificial intelligence.

1. Introduction

There are a variety of well-established and validated methods to non-invasively image the small bowel, often negating the need for less well tolerated and costly ileocolonoscopy and/or capsule endoscopy. Cross-sectional imaging techniques are now a key component of inflammatory bowel disease (IBD) diagnosis and management pathways [1,2]. MR enterography (MRE) and intestinal ultrasound (IUS) are mainly utilized, with CT enterography (CTE) usually playing a lesser role outside the acute setting given its use of ionizing radiation. Imaging plays a key role in assessing disease phenotype including extent, activity, penetrating, and stricturing complications and in therapeutic response assessment. Perienteric assessment is a crucial advantage of cross-sectional imaging over endoscopic techniques, for example, evaluating fat wrapping, increasingly implicated in disease pathophysiology and prognosis [3].

Cross-sectional imaging can image the small bowel beyond the reach of ileocolonoscopy and upstream of tight stricturing disease and is a less invasive option to whole bowel enteroscopy. There has been a paradigm shift to using objective markers of activity to try and achieve disease control and sustained deep remission [2]. A number of histological and endoscopically validated imaging-based scores of activity have been developed which provide an objective assessment of

enteric inflammation [4,5]. Cross-sectional imaging therefore plays an important role in this treat-to-target approach, with increasing evidence of responsiveness to therapeutic interventions, and convergence with endoscopic evaluation [6]. Furthermore, novel therapeutic targets are receiving considerable attention, notably transmural healing. Although currently not yet formally adopted as primary treatment target [2], early transmural healing may predict longer term response [7,8], and those patients who exhibit transmural healing have improved outcomes over those achieving endoscopic mucosal healing alone [9,10].

Crohn's disease is a lifelong condition, and patients must undergo multiple tests in their lifetime. Patient experience is thus a vital part of optimizing clinical care pathways. Patients generally prefer minimally or noninvasive tests over repeated ileocolonoscopy with MRE and IUS found to be generally acceptable for disease monitoring [11–13].

This review builds on several recent excellent reviews with an updated review of the recent literature [5,14,15]. As part of this, MEDLINE and Web of Science were searched from 2012 to 2023 inclusive for the following terms; 'magnetic resonance,' 'ultrasound,' and 'computerized tomography' cross-referenced with the keywords 'inflammatory bowel disease,' 'Crohn's disease,' 'scores,' 'activity,' 'damage,' 'transmural healing,' 'transmural remission.' It considers the current evidence base for cross-sectional

imaging in Crohn's disease to support optimal clinical decision-making. Emerging novel applications including assessing enteric motility, quantifying fibrosis, and potential use in prognostication are considered. We will highlight key priorities for future research, suggest how these may be best addressed, and speculate on how emerging trends in small bowel cross-sectional imaging may be integrated into patient care in the coming 5–10 years.

2. Optimizing cross-sectional imaging protocols-current controversies

MRE and IUS acquisition protocols are generally standardized although there remain areas of controversy.

2.1. Intravenous contrast

Current MRE protocols vary with respect to the use of intravenous contrast agents which may provide additional measures of disease activity and better evaluation of penetrating complications. There is a move away from routine intravenous contrast administration driven by pressures to reduce imaging time, costs, potential for allergic reactions and recent evidence and patient awareness of gadolinium deposition in the brain [16]. This is particularly an issue with repeated administration in tight follow-up protocols in often young patients.

The evidence that intravenous contrast increases diagnostic accuracy in Crohn's disease is relatively weak. Indeed, against a Crohn's disease Endoscopic Index of Severity (CDEIS) reference standard in 98 patients, Puylaert et al. reported no significant difference in detecting active disease between protocols using intravenous contrast enhanced MRE, diffusion-weighted imaging (DWI) alone, or combinations of both sequences. There was higher interpreter diagnostic confidence with the addition of intravenous

contrast, further improved with the combined DWI/contrast protocols [17]. The non-inferiority of DWI to intravenous contrast enhanced MRI for identifying small bowel inflammation was also reported by Seo et al. in 50 consecutive patients also using an endoscopic reference standard [18]. A sub-study of the METRIC trial utilized 27 radiologists and also found no diagnostic advantage in adding a contrast enhanced sequence to non-enhanced sequences [19].

Given this, many centers now prefer to administer intravenous contrast only in patients suspected of penetrating complications. The potential utility of contrast enhanced US (CEUS) is discussed in the 'novel cross-sectional imaging applications' section below.

2.2. Oral contrast

To provide an accurate assessment of the bowel wall and disease complications such as stricturing, small bowel luminal distention is required prior to MRE [20]. This is typically with mannitol or polyethylene glycol (PEG) with a typical preparation regime being 1.6 liters (L) of 1.67% mannitol ingested over 60 minutes. Good luminal distension using large volumes of osmotic agents must be balanced with acceptability to patients with side effects common, including abdominal cramps, bloating, and transient diarrhea. In the METRIC trial, drinking the oral bowel preparation was by far the least acceptable aspect of MRE, which overall was significantly less acceptable than IUS [7].

There is therefore interest in refining current oral preparation protocols. A sub-study by the same METRIC group found no significant difference in per patient distension quality when using mannitol or PEG as distension agents, with comparable patient tolerability. There was, however, improved jejunal distension when using mannitol versus PEG, and no difference if > or <1 L of mannitol was ingested, suggesting routine protocols can use smaller volumes [21]. Early unpublished results from our group also indicate that reduced volume preparation (1 L mannitol) has comparable qualitative and quantitative distension quality with an improved side effect profile versus standard preparation (1.6 L) in healthy volunteers. These parameters are, however, compromised when the mannitol volume was reduced further to 0.6 L.

One of the major advantages of IUS is that it does not require oral contrast. There has, however, been work investigating the utility of oral contrast prior to IUS. Parente et al. administered PEG solution orally in 102 Crohn's disease patients. There was minimally increased sensitivity for the detection of endoscopically confirmed disease with oral preparation (96.1%) versus conventional IUS performed immediately prior (91.4%). There was also significantly increased sensitivity for stricture detection (89% versus 74%) and improved interobserver agreement for bowel wall thickness (BWT) measurement and disease location [22]. In another group of 49 patients, this technique had good agreement and accuracy for surgical stricture detection and length, and penetrating complication detection [23]. A METRIC trial sub-study investigated hydrosonography where an osmotic oral preparation was given prior to the IUS to distend the small bowel lumen in an effort to improve bowel wall characterization and was found to be well tolerated and of comparable acceptability to MRE. However, this group did not find any diagnostic advantage of hydrosonography over standard IUS [13,19].

Despite potential advantages of oral contrast, current practice usually does not include routine use of oral agents prior to IUS given its impact of service efficiency and patient experience.

3. Current use of cross-sectional imaging in the assessment of inflammation and disease phenotype

Targeting small bowel inflammation is a key therapeutic strategy in Crohn's disease to control symptoms and prevent long-term bowel damage. Imaging provides contemporaneous activity assessment and then can be used for disease monitoring to guide treatment (de-) escalation, also evaluating penetrating complications. International consensus guidelines now provide a standardized, reproducible approach to reporting cross-sectional imaging for these various indications [1,14].

MRE and IUS are well tolerated and accurate in the subjective and objective assessment of disease activity and its severity in the small bowel. The METRIC study used an expert consensus panel reference standard encompassing all available clinical data including biochemical, endoscopic, and histopathological in 284 Crohn's disease patients. MRE

had a high sensitivity and specificity for active disease presence (96% and 83%) which was slightly superior to IUS in the small bowel, 90% and 77%, respectively [24]. Using endoscopic assessment as the reference standard, IUS parameters of activity have a reported accuracy ranging between 73% and 100% [24,25]. The STARDUST study group found that IUS and endoscopy have a > 90% agreement in detecting the most affected small bowel segment based on baseline BWT measurement, particularly for terminal ileal disease [7].

Several imaging parameters reflect disease activity (Figure 1) and have been validated against biochemical, endoscopic, and histopathological reference standards [1,26]. The best evaluated is bowel wall thickness with recent consensus panel recommendations that BWT >3 mm is reasonably sensitive for mural inflammation [1]. This threshold is generally accepted in both clinical practice and in the research setting. However, BWT is a nonspecific finding and can result from a number of alternative causes and other underlying pathological processes. Inflammation and fibrosis virtually always coexist, a further confounder when considering BWT alone [14].
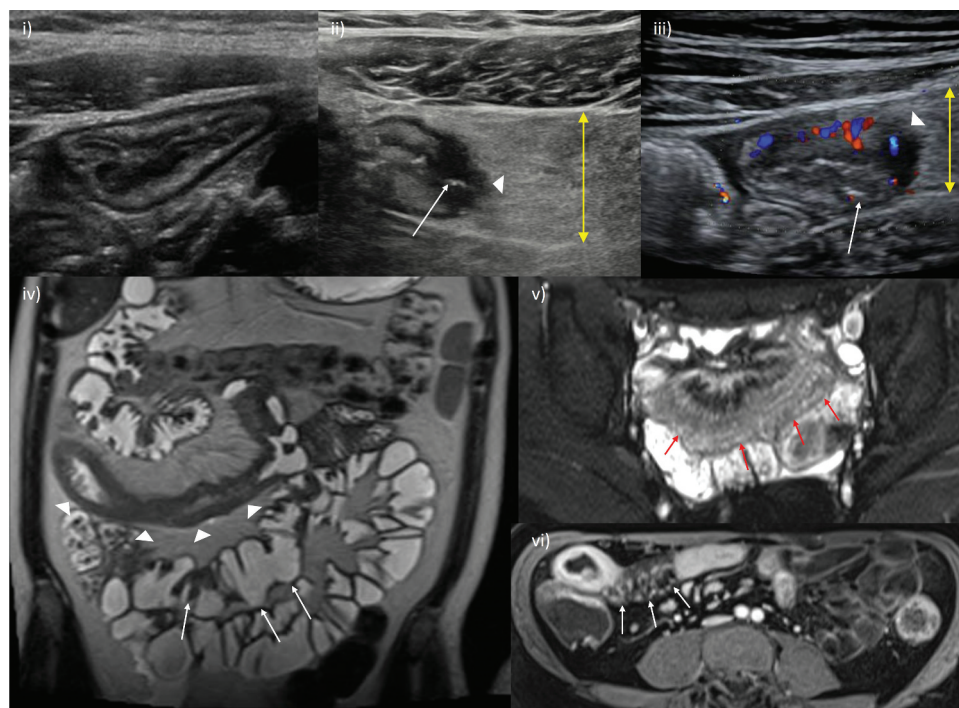
Figure 1. Cross-sectional imaging signs of active disease. i) Conventional B-mode ultrasound of the terminal ileum, including normal mural thickness (≤3 mm), mural stratification and mesentery. ii) Active disease on IUS showing disruption of mural stratification, particularly at the mesenteric border which is blurred (arrowhead). There is bowel wall thickening, including of the submucosa where there is patchy hypoechogenicity. There is also mesenteric inflammation, represented by marked mesenteric expansion (double headed arrow). Linear mural defects with gas are in keeping with deep ulceration (arrow), a sign of more severe inflammation. iii) Intestinal ultrasound image showing hypervascularity of the terminal ileum manifest as increased color Doppler signal. Note the other signs of active disease; bowel wall thickening, edema (with patchy changes in the submucosa, in contrast to i) where it is uniformly echogenic), deep ulceration (arrow), blurring of the bowel mesenteric border (arrowhead) and mesenteric expansion (double headed arrow). iv) Coronal T2-weighted MRE image showing a long segment of severely active disease involving the distal jejunum and proximal ileum (arrowheads). There is bowel wall thickening and edema, in addition to perimural free fluid, also collecting in the right iliac fossa (asterisk). Additionally, there is chronic disease of the more distal ileum (arrows) which appears damaged with multiple pseudosacculations and likely fibrotic predominant strictures. v) Axial fat-saturated T2-weighted imaging better depicts mural and perimural edema. There is severe active disease in a loop of terminal and distal ileum (arrows) with high T2 signal in part reflecting marked mural and perimural edema, including linear high signal extending into the mesentery. vi) Axial post-contrast image showing mural hyperenhancement, particularly mucosal, and engorgement of the vasa recta supplying the inflamed terminal ileal loop (arrows); the comb sign.

IUS: intestinal ultrasound; MRE: MR enterography.

Establishing the relative burden of inflammatory activity on the background of chronic, fibrotic changes necessitate using additional markers of activity, mainly mural and extramural edema and hypervascularity. On MRE, mural edema is best appreciated on fluid-sensitive MRI sequences (T2-weighted) where the fat is suppressed, meaning that edema can be largely separated from fibro-fatty proliferative changes [14]. Transmural edema is manifested by perienteric fat stranding and free fluid. On IUS, mural edema is represented by disrupted mural stratification and may be associated with visible ulceration [27,28].

Neoangiogenesis and hypervascularity are further pathophysiological processes in Crohn's disease and on MRE are represented by increased mural enhancement and engorgement of the vasa recta [1,11,14,29]. Intravenous contrast is not routinely administered in some centers, and fibrostenotic disease may also cause increased enhancement. Using IUS, a recent study found that combining BWT >3 mm with increased color Doppler signal (reflecting hypervascularity) and reduced mural stratification improved the diagnostic accuracy for inflammation over using BWT >3 mm alone [30].

Deep ulceration may give an additional clue to severe, transmural inflammation and is detected as linear mural defects often extending into the mesenteric fat [14]. A caveat is that more superficial ulceration is usually beyond the resolution of cross-sectional imaging and so cannot be depended upon in isolation to detect and grade activity.

4. Imaging based activity scores and their validation

4.1. MRE activity scores

Various scores of activity on MRE have been developed and internally and externally validated against clinical, endoscopic, and/or histopathological reference standards (Table 1) [4]. The range of scoring systems generally encompasses a similar group of independent prognostic parameters with varying weighting to provide quantitative, objective, and more reproducible activity assessment. Due to their relative complexity, the scores are not in widespread clinical use but particularly in the research and clinical trial setting they form an objective assessment of segmental and global disease activity [31,32].

The earliest and best validated MRE score of activity is the MaRIA score [4,33]. This comprises four predictors of activity: mural thickening, mural edema, ulceration, and mural hyperenhancement with a global index formed from six individual segmental indices. A threshold score of 7 has been proposed to denote active disease. It has been validated against activity ileo-colonoscopic and capsule endoscopic activity scores [34]. The MaRIA score is seldom used in routine practice as it necessitates multiple, time-consuming, manual measurements of the bowel wall on more than one MRI sequence, as well as the use of intravenous contrast.

Several of these disadvantages are circumnavigated by the simplified MaRIA (sMaRIA) score, which has also been endoscopically validated and reported to be as accurate as the full MaRIA score [35–38]. sMaRIA is less time-consuming, does not require intravenous contrast, and only considers diseased bowel segments. There is more limited evidence for the specificity and reproducibility of the sMaRIA score. A recent retrospective study of 275 bowel segments found an AUC of 0.908 (95% confidence interval [0.857–0.959]) for the sMaRIA to detect active inflammation as judged by the Simple Endoscopic Score for Crohn's Disease (SES-CD) [39].

The Clermont score is similar to the MaRIA score, although it uses DWI sequences instead of post-contrast enhanced images [12]. It also has the disadvantage of requiring time consuming

Table 1. Magnetic resonance enterography-based activity scores: summary of scores including their derivation.

Score	Equation and application	Advantages	Limitations
MaRIA*	$1.5 \times$ mural thickness $+ 0.02 \times$ RCE $+ 5 \times$ edema $+ 10 \times$ ulceration Applied to 6 individual segments to form a global score. Threshold score of 7 to denote active disease	• Endoscopically validated with currently the strongest evidence base for its clinical use • Grading disease by severity is possible Responsive	• Requires intravenous contrast • Time consuming, manual measurements on more than one MRI sequence
sMaRIA‡	$1 \times$ mural thickening >3 mm $+ 1 \times$ edema $+ 1 \times$ fat stranding $+ 2 \times$ ulcers Can form a segmental (0–5) or global (0–25) score	• Endoscopically validated • Relatively quick to calculate and does not require intravenous contrast • Can grade disease by severity Responsive	• Limited evidence for its specificity and reproducibility
Clermont	$1.646 \times$ mural thickness $- 1.321 \times$ ADC (mm2/s) $+ 8.306 \times$ ulcers $+ 5.613 \times$ edema $+ 5.039$ Proposed thresholds of 8.4 and 12.5 for active and ulcerating disease	• No need for intravenous contrast • Evidence of comparable performance to the sMARIA score • Can grade disease severity	• Time consuming to manually place regions of interest on diffusion weighted imaging
London§	$1.79 + 1.34 \times$ mural thickness $+ 0.94 \times$ mural T2 score	• Histologically and endoscopically validated • Good inter- and intra-reader reproducibility • Quick, no need for intravenous contrast	• No defined criteria to grade disease severity Only validated in the small bowel
Extended London**	Mural thickness $+$ mural T2 score $+$ perimural T2 signal $+$ contrast enhancement	• Histologically and endoscopically validated • Good inter- and intra-reader reproducibility • Relatively quick to calculate	• Requires intravenous contrast • No defined criteria to grade disease severity • Only validated in the small bowel

manual region of interest placement [34]. Further alternative MRE-based activity scores are the London and 'Extended' London scores which are partially based on mural thickening and edema, applied to either individual enteric segments or globally to the entire small bowel. Both scores have been validated against histology and endoscopy (CDEIS) with good inter- and intra-reader reproducibility [17,40].

4.2. IUS activity scores

Although numerous IUS activity scores have been proposed, they are currently less robustly validated than MRE scores and also not usually used in routine clinical practice (Table 2) [25,29]. However, large-scale validation studies are underway. Examples include the Simple US activity score [41,42], and the Bowel US score (BUSS) [43]. Scores typically include parameters generally considered as reliable markers of activity, namely, BWT, increased vascularity on color Doppler, loss of mural stratification, and perimural changes, e.g. fat wrapping, edema [27,28,30].

BUSS uses BWT and mural vascularity as independent predictors and has been prospectively tested and validated against ileocolonoscopy and the SES-CD. In a study of 49 patients starting treatment, a threshold score of 3.52 was proposed to stratify patients with endoscopically active and inactive Crohn's disease, achieving a sensitivity of 83% and specificity of 85% [43].

The International Bowel Ultrasound Segmental Activity Score (IBUS-SAS) has recently been developed through a Delphi consensus of 11 experts who identified four main parameters of activity; i) BWT, ii) bowel wall stratification, iii) bowel wall hyperemia on color Doppler, iv) inflammatory mesenteric fat. On blinded case reads, BWT had high reproducibility, and the IBUS-SAS had a near perfect correlation to a global assessment of disease activity [44]. Wang et al. recently externally tested the IBUS-SAS and simple US activity score (SUS-CD) in a retrospective study of 140 patients. They reported excellent inter-operator reproducibility (correlation coefficient of 0.96 and 0.78 respectively). There was reasonable correlation with endoscopic scores and inflammatory biomarkers for the IBUS-SAS (0.511–0.666) which was generally weaker for the SUS-CD, 0.434–0.534 [45].

As we will discuss in the 'expert opinion' section, a research priority is to investigate the interchangeability of IUS and MRE parameters of activity, and further validate IUS activity scores and test their responsiveness relative to endoscopy and MRE in larger, prospective, multicenter studies.

5. Imaging therapeutic targets and assessing response

Cross-sectional imaging is an attractive alternative to costly, invasive, and less well-tolerated ileocolonoscopy and nonspecific blood and stool markers of inflammation for assessing treatment response. It also facilitates assessment of the full thickness of the bowel wall and perienteric environment, potentially moving beyond simple endoscopic mucosal healing as a treatment target. However, for imaging to be a useful objective marker in any 'treat-to-target' paradigm [2], it must be both responsive to treatment changes and reproducible.

Four categories of therapeutic response based on cross-sectional imaging criteria have been recently proposed by an international expert consensus panel review [1,14]; i) transmural remission (all markers of activity are normalized, both mural and perimural), ii) response (unequivocal improvement in activity severity or extent in a disease segment), iii) stable (no clear change), iv) progression (unequivocal worsening of activity measures, or new sites of disease, or development of complications). In routine clinical practice, such assessments are based on the subjective opinion of the imaging reporter using established imaging activity parameters such as BWT, submucosal T2 intensity/clarity on IUS, and mesenteric changes.

Responsiveness of activity scores has mainly been investigated for MRE. Using paired MRE images from 41 patients pre- and 12 to 14 weeks post-treatment, Hanžel et al. tested the responsiveness of 4 MRE activity scores against a global assessment of response captured using a 100 mm visual analogue scale. All four scores tested exhibited moderate to large responsiveness. The sMaRIA was significantly more responsive than the London score although not the full MaRIA or extended London scores [31].

The response criteria for individual imaging parameters are less clear, as is the optimal time window for reevaluation.

Table 2. Intestinal ultrasound-based activity scores: summary of more commonly used scores.

Score	Equation and application	Advantages	Limitations
Simple ultrasound activity score (SUS-CD)	Mural thickness score [0–3] + Color Doppler score [0–2] The score for each of 5 ileocolonic segments is combined for the overall score	• Very simple and quick to calculate • Good inter-reader reproducibility • Recently externally validated	• Weaker correlation with endoscopic and biochemical assessment of activity than IBUS-SAS • Requires assessment of its responsiveness
Bowel ultrasound score (BUSS)	$0.75 \times$ Mural thickness $+ 1.65 \times$ Mural color Doppler flow Mural flow is scored 1 if present and 0 if absent Threshold score of 3.52 for active disease proposed	• Endoscopically validated • Good inter-operator reproducibility • Responsive to endoscopic changes	• Requires validation in larger, external cohorts
International Bowel Ultrasound Segmental Activity Score (IBUS-SAS)	$4 \times$ mural thickness $+ 15 \times$ inflammatory fat $+ 7 \times$ color Doppler signal $+ 4 \times$ mural stratification Global disease activity score of 0–100	• Based on an international Delphi expert consensus • Good reproducibility of mural thickness and externally validated • Strong correlation with global assessment of disease activity	• Requires more variables and calculation than SUS-CD albeit as one overall global score • Awaits more robust external validation and assessment of responsiveness

Individual imaging parameters of activity vary in their responsiveness and specificity, and response rate is influenced by disease location and phenotype. BWT is an attractive parameter for disease response assessment, being relatively quick and simple to measure. However, as yet no agreed optimal time point for response evaluation has been defined, and when used in isolation and at non-standardized time points, simple changes in BWT may not give an accurate reflection of true response status. In 2022, the International Bowel Ultrasound (IBUS) group provided an expert consensus based on a systematic review, attempting to bring clarity to some of these issues for both adult and pediatric populations [28]. They suggest that, on IUS, treatment response can be defined as BWT reduction of >25% or >2 mm, or >1 mm if there is associated reduced color Doppler signal. They suggested that IUS should be performed at baseline and response assessed at 14 ± 2 weeks (but may be beneficial in some cases at 4–8 weeks) and also 26–52 weeks. Inter-modality response comparisons, for example, between MRE and IUS remain challenging.

5.1. Transmural healing

Transmural healing is receiving considerable attention as a potentially superior treatment target to mucosal healing alone (Table 3). Transmural healing can only be assessed by cross-sectional imaging given its ability to evaluate the full thickness of the bowel wall and perienteric changes. Although there is good agreement between transmural healing and endoscopic mucosal healing based on both IUS and MRE (k = 0.63 and 0.64 respectively) [51], there is evidence that transmural healing is associated with improved disease course in terms of reduced progressive bowel damage, better long-term patient outcomes, and more predictive than endoscopic mucosal healing alone [9,10,46–48,52,53]. In an observational study of 80 patients on anti-TNF agents, 'complete' responders on IUS (improvement in all diseased segments) had an improved long-term disease trajectory, less need for surgery, steroids, and surgery, compared to partial or non-responders [46]. A recent multicentre study of 404 patients replicated these findings over 5 years of follow-up in the cohort with transmural remission on MRE and ileocolonoscopy [48]. Transmural response on MRE at only 12 weeks could predict steroid-free remission at 1 year after initiating anti-TNF agents [8].

Although the recent STRIDE (Selecting Therapeutic Targets in Inflammatory Bowel Disease) II consensus statement does not formally list transmural healing as a treatment target, it recognizes that it may represent a deeper level of healing and should be used as an adjunct to endoscopic remission [2].

Transmural healing can be assessed by both MRE and IUS. However, the definition of full imaging remission and transmural healing remain contentious [6]. Strict criteria for transmural healing comprise normalization of mural thickening (≤3 mm), normal perfusion, no mural stratification disruption, perienteric fat stranding, and on MRE, no evidence of edema (Figure 2) [1,2,28,54]. Applying a strict definition of transmural healing means a minority of patients on currently available therapeutics actually achieve this endpoint. For example, the recent STARDUST RCT found that 24% (13/54) of patients on ustekinumab achieved transmural healing on IUS [defined as normalization of all IUS parameters] at 48 weeks [7]. In another cohort on varying forms of biologic therapy, 28% (43/156) achieved transmural healing at 1 year [49]. The VERSIFY trial of 101 patients treated with vedolizumab found a radiological remission rate based on a MaRIA score <7 of 22% at 26 weeks and 38% at 52 weeks, although a MaRIA <7 permits some minor residual bowel wall abnormalities which may explain this higher rate of response compared to trials requiring full normalization of the bowel wall [50]. The recent IBUS group expert consensus statement suggested that transmural response is best assessed at 26–52 weeks [28].

A more pragmatic and less stringent definition of transmural healing may ultimately be more appropriate. A recent study of 40 patients starting anti-TNFα therapy reported a threshold BWT of 3.2 mm best predicted endoscopic remission (SES-CD = 0) at 12–34 weeks. The same study found that those destined to reach endoscopic remission had significantly lower BWT as early as 4–8 weeks after starting therapy compared to those not achieving remission [55]. Similarly, the STARDUST study group found that when response criteria were relaxed to BWT >3 mm, 32% of patients were now deemed to be in sonographic remission (versus 24% using complete bowel wall normalization). This less stringent definition would accommodate the often multiple, subtle residual changes on imaging, particularly in the context of a long disease course and progressive bowel damage. The prognostic significance of 'full' bowel wall normalization versus 'near full normalization' remains to be determined.

5.2. Cumulative bowel damage

Irreversible bowel damage can result from repeated cycles of inflammation and healing long term. The Lémann index measures this cumulative, irreversible bowel damage including the longitudinal extent and severity of stricturing and penetrating disease, and surgical resection on MRI, CT, and/or endoscopy [56,57]. The index has been validated and updated by the original authors. It may evaluate treatment efficacy beyond simply the burden of disease activity, potentially capturing irreversible damage at an early stage, and also in disease modification trials. The prospective METRIC-EF study (ISRCTN76899103) will report on the predictive ability of the Lémann index, in addition to other disease scores, for disabling disease at 5 years in newly diagnosed Crohn's disease patients [58].

## 6. Clinical integration of cross-sectional imaging modalities

The current ECCO-ESGAR guidelines suggest either MRE, IUS, or capsule endoscopy are appropriate for diagnosis and follow-up in Crohn's disease [1]. Deciding which test is most appropriate for imaging the small bowel is dependent on patient factors (e.g. body mass index, claustrophobia, individual preferences), disease factors (e.g. penetrating disease),

Table 3. Transmural healing: cross-sectional imaging criteria used in recent studies, rates of transmural healing achieved and clinical outcomes.

Reference	Study design	Participants	Imaging modality	Endoscopic mucosal healing	Transmural healing/remission definition	Transmural healing rate	Clinical outcomes
Kucharzik et al, STARDUST study group, 2023 [7]	Randomized controlled trial, multicentre	N = 77 On ustekinumab	IUS	9% (7/77) at week 48	Normalization of BWT, blood flow (color Doppler signal), bowel wall stratification, and inflammatory mesenteric fat	24% (13/54) at week 48 32% when definition relaxed to BWT <3 mm	-
Ma et al, 2021 [10]	Prospective, single center, 6 months follow up	N = 77	IUS	40% (31/77)	BWT ≤3 mm, normalization of stratification, no hypervascularization, resolution of mesenteric inflammatory fat, no abscess or fistula	32% (25/77)	TH independently predicted steroid-free clinical remission (OR, 52.6], drug escalation (OR, 0.1), and hospitalization (OR, 0.05)
Zorzi et al, 2020 [46]	Prospective, single center, 5 years follow up	N = 80 On anti-TNF therapy	IUS	-	Normalization of BWT, absence of any length of disease, perienteric inflammation, fistulas, phlegmon, or abscess	51% (41/80)	Lower cumulative probability of need for surgery, hospitalization, and need for steroids
Lafeuille et al, 2021 [47]	Retrospective, single center	N = 154	MRE	10% (16/154)	Combination of endoscopic and MRI healing (no MRI signs of inflammation and no complication)	18% (28/154)	Reduced risk of major outcomes (time to surgery, bowel damage progression, hospitalization) with TH versus MH (HR = 0.28 [0.00–0.74]) and relapse-related drug discontinuation (HR = 0.35 [0.13–0.95])
Fernandes et al, 2023 [48]	Retrospective, multicentre, end points assessed at 5 years	N = 404	MRE	23% (94/404)	Inactive colonoscopy and MRE BWT ≤3 mm, absence of increased T2 mural intensity or increased contrast enhancement	21% (84/404)	Lower risk of hospitalization (OR 0.244 [0.111–0.538]), surgery (OR 0.132 [0.030–0.585]), steroid use (OR 0.283 [0.159–0.505]), and treatment escalation (OR 0.088 [0.044–0.176]) versus no remission
Calabrese et al, 2022 [49]	Prospective, multicentre	N = 188 Biologic therapy	IUS	-	Normalization of all IUS parameters	28% (43/156) at 1 year	-
Danese et al, 2019 [50]	Prospective, single center	N = 101 On vedolizumab	MRE	Week 26: 12% Week 52: 18%	MaRIA score <7	22% (22/101) at 26 weeks, 38% (38/101) at 52 weeks	-
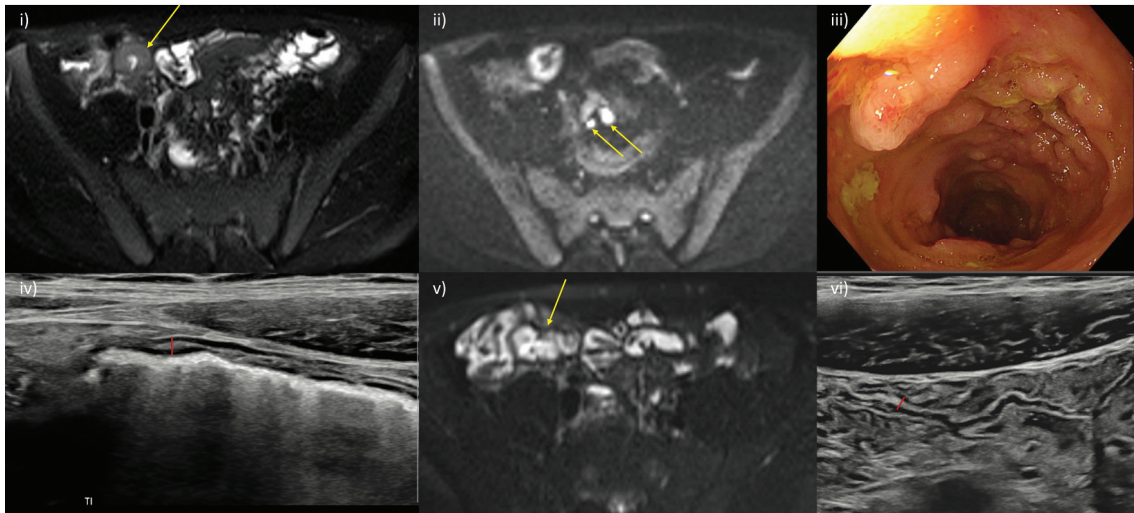
Figure 2. Transmural healing. A 15-year-old male patient with newly diagnosed Crohn's disease. At baseline, MRE showed moderately active disease involving the terminal and distal ileum (i) axial fat-saturated T2-weighted MRI image showing terminal ileal mural thickening and increased mural T2 signal (arrow), and mesenteric free fluid mainly in the right iliac fossa, ii) corresponding high signal on diffusion weighted images with enlarged reactive mesenteric nodes (arrows). iii) Baseline ileocolonoscopy documented a simple endoscopic score (SES-CD) of 15 iv) after 6 months of infliximab and methotrexate therapy ultrasound fulfilled the criteria for true transmural healing with normal mural thickness (≤3 mm) and stratification, and complete resolution of mesenteric changes. Small bowel motility was subjectively normal. Axial fat-saturated MRE image confirmed transmural healing of the terminal ileum (arrow) was maintained at 12 months (v), and at again at 18 months on IUS (vi). MRI: Magnetic resonance imaging; MRE: MR enterography; IUS: intestinal ultrasound.

and the specific clinical question and access (e.g. availability of imaging platforms and a trained workforce).

A robust IBD service should ideally have access to all imaging modalities which requires investment in technology and training. In the UK for example, IUS is underused in some centers, often due to difficulty in accessing training for radiologists and/or gastroenterologists, and because referral pathways traditionally utilize MRE and CT. Indeed, a national UK survey reported that clinicians were less confident in basing their treatment decisions on IUS findings than MRE [59].

IUS, especially at the point of care, has the advantage of enabling real-time clinical decisions and immediate patient feedback and seems cost-effective [24]. No requirement for oral preparation also contributes to it being an excellent option for regular disease monitoring. The largest study to date directly comparing IUS and MRE in new diagnosis and suspected relapse Crohn's disease cohorts was the multicenter, prospective METRIC trial, and included 288 patients [24]. Although both IUS and MRE were well tolerated, IUS was generally reported as being more acceptable to patients than MRE, mostly due to the oral bowel required for the latter [7]; 99% patients were willing to repeat the test versus 91% for MRE [13,24]. Despite this, patients generally considered diagnostic accuracy as the most important factor and so this should always be considered when counseling patients in joint decision-making.

MRE and IUS are both accurate in the initial diagnosis and assessment of Crohn's disease, and there is good agreement between these two modalities [24,60,61]. The METRIC study group reported that the sensitivity of MRE was slightly greater than IUS for detecting active small bowel disease, 97% and 92%, respectively. Their respective specificities were 96% and 84% [24]. Furthermore, there is high concordance between IUS and MRE in disease longitudinal length assessment [62]. However, in the METRIC trial, MRE was superior in assessing the full extent of disease in the small bowel [1,20,55]; the sensitivity and specificity for small bowel disease extent was 80% and 95% for MRE, significantly greater than IUS (70% and 81% respectively). Of note, compared to MRE, IUS had higher sensitivity for colonic disease in newly diagnosed patients.

A meta-analysis comparing capsule endoscopy, MRE and IUS found a comparable diagnostic accuracy for the three modalities in detecting small bowel disease in both suspected and established Crohn's disease [63], although it was published just before the METRIC trial. Capsule endoscopy was superior to MRE in detecting proximal small bowel disease; portions of the jejunum are often sub optimally distended using traditional MRE oral preparation protocols. No significant difference was observed in detecting severe disease on resected surgical specimens between IUS and contrast-enhanced IUS, compared to MRE [62].

The METRIC study findings were replicated in a recent retrospective study of 115 patients. MRE had a greater diagnostic accuracy for detecting small bowel disease versus IUS and CTE. However, there was no significant difference between the accuracy for active disease between MaRIA and IBUS-SAS against an endoscopic SES-CD reference standard [64].

MRE and IUS have both been shown to have a large impact on the decision-making process.

In one study by Allocca et al., 60 patients with ileocolonic disease were assessed with MRE, IUS, and ileocolonoscopy. The resultant management changes were highly concordant between these IUS and MRE (0.8) [60]. A sub-study of the METRIC trial also found similar impact of MRE and IUS on clinical decision-making [19]. MRE alone was found to be sufficient to make a management decision in 80% of 100 Crohn's disease patients versus 34% using ileocolonoscopy alone. In another study, 100 patients with ileocolonic disease underwent both MRE and ileocolonoscopy within 1 week of

each other. The addition of MRE information to endoscopic findings led to therapeutic change in 28% of cases and increased the clinicians' level of confidence. Interestingly, surgery and anti-tumor necrosis factor (TNF) therapy were indicated more often when MRE was performed before endoscopy [65].

Ultimately, MRE and IUS both play an important role in the management of Crohn's disease and local clinical pathways should maximize their relative advantages. We await robust data on the interchangeability of MRE and IUS markers and scores of activity, a common conundrum when different modalities are used in the follow-up schedule.

7. Novel cross-sectional imaging applications

7.1. Imaging fibrostenotic disease

Invariably both fibrosis, muscle hypertrophy, and inflammation co-exist in strictures due to progressive bowel damage accumulated over time. A challenging aspect in Crohn's disease management is the assessment of fibrosis relative to the inflammatory burden, particularly as this may be distributed heterogeneously even within an individual stricture. Each of these components is targeted in different ways depending on the predominant phenotype, conventionally medical therapy for inflammation and endoscopic balloon dilation and/or surgical, e.g. stricturoplasty, for fibrosis predominance. New antifibrotic therapies are being developed which may impact on current therapeutic paradigms. An advantage of cross-sectional imaging is the transmural assessment of a stricture, in contrast to the limited mucosal interrogation during endoscopy, even if the stricture is endoscopically accessible [66].

If fibrosis becomes a therapeutic target, it is crucial to establish a standardized, reproducible, and validated definition of a stricture to triage patients into clinical trials and then assess response. To date, heterogeneous definitions have been applied in the literature. The STAR consortium [15] and the CONSTRICT expert consensus panel [67] comprising gastroenterologists and radiologists define a stricture on MRE as i) luminal narrowing >50%, ii) BWT > 25% relative to adjacent normal bowel, and iii) pre-stenotic bowel dilation >3 cm. Requiring all three criteria maximizes specificity, likely at the cost of reduced sensitivity, although this may be the most robust approach for initial trials of new therapeutics.

Many of the imaging parameters used to assess disease activity are influenced by fibrosis, particularly BWT and mural hyperenhancement. A recent systematic review found that the sensitivity and specificity of MRE for histopathologically confirmed fibrosis was 75–100% and 91–96%, respectively, and that of IUS was 80–100% and 63–75%, although stricture definitions varied or were not stated [15].

Active inflammation tends to produce mucosal enhancement, ulceration, and blurring of mural stratification and margins. Conversely, delayed progressive enhancement at 7 minutes has been reported to correlate with underlying fibrosis [60]. Another promising MRI technique is the magnetization transfer ratio (MTR, Figure 3). As collagen is deposited in the bowel wall, this along with other macromolecules can be estimated. Several mainly single-center studies have reported that MTR is related to histopathologically quantified fibrosis [68]. However, in a recent prospective multicenter study of 60 patients, neither delayed contrast enhancement nor MTR reliably differentiated between grades of fibrosis [69], emphasizing the translation gap between single and multisite research.

Other promising MRI techniques include T1 mapping, which has been used in other organs, most notably the heart, and the DWI perfusion fraction (as a surrogate for tissue blood flow) [70], although the research in the area is relatively immature.

IUS elastography can quantify tissue stiffness, either through strain or shear-wave elastography, acting as a surrogate for fibrosis. A recent systematic review of 275 patients reported an overall moderate to good accuracy for IUS elastography to detect histologically confirmed fibrosis (in 10 out of 12 studies, using varied measures) [71], and in patients on anti-TNF therapy, elevated strain ratios were predictive of future surgery, with lower ratios present in patients with transmural healing [72]. Currently, IUS elastography remains mainly a research tool with multi-center validation studies still pending.

It is also possible to measure bowel wall stiffness on MRI using shear waves produced by external hardware. Again, research is in its infancy but a recent prospective study of 69 patients found a threshold of 3.57 kPa was predictive of
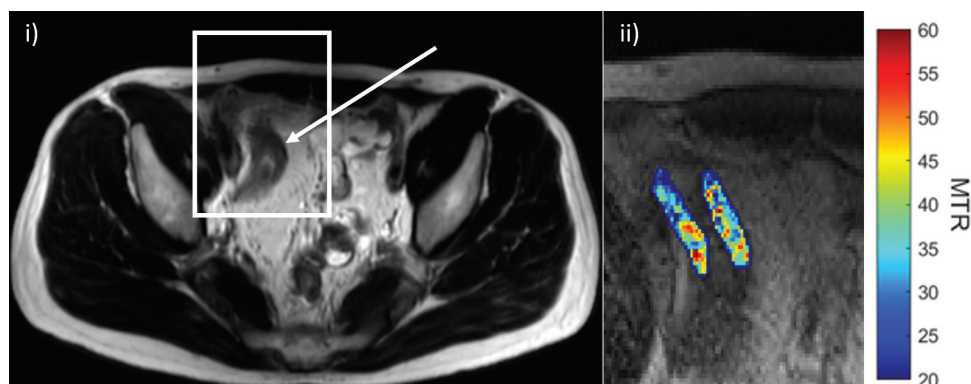
Figure 3. Imaging and quantifying fibrosis. i) Axial T2-weighted image of the pelvis demonstrating a long stricture of the terminal ileum (arrow). ii) Corresponding magnetization transfer imaging of the stricture alongside a quantitative color scale shows decreased magnetization transfer ratio (MTR) in the wall of this segment with a range of 20 to 60.
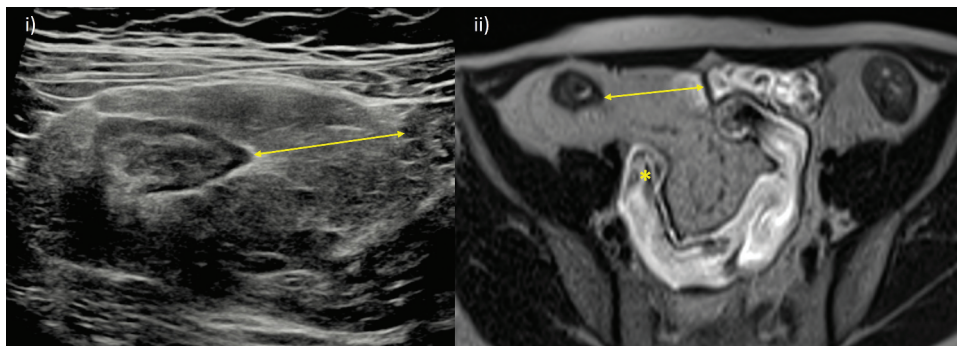
Figure 4. Mesenteric fat wrapping. A 29-year-old female Crohn's disease patient with signs of extensive fat wrapping of the terminal ileum. i) IUS with mesenteric fat wrapping involving most of the small bowel circumference and displacing a loop of ileum (arrow). ii) Comparable axial T2-weighted MRE image, also showing resultant separation of the terminal ileum from other loops of pelvic ileum (arrow). MRE also demonstrates terminal ileal stricturing disease with reduced luminal caliber and mild pre-stenotic dilation (asterisk).

IUS: intestinal ultrasound; MRE: MR enterography.

adverse clinical events over a median follow-up of 450 days [73].

Functional nuclear medicine techniques also show promise in fibrosis quantification, particularly when combined with conventional MRI sequences. Gallium-68 labeled fibroblast activation protein inhibitor positron emission tomography MR (^{68}Ga-FAPI PET/MR) enterography is of particular current interest. Scharitzer et al. used histopathological FAPI expression in the bowel wall as a reference standard to show that ^{68}Ga-FAPI uptake was significantly greater in fibrotic segments across all bowel layers (mean maximum standardized uptake value [SUV_{max}] of 7.6 versus 2.0 without fibrosis). Further, it was able to distinguish between mild, moderate, and severe grades of histological fibrosis [74]. Using a cut-off SUV_{max} value of 3.2, the AUC for fibrosis prediction was 0.94. New total body PET technology will significantly reduce the radiation exposure for PET scanning techniques [75].

7.2. Fat wrapping

There is increasing recognition of the role of adipose tissue in several physiological and disease pathways, including the inflammatory disease [76]. In the context of Crohn's disease, mesenteric fat hypertrophy or fat wrapping is not simply a bystander of chronic inflammation but may in part be driving the underlying pathophysiology.

Fat wrapping is linked to transmural inflammation, fibrosis, and stricturing on histopathology [77]. Mesenteric fat dysfunction may play an active role in the inflammatory process as adipocytes have been shown to be a source of pro-inflammatory and pro-fibrotic cytokines in Crohn's disease [78]. Further indicators for this role come from the observation of reduced disease recurrence following small bowel resections which include the mesentery [79]. In surgical resection specimens, translocated bacteria cause immune cell activation and production of pro-adipogenic and pro-fibrotic factors [80]. Therefore, as our knowledge of Crohn's disease pathophysiology grows, we can start to consider fat wrapping as a potential novel therapeutic target and predictor of disease course.

Mesenteric fat wrapping may be observed on MRE, usually manifesting as loop and mesenteric vessel separation. Often, it is more readily delineated on IUS with fat 'creeping' around >180° of the small bowel circumference (Figure 4). Fat wrapping as measured by MRI has been shown to reduce with successful anti-TNF therapy [81]. Fat wrap may also act as a further noninvasive marker of intestinal fibrosis. A mesenteric creeping fat index formed by measurements on CTE has been proposed. This index was moderately accurate for distinguishing mild and moderate-severe fibrostenotic disease in surgical specimens [82].

Body fat distribution and muscle quality (sarcopenia) can be accurately measured using both CT and MRI. An increased ratio of visceral to subcutaneous fat in Crohn's disease is linked to disease activity, e.g. biochemical and clinically based disease activity scores [83] and following therapy, the prognosis for patients who exhibit sarcopenia and high visceral to subcutaneous fat ratio may be worse [84].

Cross-sectional imaging assessment of fat and muscle may play an increasing role in disease activity assessment and prognostication.

7.3. Motility

Inflamed small bowel exhibits reduced peristaltic motility from a variety of underlying, often coexistent, processes. Motility can now be assessed using cine-MRI techniques where multiple images of the same bowel loop are taken in either a 2- or 3-dimensional plane. IUS enables clinically useful real-time, subjective assessment of enteric motility, although validated, reproducible quantitative parameters of IUS motility are as yet lacking.

Software (e.g. using image registration techniques [85]) can now quantify both segmental and global bowel motility on MRI (Figure 5). Inflamed small bowel segments demonstrate reduced motility which is correlated with endoscopic and pathological inflammation, i.e. motility on MRI is a biomarker of activity [72,73]. A multicenter, prospective study noted a negative correlation of terminal ileal motility with the CDEIS and a histologic inflammatory score and highly sensitivity (93% and 92% respectively), outperforming
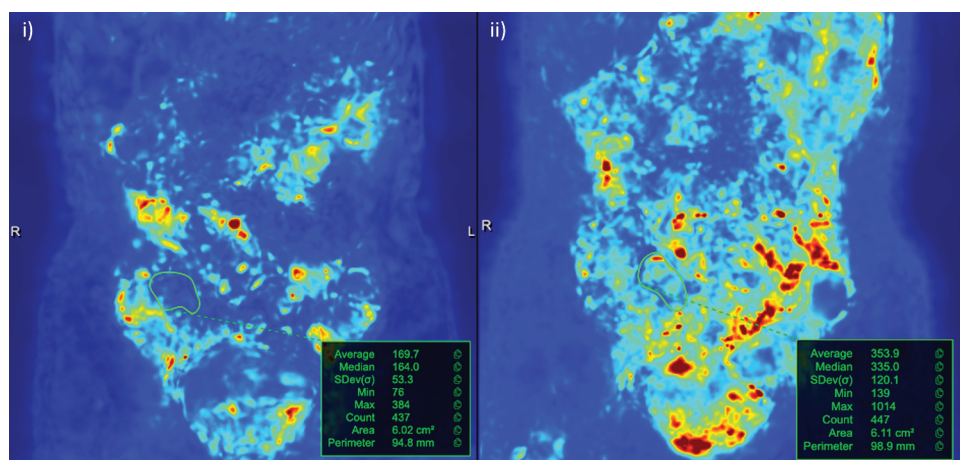
Figure 5. Software assisted quantification of motility. i) Pre-treatment motility map of active terminal ileal disease (region of interest drawn based on a reference image) with an average motility value of 170. ii) After 8 weeks on treatment, disease in the terminal ileum responded clinically and based on MRE parameters of activity. This included a measurable improvement in motility; average of 354.

MRE: MR enterography.

the MaRIA score (78% and 75%) [86]. Motility is also responsive to changes in therapy [87]. Patients clinically responding to biological treatment have significantly improved motility from baseline compared to non-responders, as early as 12 weeks [88]. The MOTILITY trial (ISRCTN14481560) will shortly report on the ability of segmental small bowel motility measurements to improve prediction of therapeutic response at 1 year in patients starting biologic therapy for small bowel Crohn's disease in comparison to plasma C-reactive protein (CRP).

Abnormal patterns of motility in small bowel remote from diseased segments have been associated with the severity of abdominal symptoms and may have mechanistic insights into abdominal pain in patients with Crohn's disease [89].

7.4. Diffusion-weighted imaging

DWI is an additional MRI method which provides information on tissue composition and histology. The differential Brownian motion of water molecules within tissues is captured. When this random motion is impeded, e.g. hypercellular tissue, there is a corresponding higher value on DWI (diffusion restriction).

DWI is reported to accurately separate active inflammation and inactive disease, reported 80–100% sensitivity against a range of reference standards of differing quality [90]. However, fibrosis also restricts diffusion and so in itself DWI is not a 'magic bullet' for the quantification of enteric inflammation. Indeed, it has relatively low specificity for inflammation with a false-positive rate as high as 40% [90]. Nonetheless, it plays a useful role in clinical practice.

One of the potential uses of DWI is to negate the need for intravenous contrast. A modified sMaRIA score using DWI had a comparable diagnostic performance for active inflammation as the original sMaRIA using intravenous contrast, and both protocols were moderately correlated with the SES-CD [39]. This finding was replicated in a group of 61 patients, where DWI was non-inferior to intravenous contrast enhanced MRI

sequences for identifying small bowel inflammation using an endoscopic reference standard [17,18].

ADC maps are calculated from DWI and provide quantitative information on the diffusion of water molecules in tissues. A recent meta-analysis of 21 studies found a pooled correlation coefficient of −0.8 between the ADC value and endoscopic inflammation (CDAI) and −0.66 for both SES-CD and MaRIA score [91]. There is some evidence that low ADC values are linked to histologically confirmed fibrosis, including from a prospective, multicenter study of Crohn's disease patients with fibrostenotic disease prior to surgery [69,92]. However, as noted, the overlap of inflammation and fibrosis effects on DWI and ADC means reliable separation between both process is currently not possible.

7.5. Contrast enhanced ultrasound

CEUS is an adjunct to conventional B-mode IUS and has been used widely to image blood flow in the macro- and micro-circulation in a variety of organs. It uses intravenous contrast agents comprising microbubbles or nanobubbles of gas which oscillate in response to applied sonographic waves. The need for an intravenous injection of a contrast agent means compared to conventional IUS, CEUS is a more timely, costly, and potentially less acceptable option for patients.

The additional value of CEUS to assess for activity remains controversial and is infrequently used in practice and currently mainly reserved for the research setting. CEUS and conventional IUS have comparably high levels of sensitivity and specificity to detect activity [43,62]. CEUS can provide a more quantitative assessment of mural and extramural vascularity, e.g. time intensity curve analysis derived parameters; however, to date, there is little evidence that this adds to accuracy for disease activity or responsiveness to changes [62,93].

There are preliminary data in small cohorts suggesting CEUS may help separate fibrosis from inflammation in

stricturing disease, but utility for this indication remains to be fully validated [93].

7.6. Dual energy CT

Given its use of ionizing radiation, CT is mainly used in the acute setting. However, new techniques such as iterative reconstruction are reducing radiation doses from CT. Dual energy CT (DECT) simultaneously gathers data from two different energy levels enabling creation of distinct datasets such as iodine maps of tissue iodine accumulation. These maps can act as a surrogate marker of perfusion. This technique facilitates improved detection of differences in bowel wall characteristics between adjacent loops as well as extramural findings [94].

Iodine levels are greater with bowel inflammation and a recent systematic review reported reasonable accuracy for active disease (optimal iodine cutoff values of 2–3.7 mg/ml based on endoscopic reference standards), although there was insufficient evidence to show any superiority of DECT relative to conventional CT [95]. A normalized measure of iodine concentration was accurate in differentiating endoscopic mucosal healing from non-mucosal healing in 94 patients post-infliximab therapy (AUC 0.929), further improved with the addition of fecal calprotectin levels (AUC 0.964) [96].

The utility of DECT awaits multicenter clinical trial validation.

7.7. Harnessing artificial intelligence

Artificial intelligence (AI) has several applications to augment our ability to assess the small bowel and potentially streamline clinical practice. One key emerging trend is semi-automated bowel segmentation to identify and quantify inflammation in a reproducible manner, which is less subjective than individual reporter interpretation alone [97,98]. These segmentation tools more objectively extract small bowel features like BWT, luminal diameter, and length of disease. 3D segmentation models are likely to emerge in the near future, validated against endoscopy and assessed for inter-reader agreement, key to any potential clinical use.

There has been a surge in interest in radiomics where software can extract a large number of candidate quantitative imaging-based features which are assessed for prognostic value. A few radiomics-based models pertaining to Crohn's disease have appeared in the literature. One such developed radiomics model uses features on MRE and CTE to identify moderate-to-severe fibrosis with a similar accuracy as the interpreting radiologists [31]. A recent mouse model of intestinal fibrosis found that the bowel wall magnetization transfer ratio and textural analysis on T2-weighted MRI can noninvasively distinguish histological fibrosis. The MRI textural feature of entropy was superior in inflammation detection with coexistent fibrosis and able to assess response to antifibrotic therapy [99]. Furthermore, there are models which can automatically extract the most discriminatory imaging features without prior human interaction, deep-learning models. One

such model has been found to exceed the ability of radiologists to identify fibrosis on CTE [100].

The precise nature of how these promising AI solutions may be implemented in practice is unclear, but it is a rapidly evolving field with potential to improve automated analysis, diagnostic accuracy, radiology workflow, and reduce interobserver variation. A key limitation is that models are generally poorly externally evaluated, partly due to suboptimal reporting of the parameters required to validate the index model, and difficulties accessing the large number of external datasets need for validation. It is also crucial that radiomics models incorporate clinical variables given their already proven utility. Ultimately, such techniques must be shown to improve patient outcomes if they are to be widely adopted.

8. Predicting disease trajectory and response to treatment

Cross-sectional imaging may have a role in predicting clinical outcomes and progressive bowel damage [101,102]. Early, noninvasive biomarkers of therapeutic response and disease course are a crucial research interest in IBD. The use of transmural healing as a treatment target has been discussed above, but imaging features at baseline may also have prognostic utility.

8.1. IUS predictors

BWT just prior to starting treatment may predict response on IUS. In a prospective cohort of 188 patients starting varying biological therapies, a greater BWT at baseline IUS independently predicted reduced rates of transmural healing at 3 and 12 months in [49]. Contrast enhanced IUS washout rate and absence of color Doppler signal improved accuracy of a predictive model for early endoscopic response at 4–8 weeks versus reduced BWT alone in patients commencing anti-TNF therapy [55].

In a large prospective study of ileocolonic Crohn's disease including 49 patients, baseline BUSS predicted endoscopic response with an accuracy of 80%, and remission with 78% accuracy. At 12 months, BUSS also predicted adverse disease outcomes, and a baseline complication, e.g. penetrating or stricturing disease, was predictive of future surgery [43].

8.2. MRE predictors

A recent longitudinal cohort study of 72 patients with at least 5 years of follow-up identified MRE parameters predicting long-term bowel damage. The baseline predictors were ileal disease location, stricturing, and/or fistulating disease phenotype. Disease duration >10 years was also predictive [103]. In a multicenter study of 142 Crohn's disease patients, 39.4% had signs of bowel damage on cross-sectional imaging at diagnosis. Using multivariable analysis, bowel damage independently predicted future surgery and hospitalization (hazard ratios of 3.21 and 1.88 respectively) [104]. Other reported potential MRE predictors for future surgical intervention include increased disease length, perienteric inflammation, diffusion restriction, complex fistulation, mesenteric fat wrapping, and stricturing

with pre-stenotic dilation [105], although such data require prospective external validation.

There are emerging data that residual cross-sectional imaging changes in the neoterminal ileum following surgery may better predict recurrence than mucosal assessment with endoscopy. Specifically in a retrospective analysis of 216 patients undergoing endoscopy and either CTE or MRE after resection, those negative on endoscopic assessment but with positive imaging for active disease (41.7%, 90/216) had greater future endoscopic and surgical recurrence (hazard ratio 4.16) [106].

The ongoing prospective METRIC-EF study (ISRCTN76899103) will report on the predictive ability of disease activity and severity scoring systems, including MaRIA and sMaRIA scores, for disabling disease at 5 years in newly diagnosed Crohn's disease patients [58].

9. Conclusion

MR enterography and ultrasound are accurate, objective techniques for diagnosis, disease phenotyping and response assessment in Crohn's disease. These qualities can be harnessed to update therapeutic targets to sustained, deep remission, and transmural healing as part of a 'treat-to-clear' paradigm. The value added by cross-sectional imaging is ever-increasing, with objective validated scores of disease activity and severity, quantitation of motility, evolving techniques to measure fibrosis, harnessing artificial intelligence, and identifying predictors of disease trajectory and response.

Making full use of the technology available to non-invasively image the small bowel in a standardized manner can improve timely clinical decision-making, lead to better patient outcomes and experience, contribute to a more personalized management approach, and accelerate pharmacological development.

10. Expert opinion

Cross sectional imaging is established in the management of small bowel Crohn's disease. We know its accuracy for diagnosis and staging, activity assessment and increasingly for treatment response evaluation. We also know the importance of training, the range of interobserver variability, and the strengths and limitations of the various imaging modalities. However, there is much still to be done.

Much imaging research suffers from being single center with relatively small patient cohorts. In recent years, there have been several pivotal prospective multicenter trials of cross-sectional imaging in IBD, but more are needed. MRE, IUS, and CT all play a role in managing Crohn's disease patients. Radiologists need to work closely with their clinical colleagues to establish care pathways which define how the various imaging modalities are best employed, considering availability, cost-effectiveness, and patient preference. We need to understand the interchangeability of MRE and IUS biomarkers of activity, fibrostenotic disease, and other complications. We currently do not fully understand which modality (if any) is superior in assessing treatment response, but it is clear all have utility. Multicenter, multi-arm prospective trials need to assess if they can be used interchangeably, and their respective concordance and accuracy for categorizing response. Such data would inform training and aid service planning.

It is crucial that imaging is integrated with other clinical information, including blood and stool markers and endoscopy. The clinical and cost-effectiveness of a combined clinical-radiological pathways needs investigation. Suggested endpoints for disease modification trials by the SPIRIT-IOIBD consensus group comprise patient quality of life outcomes, medium-term complications, e.g. accumulated bowel damage, surgery, hospitalization, permanent stoma, and long-term complications [107], and are an example of a synergistic approach.

MRE disease activity scores are generally better validated than IUS scores, but larger scale trials of the latter are underway which will provide important data to justify wider use. Imaging activity scores are currently not accepted as primary endpoints in clinical trials of new therapeutics but are an attractive alternative to nonspecific patient symptom scores and invasive colonoscopy. It is crucial that we collate multicenter trial data to assess the responsiveness and reproducibility of these scores in the 'real world,' their association with currently accepted primary trial endpoints, and ultimately on patient outcomes.

Going further, transmural healing is associated with better long-term patient outcomes but is hard to achieve with current therapeutics and as not yet a primary treatment target. An internationally agreed definition of transmural is required, with arguments both for complete normalization of the bowel wall, or for allowing minor persisting changes. Data suggest that in many patients with reassuring colonoscopy, the presence of residual imaging abnormalities infers a worse prognosis, but a strict definition requiring bowel wall normalization ('treat-to-clear') may not be pragmatic in a real world setting given how difficult it is to achieve currently.

With new anti-fibrotic drugs on the horizon, there is a need for imaging to be better able to quantify fibrosis and muscle hypertrophy. Significant advances have been made by the STAR and CONSTRICT consortia to unify stricture definitions and response criteria in anticipation of clinical trials [15,67]. These definitions currently use morphological observations such as bowel wall thickening and upstream bowel dilation. Imaging techniques that directly probe stricture composition such a delayed contrast enhanced enhancement and MTR for MRI and elastography for IUS are still undoubtedly worthy of research, but early multicenter trials have not been promising to date. Lessons must be learned from such trials for the next iterations. Research into new imaging techniques including functional tracers, for example 68 Ga-FAPI, are a priority. In future years, radiation dose exposure will fall significantly with the development of total body PET technology, removing a significant barrier to wider use of nuclear medicine techniques.

The role of imaging in prognostication both at diagnosis and as part of treatment pathways is another area requiring further investigation. Initial data suggest that those with more advanced imaging activity parameters may have worse longer-

term outcomes, but this needs to be replicated in large prospective studies. The utility, if any, of imaging in the decision to stop biologics is also unknown.

As a community, we should not neglect training the next generation. Radiologists and clinicians most work together to develop robust training infrastructure informed by consensus guidelines and put aside any 'turf wars' for the ultimate benefit of patients.

Looking further forward, it is clear AI will play a major role in modern IBD management. Imaging analysis will likely become (semi)automated and although very much in its infancy, machine learning and radiomics techniques may extract useful data from medical image beyond the resolution of the human eye.

Looking forward over the next 5 years or so, we speculate that multidisciplinary collaborative efforts between key stakeholders including patients, radiologists, gastroenterologists, endoscopists, histopathologists, and surgeons will translate into better defined patient care pathways and integration of cross-sectional imaging. Such efforts will lead to improved training pathways and resource planning.

Cross-sectional imaging disease response assessment criteria will become standardized and supported by large-scale trial data. The large number of cross-sectional imaging-based activity scores will be further validated and play an increasing role in therapeutic trials, particularly those targeting the small bowel.

Transmural healing will be better defined and will become formally accepted as a primary treatment target and potentially included as an end point for clinical trials. Trials of new antifibrotic agents will have commenced with imaging at the forefront of patient selection and response assessment. Such trials will allow testing of novel imaging techniques to better define stricture composition and quantify the relative fibrotic and inflammatory burden. Falling radiation doses from PET scanning will facilitate wider use of novel tracers. We envisage that extraction of data from cross-sectional imaging will become increasingly automated and new metrics such as motility will be more widely used. Baseline predictors of disease course will be invaluable to provide a more personalized patient management pathway and improved transparency in clinical decision-making. AI technology will be implemented to better monitor patients' progress and facilitate early investigations and treatment.

Abbreviations

AI	Artificial Intelligence
AUC	Area Under the receiver operating characteristic Curve
BUSS	Bowel US Score
BWT	Bowel Wall Thickness
CDEIS	Crohn's Disease Endoscopic Index of Severity
CEUS	Contrast Enhanced Ultrasound
CDAI	Crohn's disease Activity Index
CRP	C-reactive protein
DECT	Dual Energy Computed Tomography
DWI	Diffusion Weighted Imaging
ECCO	European Crohn's and Colitis Organisation
ESGAR	European Society of Gastrointestinal and Abdominal Radiology
^{68}Ga-FAPI PET	Gallium-68 labeled fibroblast activation protein inhibitor positron emission tomography
IBD	Inflammatory bowel disease
IBUS-SAS	International Bowel Ultrasound Segmental Activity Score
IUS	Intestinal Ultrasound
MaRIA	Magnetic Resonance Index of Activity
MRI	Magnetic Resonance Imaging
MRE	Magnetic Resonance Enterography
MTR	Magnetization Transfer Ratio
POCUS	Point of Care Ultrasound
PEG	polyethylene glycol
SES-CD	Simple Endoscopic Score for Crohn's Disease
sMaRIA	simplified Magnetic Resonance Index of Activity
STRIDE	Selecting Therapeutic Targets in Inflammatory Bowel Disease
SUS-CD	Simple US activity score
SUV_{max}	maximum standardized uptake value
TNF	Tumor Necrosis Factor
Treat-to-Target	treat to target approach in inflammatory bowel disease.

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