



Original Article

# Defining Transabdominal Intestinal Ultrasound Treatment Response and Remission in Inflammatory Bowel Disease: Systematic Review and Expert Consensus Statement

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## Abstract

**Background and Aims:** No consensus exists on defining intestinal ultrasound response, transmural healing, or transmural remission in inflammatory bowel disease, nor clear guidance for optimal

timing of assessment during treatment. This systematic review and expert consensus study aimed to define such recommendations, along with key parameters included in response reporting.

**Methods:** Electronic databases were searched from inception to July 26, 2021, using pre-defined terms. Studies were eligible if at least two intestinal ultrasound [IUS] assessments at different time points during treatment were reported, along with an appropriate reference standard. The QUADAS-2 tool was used to examine study-level risk of bias. An international panel of experts [ $n=18$ ] rated an initial 196 statements [RAND/UCLA process, scale 1–9]. Two videoconferences were conducted, resulting in additional ratings of 149 and 13 statements, respectively.

**Results:** Out of 5826 records, 31 full-text articles, 16 abstracts, and one research letter were included; 83% [40/48] of included studies showed a low concern of applicability, and 96% [46/48] had a high risk of bias. A consensus was reached on 41 statements, with clear definitions of IUS treatment response, transmural healing, transmural remission, timing of assessment, and general considerations when using intestinal ultrasound in inflammatory bowel disease.

**Conclusions:** Response criteria and time points of response assessment varied between studies, complicating direct comparison of parameter changes and their relation to treatment outcomes. To ensure a unified approach in routine care and clinical trials, we provide recommendations and definitions for key parameters for intestinal ultrasound response, to incorporate into future prospective studies.

**Key Words:** Intestinal ultrasound; inflammatory bowel disease; treatment response; transmural remission; transmural healing

## 1. Introduction

Transabdominal intestinal ultrasound [IUS] is gaining acceptance as a point-of-care test to objectively assess disease activity in inflammatory bowel disease [IBD].<sup>1</sup> IUS has several advantages over conventional cross-sectional imaging modalities: it is non-invasive, patient-friendly, easily repeated while being preparation and radiation free. Thus, the clinician can directly assess inflammatory activity in real time, helping patients understand their disease while facilitating clinical decisions without delay.<sup>2,3</sup>

IUS's ability to assess colonic and small bowel inflammation has been compared with clinical scores, biologic markers, endoscopy, and radiological modalities at diagnosis and during disease flare, with good accuracy in ulcerative colitis [UC]<sup>4</sup> and Crohn's disease [CD].<sup>5</sup> However, the role of IUS as a monitoring tool after treatment initiation has not been standardised.<sup>2,4,6,7</sup> Currently, no consensus definition exists for IUS response or transmural remission/healing [TR], nor clear guidance for optimal assessment intervals during follow-up.<sup>8,9</sup> These standards are vital for the consistent application of IUS as a modality to assess treatment outcomes and establish therapeutic targets, to ensure comparability between future studies.

We aimed to provide expert recommendations for IUS assessment of treatment response in IBD and define IUS key parameters to include in response reporting. We therefore conducted a systematic review of the literature, followed by a RAND/UCLA [University of California at Los Angeles] expert panel appropriateness process.<sup>10</sup>

## 2. Materials And Methods

### 2.1. Information sources and searches

The systematic review was conducted in accordance with the PRISMA recommendations [PROSPERO-ID CRD42019136983]. A systematic search of Embase [Ovid, 1984], Medline [Ovid, 1946], and Cochrane Central from database inception to February 27, 2020, laid the foundation for the expert consensus process. After the consensus process, an additional systematic search on Embase [Ovid, 1984], Medline [Ovid, 1946], and Cochrane Central from

February 27, 2020, to July 26, 2021, was performed. The detailed search strategies and the outcomes of interest, eligibility, and exclusion criteria are outlined in [Supplementary Material 1, available as Supplementary data at ECCO-JCC online](#). In the tables and figures, updated search articles are identified by a light grey background.

### 2.2. Study selection and data extraction

All studies were uploaded to the Covidence systematic review software, with automatic removal of duplicates.<sup>11</sup> Using a priori defined eligibility criteria, two researchers screened all uploaded titles and abstracts independently. Studies were eligible for inclusion if patients were diagnosed with IBD, in all disease stages, receiving any pharmacological treatment. Patients should undergo at least two IUS assessments during the study period and disease activity should be assessed by either clinical scores, biochemistry, faecal calprotectin [FC], endoscopy, other cross-sectional imaging, or a combination of the above. When published in peer-reviewed journals/presented at conferences, prospective and retrospective full-text articles and abstracts of international conferences were included. Titles and abstracts that met the eligibility criteria and studies with uncertain eligibility were included for full-text screening. The same two researchers independently reviewed these full-text studies to verify the in- and exclusion criteria. Reference lists from reviews and scoring studies were screened for eligibility before exclusion. Articles reporting on the performance of IUS scores were excluded since the performance of these scores has been evaluated elsewhere.<sup>7,12</sup> In case of disagreement of eligibility, a third researcher was consulted, and consensus through discussion was obtained. During the inclusion process, researchers were not blinded to journal titles, study authors, or institutions. If missing or incomplete data were crucial for the eligibility assessments, study authors were contacted [maximum one email attempt]. All included studies were extracted in accordance with the study protocol. A meta-analysis was not planned, given the expected heterogeneity among studies. The data underlying this article will be shared at reasonable request to the corresponding author.

### 2.3. Quality assessment

All included studies were independently assessed for risk of bias by at least two researchers, according to the QUADAS-2 tool.<sup>13</sup> Risk of bias was evaluated across four domains: patient selection, index test, reference standard, and flow and timing. Applicability concerns were evaluated across three domains: patient selection, index test, and reference standard. Any disagreements were first handled between two researchers. A third researcher was consulted if a consensus could not be reached.

### 2.4. RAND/UCLA process

An expert panel consisting of 18 international IUS experts, all active researchers within IBD and IUS, participated in the modified RAND/UCLA process.<sup>10</sup> Experts were selected from the International Bowel Ultrasound [IBUS] group's executive or scientific committees or close collaborators and active researchers within the topic of this review. There were 195 statements generated based on the evidence from the systematic review, along with additional general statements not covered by the literature search. The expert panellists were asked to individually score the appropriateness of each statement on a Likert scale from 1 [highly inappropriate] to 9 [highly appropriate]. An agreement was met when four or more panellists rated outside the 3-point region containing the median [1–3, 4–6, and 7–9] using the survey tool in REDCap.<sup>14,15</sup> Dependent on the area of expertise, experts did not vote on all statements [total vote count ranging from 14 to 18, see [Supplementary Material 2, available as Supplementary data at ECCO-JCC online](#)]. In particular, some statements on ulcerative colitis [UC] received fewer votes, which reflects the individual panel members' unwillingness to make a statement based on the low number and quality of published UC articles. Based on the first voting round, the panel met in June 2020 to discuss the voting results via an online videoconference, which led to rephrasing and adding statements for clarification, followed by the second round of individual online rating of 149 statements. A final online videoconference was held to clarify the remaining uncertainties and contradictions in November 2020. A closing voting round with 13 statements followed shortly thereafter.

## 3. Results

### 3.1. Systematic review

The first part of the systematic review [database inception to February 27, 2020] resulted in 5419 identified records; 25 articles, 13 abstracts, and one research letter passed the eligibility criteria [[Figure 1, white background](#)]. Corresponding authors for three additional articles and five abstracts were contacted for vital data; none rendered any response, and these articles/abstracts were consequently excluded. Only three Crohn's disease [CD] studies and one UC study report sample sizes over 100 patients. Six CD and three UC studies report sample sizes between 50 and 100, and 24 CD and five UC studies report sample sizes between 11 and 48 and 7 and 26, respectively [[Tables 1 and 2; and Supplementary Tables 2 and 3, available as Supplementary data at ECCO-JCC online](#)] [three studies examine both CD and UC]. The selected studies applied to the study questions. However, most studies had high risk of bias in at least one domain. The majority used an inaccurate reference standard, like clinical scores or biochemistry [[Figure 2](#)]. Endoscopy or radiological reference standards exhibited low risk of bias. There were 31/39 failing to report the time between IUS and reference standard. The index test [IUS] risk of bias was evenly distributed

between the low [12], high [11], or unclear [16] categories. A large proportion of unclear assessments came from the included abstracts, 48% [12/25] [[Supplementary Figure 1, available as Supplementary data at ECCO-JCC online](#)].

After the RAND/UCLA process, the additional search resulted in 407 new records, with six articles and three abstracts meeting eligibility criteria [[Supplementary Figure 1](#)]. Despite a high risk of bias, all studies applied to the study question [[Supplementary Figure 2, available as Supplementary data at ECCO-JCC online](#), with a light grey background, and [Supplementary Figure 3, available as Supplementary data at ECCO-JCC online](#)]. Total study populations ranged from 13 to 244. The new data provide a more complete and updated systematic review with more accurate comments on consensus results.

### 3.2. Rand/UCLA process

The results from the RAND/UCLA process [[Table 3](#)] are presented together with the results from the systematic review, most recent published data, and expert opinion. The RAND/UCLA statements during all three votes can be viewed in [Supplementary Material 2](#). Under inappropriate [InA], uncertain [Unc], and appropriate [App], the number of panellists voting as either 1–3, 4–6, or 7–9 is presented.

### 3.3. Statements for both Crohn's disease and ulcerative colitis

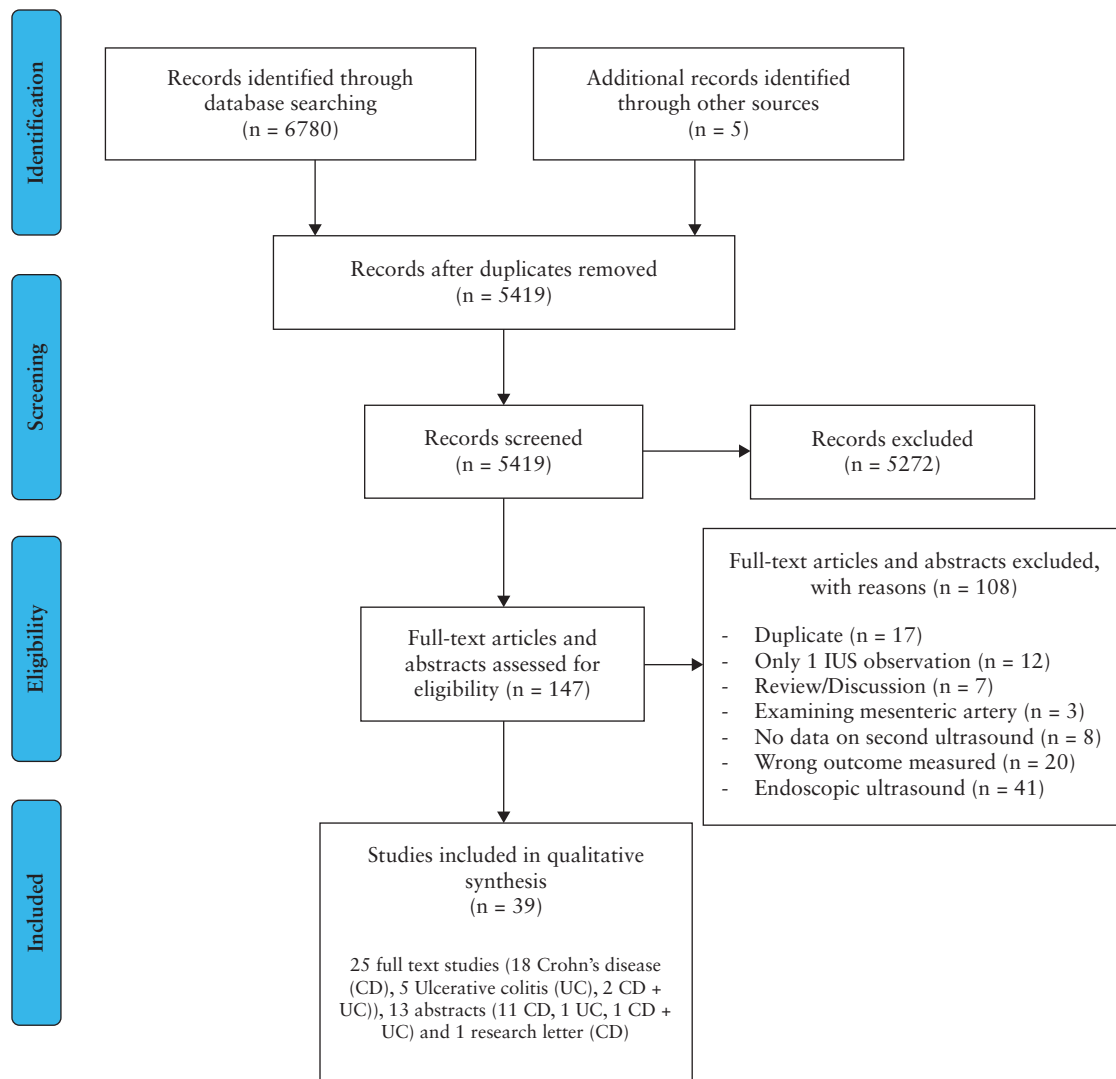
#### 3.3.1. Machine recommendations.

- 3.3.1.1. Treatment response can be assessed by intestinal ultrasound. [InA. 0, Unc. 0, App. 17]
- 3.3.1.2. Response should be assessed with:
  - 3.3.1.2.1. the same type of probe [high frequency vs abdominal probe]; [InA. 0, Unc. 2, App. 15]
  - 3.3.1.2.2. constant machine settings [Doppler scale, presets, etc.]. [InA. 1, Unc. 1, App. 15]

A mid- to high-frequency ultrasound probe, >5 MHz, gives higher resolution when imaging the intestine and should therefore be used when assessing inflammation, treatment response, and remission.<sup>49</sup> An abdominal probe may be useful to map out deeper pelvic structures or complications, but lower-frequency probes do not exhibit sufficient resolution for assessing mural inflammation.<sup>50</sup> Consistent machine settings using the same type of probe during all IUS examinations reduce confounding factors, ensuring that changes in IUS are attributable to alteration in pathophysiology rather than equipment/acquisition settings. Although consensus was not achieved, using the same machine during follow-up might be preferable, certainly when assessing colour Doppler signals [CDS] [[Supplementary Material 2; second round voting results, 1.2](#)].<sup>51</sup>

#### 3.3.2. Response rate.

- 3.3.2.1. Response rate detected by intestinal ultrasound is comparable with:
  - 3.3.2.1.1. rate of improvement in luminal inflammation, assessed by endoscopy; [InA. 0, Unc. 3, App. 14]
  - 3.3.2.1.2. rate of magnetic resonance enterography improvement. [InA. 0, Unc. 0, App. 17]



**Figure 1.** PRISMA flow diagram, summarising the study selection process and results, stop date February 27, 2020.

Therapeutic response rates in IBD are at least in part influenced by the individual therapeutic mechanisms of action, compared with placebo response and the severity and chronicity of disease. Response rates also vary depending on the measure, whether clinical, endoscopic, or a radiological modality. These factors make inter-modality comparisons challenging. Nevertheless, published data support IUS findings demonstrating response rates comparable to those seen on endoscopy and magnetic resonance enterography [MRE]. The largest CD IUS trial by Kucharzik *et al.* [ $n = 234$ ] showed that 75% of patients exhibited increased bowel wall thickness [BWT] in the terminal ileum and 47% in the sigmoid colon at baseline. After 12 months of therapy, the rates were reduced to 36% and 23%, respectively [ $n = 134$ ].<sup>20</sup> In UC, Maaser *et al.* [ $n = 224$ ] showed that 89% exhibited increased BWT in the sigmoid colon at baseline, followed by 38% at Week 12 [ $n = 178$ ].<sup>40</sup> Similar rates of improvement are reported for endoscopy by Bouguen *et al.*<sup>52</sup> and Vasudevan *et al.*<sup>53</sup> and for MRE by Ordás *et al.*<sup>54</sup> and Castiglione *et al.*<sup>19</sup>

- 3.3.2.2. Response rate in intestinal ultrasound is dependent on:
- 3.3.2.2.1. class of drug (5-aminosalicylate [5-ASA] vs. steroids vs. immunosuppressants vs. Biologics); [InA. 1, Unc. 3, App. 13]
- 3.3.2.2.2. disease duration [new-onset vs. long-term established disease]; [InA. 0, Unc. 2, App. 15]
- 3.3.2.2.3. histological composition of a pathological segment [active inflammation only vs. fibrotic only vs. combined].

Regardless of the reference standard, response rates in IBD are drug dependent.<sup>9</sup> IUS accurately reflects this during follow-up. No study specifically reports data on 5-ASA-treated patients, IUS demonstrates a rapid response to steroids. In CD patients, early changes are seen after 3–8 days, with an increasing likelihood of observed change after 4 weeks.<sup>22</sup> In UC, IUS response can be detected after

**Table 1.** Crohn's disease—full-text articles—adults.

Author	No. of patients	Treatment	Time point of assessment	Reference standard	IUS response/remission definition	BWT decrease or no. of patients without increased BWT	CDS decrease or no. of patients without increased CDS	IUS remission	IUS response/remission association with reference standard
Paredes 2019 <sup>16</sup>	33	Anti-TNF	Baseline, 12 weeks, 1 year	CDAI	Response: decrease in BWT >2 mm and CDS decrease by 1 grade. Remission: BWT ≤3 mm and CDS grade 0 or 1	Week 12: Median decrease 1.5 mm [24%]	Baseline: CDS 2 or 3: 28 [85%] Week 12: 11 [33%], <i>p</i> <0.001	Week 12: 7 [21%], 1 year: 14 [42%]	N/A
Paredes 2010 <sup>17</sup>	24	Anti-TNF	Baseline, 2 weeks after induction	CDAI	Response: BWT decrease >0.5 mm and CDS decrease by 1 grade. Remission: BWT ≤3 mm, CDS grade 0, no intraabdominal complications	Decrease in 11 [46%] patients. Responders [mean ± SD]: 1.2 ± 1.6 mm [19%]. Non-responders: 0.1 ± 0.2 mm, <i>p</i> = 0.01	Baseline: CDS 2 or 3: 17 [71%] 2 weeks after induction: 11 [46%] <i>p</i> <0.02. CDS decreased in 10 [42%]	BWT normalisation: 29%. CDS normalisation: 33%. Transmural complications: 50%	No decrease of BWT or CDS in patients without treatment response, <i>p</i> <0.05
Castiglione 2013 <sup>18</sup>	133	Anti-TNF or AZA/6-MP	Baseline, 2 years	CDAI, SES-CD, CRP	Response: N/A. Remission: BWT <3 mm	Mean decrease anti-TNF: 2.0 mm [33%], AZA/6-MP: 0.4 mm [6%]	N/A	Anti-TNF: 17/66 [25%] .AZA/6-MP: 3/67 [5%]	TR with ER: $\kappa$ = 0.63, <i>p</i> = 0.01. 2 TR cases were without ER. TR with CDAI: $\kappa$ = 0.27, <i>p</i> <0.01. TR with CRP: $\kappa$ = 0.79, <i>p</i> = 0.02
Castiglione 2017 <sup>19</sup>	40	Anti-TNF	Baseline, 2 years	CDAI, SES-CD, MRE	Response: N/A. Remission: BWT ≤3 mm	Mean decrease IUS: 2.2 mm [36%]. MRE: 2.7 mm [N/A]	N/A	10 [25%]; Type of anti-TNF did not determine a significant difference in TR outcome	IUS remission and ER $\kappa$ = 0.63, <i>p</i> <0.01. IUS remission and MRE remission $\kappa$ = 0.90; <i>p</i> <0.01. CRP and TR $\kappa$ = 0.27, <i>p</i> = <0.01. TR and CRP $\kappa$ = 0.79, <i>p</i> = 0.02

Table 1. Continued

Author	No. of patients	Treatment	Time point of assessment	Reference standard	IUS response/remission definition	BWT decrease or no. of patients without increased BWT	CDS decrease or no. of patients without increased CDS	IUS remission	IUS response/remission association with reference standard
Kucharzlik 2017 <sup>20</sup>	234	CS, anti-TNF, AZA/MTX, 5-ASA	Baseline, 3 months, 6 months, and 12 months	HBI	Abnormal BWT TI: >2 mm. Colon: >3 mm. Response: N/A. Remission: N/A	Sub-group 1 [all scans, N = 134]: abnormal BWT at baseline, 3, 6, and 12 months: TI: 75%, 57%, 44%, and 36%. Sigmoid: 47%, 22%, 27%, 23%. All with <i>p</i> -values <0.05. Sub-group 2 [baseline, 3 months, N = 182] TI normalisation: 107 [59%]. A 10% or 25% BWT reduction was found in 95% and 80% of patients, respectively	Sub-group 1: CDS 3 + 4. Baseline, 3, 6, and 12 months: 44%, 18%, 14%, and 10%, <i>p</i> <0.001	N/A	Sub-group 2: BWT reduction = HBI reduction in 86%. CDS change [3 + 4 = >1 + 2] correlated with CRP at Months 3 and 12 in both sub-groups. Sub-group 2: correlation between CRP and BWT [TI], Spearman = 0.46 and BWT and HBI [transverse colon], Spearman 0.42
Ripolles 2016 <sup>21</sup>	51	Anti-TNF Anti-TNF + AZA/MTX	Baseline, 12 weeks, 1 year, 2 years [clinical]	HBI, CRP	Response: decrease in BWT [ $\geq 2$ mm], CDS [ $\geq 1$ ], GEUS—mural enhancement [ $\geq 20\%$ ] and/or absence of complications. Remission: BWT $\leq 3$ mm, CDS = 0, no complications	12 weeks mean decrease: 1.2 mm [18%], <i>p</i> <0.05. 52 weeks: 1.5 mm [24%], <i>p</i> = NS	Baseline CDS 3–4: 43 [84%]. 12 weeks: 19 [37%] <i>p</i> = 0.0001. 52 weeks: 19 [37%] <i>p</i> = NS, 26 [51%] improved with normalisation in 7	N/A	N/A
Ripolles 2008 <sup>22</sup>	28	5-ASA or CS $\pm$ AZA	Baseline, 3–8 days, 4 weeks	CDAI, CRP	BWT >= 3 mm abnormal. Response: decrease in CDS [3 = >2 or 2 = >0/1, not from 1 = >0] and BWT [ $\geq 25\%$ decrease]. Sonographic active disease: CDS $\geq 2$ or BWT >5 mm	4 weeks mean decrease 0.8 mm [12%], <i>p</i> = NS	Baseline: grade 2–3 vascularity: 18/22 [82%]. CDAI >150 and 4/6 [67%]. CDAI <150 2nd examination: improvement	N/A	No correlation between clinical and sonographic changes between baseline, 2nd and 3rd examination



Table 1. Continued

Author	No. of patients	Treatment	Time point of assessment	Reference standard	IUS response/remission definition	BWT decrease or no. of patients without increased BWT	CDS decrease or no. of patients without increased CDS	IUS remission	IUS response/remission association with reference standard
Dubbins 1984 <sup>23</sup>	19	AZA/MTX	Baseline, 2–4 months	N/A	N/A	Mean decrease 6 mm [60%] 1-year recurrence: 2.5/2.5 [100%]. BWT median [range] 5 mm [3.5–10]. 3.5 mm in one patient with Rutgeerts' i0.	N/A	N/A	N/A
Onali 2010 <sup>24</sup>	25	5-ASA ± CS	1 year, 2 years, 3 years	CDAI, Rutgeerts' score, SBFT	CD recurrence: 1 [BWT >3 mm, 2] stiff loop = increased BWT, not distended by oral contrast. 3] small bowel dilation, diameter >2.5 cm	10. 2 years: 21/21 [100%]. 3 years: 15/15 [100%]. 3.5 mm in one patient with Rutgeerts' i0	N/A	N/A	N/A
Moreno 2014 <sup>25</sup>	30	Anti-TNF ± AZA/6-MP	Baseline, 14 months [range: 13–25 months]	CDEIS	Remission: BWT ≤3 mm, CDS = 0–1, and CEUS peak enhancement <46%	Mean decrease 3 mm [40%], $p = <0.05$	Baseline CDS 3–4: 27 [90%]. After treatment: 6 [20%], $p \leq 0.001$	Segmental assessment: 37/59 [64%]. Overall assessment: 15/30 [50%]	Segmental: association: TR vs. ER: $\kappa = 0.76$ ; $p < 0.001$ . BWT ≤3 mm predicts ER [93%]. Overall: TR vs. ER: $\kappa = 0.73$ , $p < 0.001$ BWT ≤3 mm predicts ER [96%] N/A
Orlando 2018 <sup>26</sup>	30	Anti-TNF	Baseline, 14 weeks, 52 weeks	Surgery is outcome	Remission: BWT ≤3 mm	Mean SD decrease 0.74 ± 1.2 mm [1.25 ± 1.95%], $p \leq 0.05$ . ADA vs. IFX = NS	BWT variations and TR were not influenced by CDS or BWS [ $p = NS$ ]	Week 14: 8 [27%]. Week 52: 9 [30%]	N/A
Socaciu 2015 <sup>27 A</sup>	13	N/A	Baseline, 12 weeks	CDAI	N/A	12 weeks decrease: 1.7 mm [2.5%]	N/A	N/A	Wilcoxon [ $z = 213$ , $p = 0.033$ ]. Spearman: $\rho = 0.65$ , $p = 0.015$

Table 1. Continued

Author	No. of patients	Treatment	Time point of assessment	Reference standard	IUS response/remission definition	BWT decrease or no. of patients with/without increased BWT	CDS decrease or no. of patients with/without increased CDS	IUS remission	IUS response/remission association with reference standard
Goertz 2018 <sup>28</sup> <sup>a</sup>	11	VED	Baseline, 2 weeks, 6 weeks, 14 weeks	HBI	N/A	5 responders: baseline: 5.3 ± 0.8 mm. Week 14: 5.3 ± 1.8 mm. 6 non-responders: baseline: 6.6 ± 0.6 mm. 14 weeks 6.1 ± 1.2 mm	5 responders: baseline: 2.4 ± 0.9. Week 14: 1.2 ± 0.8. 6 non-responders: baseline: 2.0 ± 0.6, 14 weeks 1.5 ± 0.8	N/A	N/A
Quaia 2019 <sup>29</sup>	115	Anti-TNF ± CS	Baseline, 6 to 18 weeks	CDAI, CDEIS	N/A	12 weeks decrease: response group: 3.0 mm [43%]. Non-response group: 1.0 mm [14%]	N/A	N/A	N/A
Saevik 2014 <sup>30</sup>	14	CS or anti-TNF	Baseline, 1 month, 3 months, 12 months	CDAI	BWT > 2 mm abnormal if lumen > 0.5 cm or abnormal if BWT > 3 mm + lumen < 0.5 cm	1-month decrease: 0.3 mm [5%]. 12 weeks: 0.01 mm [0.2%]. 1 year: 1.6 mm [34%]	N/A	N/A	N/A
Chen 2018 <sup>31</sup>	29	AZA + EEN	Baseline and when clinical parameters became normal	CDAI, SES-CD	Remission: ≤ 3 mm and normalisation of IUS parameters. <sup>b</sup> CDS 3/4: positive	Decrease 4.4 mm [47%], <i>p</i> < 0.05	Positive baseline: 90%. During follow-up: 17%, <i>p</i> < 0.05	5 [17%]	N/A
Hoffman 2019 <sup>32</sup>	57	UST	Baseline, 24 ± 6 weeks, 24–48 ± 6 weeks	HBI	Response: ≤ 3 mm	Baseline abnormal BWT: 19/22 [79%]. 24 ± 6 weeks, 8/13 steroid free clinical remission/ response vs. 5/13 non-response. 6/13 [46%] had BWT > 3 mm, <i>p</i> = 0.43. Weeks 24–48 ± 6: 6/13 in response /remission with improvement or no inflammation vs. 5/13 non-response, <i>p</i> = NS	N/A	N/A	N/A



Table 1. Continued

Author	No. of patients	Treatment	Time point of assessment	Reference standard	IUS response/remission definition	BWT decrease or no. of patients without increased BWT	CDS decrease or no. of patients without increased CDS	IUS remission	IUS response/remission association with reference standard
Zorzi 2019 <sup>33</sup>	80	Anti-TNF	Baseline, 18 months [median]	ER	BWT: >3 mm, abnormal. Improved lesions: [a] BWT improvement [≥1 mm] or normalisation TI <3 mm; colon <4 mm; [b] decreased length; [c] no worsening of other IUS parameters <sup>e</sup>	41 [51%] were classified as responders, 27 [34%] as partial responders, and 12 [15%] as non-responders. There was a significant relationship between ultrasonographic response and clinical outcomes considered	N/A	N/A	N/A
Calabrese 2021 <sup>34</sup>	188	ADA, IFX, UST, VED	Baseline, 3 months, 6 months, 12 months	HBI, CRP, FCP	Remission: ileum BWT ≤ 3 mm, colon BWT ≤ 4 mm and normalisation of other parameters <sup>d</sup>	Ileum: median decrease 3 months: 0.5 mm [8%]. 6 months: 1 mm [17%]. 12 months: 1 mm [17%], <i>p</i> <0.05. Colon: 3 months: 0.85 mm [14%]. 6 months: 1.45 mm [23%]. 12 months: 2.35 mm [37%], <i>p</i> <0.05	Ileum: baseline: 12.5/158 [79%] with increased CDS. 3 months: 89/158 [56%]. 6 months: 67/156 [43%]. 12 months: 52/133 [39%], <i>p</i> <0.05. Colon: baseline: 22/30 [73%]. 3 months: 14/30 [47%]. 6 months: 10/25 [40%]. 12 months: 9/23 [39%], <i>p</i> <0.05	3 months: 31/188 [16%]. 6 months: 42/171 [25%]. 12 months: 43/156 [28%] [ADA 27%, IFX 37%, VED 27%, UST 20%]	N/A
Hoffman 2020 <sup>35</sup>	23	UST	Baseline, 8 weeks	CDAI, CRP	Response: decrease of BWT ≥1.0 mm	10/23 [43%] responded	Baseline: 9 patients with Limberg 2.8 weeks: 4	N/A	Responders: substantial decrease in CDAI ≥70 points and CRP ≥0.5 mg/dl in 9/10 and 8/10, respectively

Table 1. Continued

Author	No. of patients	Treatment	Time point of assessment	Reference standard	IUS response/remission definition	BWT decrease or no. of patients without increased BWT	CDS decrease or no. of patients without increased CDS	IUS remission	IUS response/remission association with reference standard
Li Ma 2021 <sup>36</sup>	77	AZA/MTX ± Anti-TNF, 5-ASA	Baseline, 6 months	CDAI, CRP, SES-CD, CTE, MRE	Remission: BWT ≤ 3 mm and normalisation of other parameters <sup>a</sup>	N/A	N/A	6 months: 25/77 [32%]	TR and ER poorly correlated, $k = 0.387$ , $p < 0.05$ TR and CTE highly correlated, $k = 0.793$ , $p < 0.005$ N/A
Helwig 2021 <sup>37,1</sup>	180	AZA/MTX ± anti-TNF, anti-integrin, systemic CS	Baseline, 12 ± 4 weeks, 52 ± 4 weeks	HBI	Response: BWT reduction >2.5% or a normalisation of BWT. Remissions: three different definitions. 1) Normalisation of BWT [ileum ≤ 2 mm, sigmoid ≤ 4 mm, rest of colon ≤ 3 mm] and normalised CDS. 2) normalised BWT and CDS, restored BWS and no I-fat [minus one factor that could not be assessed]. 3) All factors normalised	N/A	N/A	12 weeks: No. of patients with response: 77/118 [65%]	Definition: 1: 58/180 [32%] <sup>2</sup> 67/180 [37%] <sup>3</sup> 43/180 [24%]
Jessen 2020 <sup>38,8</sup>	21 CD, 20 UC	IFX	Baseline, Week 6	HBI, partial Mayo score	N/A	N/A	Data not stratified by disease. Responders: median 1 CDS point decrease Non-responders: median 0 CDS points decrease	N/A	N/A

5-ASA, mesalazine; ADA, adalimumab; anti-TNF, infliximab and adalimumab; AZA, azathioprine; AZA/6-MP, azathioprine/mercaptopurine; AZA/MTX, azathioprine/methotrexate; BWS, bowel wall stratification; BWT, bowel wall thickness; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CDS, colour Doppler signal; CRP, C-reactive protein; CS, corticosteroids; CTE, computer tomography enterography; EEN, Total Protein Enterical Nutritional Powder; ER, endoscopic remission; FCP, faecal calprotectin; HBI, Harvey-Bradshaw Index; IFX, infliximab; IUS, intrasulcus ultrasound; MRE, magnetic resonance enterography; N/A, not available; NS, not significant; UST, ustekinumab; SBFT, small bowel follow-through; SD, standard deviation; SES-CD, Simple Endoscopic Score—Crohn's Disease; TI, terminal ileum; TR, transmural remission; UC, ulcerative colitis; VED, vedolizumab; CEUS, contrast-enhanced ultrasound.

<sup>a</sup>No colour Doppler signal, normal five-layer bowel wall stratification, no inflammatory fat, no lymph node enlargement, or presence of strictures or pre-stenotic dilation.

<sup>b</sup>No colour Doppler signal, normal bowel wall stratification, no pre-stenotic dilations, strictures, fistulae, inflammatory fat, abscesses, lymphadenopathy, or ascites.

<sup>c</sup>Or fistulising disease.

<sup>d</sup>Colour Doppler signals, length of disease, bowel wall stratification, inflammatory mesenteric fat, lymph nodes, stenosis, pre-stenotic dilation, abscess, fissures, and fistulae.

<sup>e</sup>Colour Doppler signals, bowel wall stratification, inflammatory mesenteric fat, abscesses, and fistulae.

<sup>f</sup>Report data on both Crohn's disease and ulcerative colitis, stratified by disease.

<sup>g</sup>Report data on both Crohn's disease and ulcerative colitis, not stratified by disease.

**Table 2.** Ulcerative colitis.

Author	Total no. patients	Treatment	Time of assessment	Reference standard	IUS response/remission definition	BWT decrease or no. of patients with/without increased BWT	CDS decrease or number of patients with/without increased CDS	IUS remission	IUS response/remission association with reference standard
Socaciu 2015 <sup>27b</sup>	25	N/A	Baseline, 3 months	Truelove-Witts	N/A	Median decrease 0.15 mm [3%]	N/A	N/A	Wilcoxon [Z = 0.85, p = NS], Spearman: [rho = 0.28, p = NS] N/A
Goertz 2018 <sup>8b</sup>	7	VEDO	Baseline, 2 weeks, 6 weeks, 14 weeks	Mayo score	N/A	Responders: N = 4, 10 mm [17%], Non-responders: N = 3, NS N/A	N/A	N/A	3 months: $\kappa = 0.76$ 9 months: $\kappa = 0.88$ 15 months: $\kappa = 0.9$ N/A
Parente 2010 <sup>39</sup>	74	CS	Baseline, 3 months, 9 months, 15 months	Baron endoscopic score	US severity [0–3] Grade 0 = BWT <4 mm, CDS 0–1 Grade 1 = BWT 4–6 mm, CDS ≥2 Grade 2 = BWT 6–8 mm, CDS ≥2 Grade 3 = BWT >8 mm, CDS ≥2		N/A	N/A	
Maaser 2019 <sup>40</sup>	224	CS, AZA/6-MP, Anti-TNF, Anti-integrin	Baseline, 2 weeks, 6 weeks, 12 weeks	SCCAI	Normal colon = sigmoid colon ≤4.0 mm, descending, transverse and ascending colon ≤3.0 mm	Increased BWT: sigmoid colon at baseline, 2, 6, and 12 weeks 89%, 39%, 35%, and 32% Descending colon at baseline, 2, 6, and 12 weeks 83%, 43%, 43%, and 38%	Improvements in CDS: sigmoid colon at baseline, 2, 6, and 12 weeks 35%, 23%, 16%, and 13%. Descending colon at baseline, 2, 6, and 12 weeks 15%, 7%, 5%, and 7%	N/A	N/A
Maconi 1999 <sup>41</sup>	30	CS ± 5-ASA ± salazopyrine	Baseline, 2 months	Truelove-Witts X-ray double-contrast barium enema	Abnormal BWT ≥4 mm	2 months: 16 [53%] improved. Decrease of 2.3 mm [31%]. 14 [47%] did not improve +0.7 mm, p = NS	N/A	N/A	N/A
Yoshida 2011 <sup>42</sup>	26	Cytapheresis ± CS + 5-ASA	Baseline, 2–3 weeks	UC-DAI score, at baseline and 12 months	Early ultrasonic response [EUR]; decrease in BWT by >2.5 mm	EUR in 11 [42%]	N/A	N/A	1-year relapse: 1 in EUR group, 9 in non-EUR group N/A
Hean 2019 <sup>43a</sup>	9	N/A	Baseline + 11 months [mean]	N/A	N/A	BWT improvement: sonographic remission 1.6 mm, p = 0.04. No sonographic remission 0.1 mm, p = NS	2 [22%]	N/A	N/A

Table 2. Continued

Author	Total no. patients	Treatment	Time of assessment	Reference standard	IUS response/remission definition	BWT decrease or no. of patients with/without increased BWT	CDS decrease or number of patients with/without increased CDS	IUS remission	IUS response/remission association with reference standard
Maaser 2019 <sup>44</sup>	65/224 [29%] from study nr 4	Anti-TNF	Baseline, 2 weeks, 6 weeks, 12 weeks	SCCAI, CRP, FCP	Abnormal BWT sigmoid colon, >4 mm, descending colon >3 mm	Week 6: 44 received anti-TNF21 [48%] normalised.15 [34%] decrease in BWT	Increased CDS at Weeks 6 and 12 had higher SCCAI than no CDS [ $p < 0.001$ ]	N/A	N/A
Arienti 1996 <sup>45</sup>	57	High doses of IV CS	Baseline, 10 days	Truelove-Witts	Normal BWT <3mm "ultrasonic activity index" = the sum of maximum BWT in all four segments [in mm]	IUS activity in the severe group. All: before treatment: 1.89 mm, after treatment 1.49 mm, $p = 0.001$ Non-operated: before 1.84 mm, after 1.27 mm, $p = < 0.001$ . Operated: before 1.97 mm, after 1.84, $p =$ NS IUS activity in the moderate group. All: before 1.02 mm, after 6.3 mm, $p < 0.001$ . Non-operated: before 9.9 mm, after 5.6 mm, $p < 0.001$ . Operated: before 1.20, after 1.10 $\pm$ 1.1, NS	N/A	N/A	In the 8/41 [19.5%] patients that underwent surgery 3 months later, none had an improvement in IUS parameters, some worsening 5/41 [12%] non-operated patients had no IUS response, with clinical parameters fully recovered
De Voogd 2021 <sup>46a</sup>	62	TOF	Baseline, 8 weeks	Endoscopic Mayo score, Robarts Histology Index	N/A	Endoscopic remission group: BWT sigmoid mean reduction, $2.59 \pm 1.44$ mm, descending colon, $1.82 \pm 1.01$ mm, $p = < 0.05$ . Endoscopic remission showed a cut-off value for BWT in sigmoid $\leq 2.87$ mm [AUROC: 0.91 [0.83–0.99], sensitivity 83% and specificity 100%] and for descending, $\leq 2.80$ mm [AUROC: 0.98 [0.94–1.00], sensitivity 91% and specificity 92%]	N/A	N/A	BWT and endoscopic Mayo score showed high correlation [rho 0.68 sigmoid colon, rho 0.75 descending colon, $p < 0.05$ ]. BWT and Robarts Histology Index moderate correlation [rho 0.49, $p < 0.05$ ]

Table 2. Continued

Author	Total no. patients	Treatment	Time of assessment	Reference standard	IUS response/remission definition	BWT decrease or no. of patients with/without increased BWT	CDS decrease or number of patients with/without increased CDS	IUS remission	IUS response/remission association with reference standard
Helwig 2021 <sup>37b</sup>	171	AZA/MTX ± Anti-TNF, Anti-integrin, systemic CS	Baseline, 12 ± 4 weeks	SCCAI	Response: BWT reduction >25% or a normalisation of BWT. Remission: three different definitions. 1] Normalisation of BWT [ileum ≤2 mm, sigmoid ≤4 mm, rest of colon ≤3 mm] and normalised CDS. 2] Normalised BWT and CDS, restored BWS and no I-fat [minus one factor that could not be assessed]. 3] All factors normalised	12 weeks: no. of patients with response: 100/131 [76%]	N/A	12 weeks: Definition 1] 90/171 [53%], 2] 105/171 [61%], 3] 77/171 [45%]	N/A
Jessen 2020 <sup>38c</sup>	21 CD, 20 UC	IFX	Baseline, Week 6	HBI, partial Mayo score	N/A	N/A	Data not stratified by disease. Responders: median 1 CDS Non-responders: median 0 CDS	N/A	N/A
Kucharzik 2020 <sup>37a,c</sup>	21 CD, 29 UC	Biologics, JAK2 inhibitor	Baseline, Week 12	HBI, SCCAI	Abnormal BWT: sigmoid colon >4 mm, rest of colon and ileum >3 mm	Data not stratified by disease. Pathological segments baseline: 121 [54.8%]. Week 12: 53 [24%], <i>p</i> <0.05	Data not stratified by disease. Baseline: 25 [50%] patients with increased CDS. Week 12: 7 [14%], <i>p</i> <0.05	N/A	N/A

Table 2. Continued

Author	Total no. patients	Treatment	Time of assessment	Reference standard	IUS response/remission definition	BWT decrease or no. of patients with/without increased BWT	CDS decrease or number of patients with/without increased CDS	IUS remission	IUS response/remission association with reference standard
Maaser 2020 <sup>8a</sup>	244	N/A	Baseline, Week 12	Stool frequency and rectal bleeding	Abnormal BWT: sigmoid colon >4 mm	N/A	N/A	N/A	Rectal bleeding correlation with abnormal BWT: $r = 0.417$ . Stool frequency correlation with abnormal BWT: $r = 0.483$ . The two combined: $r = 0.518$

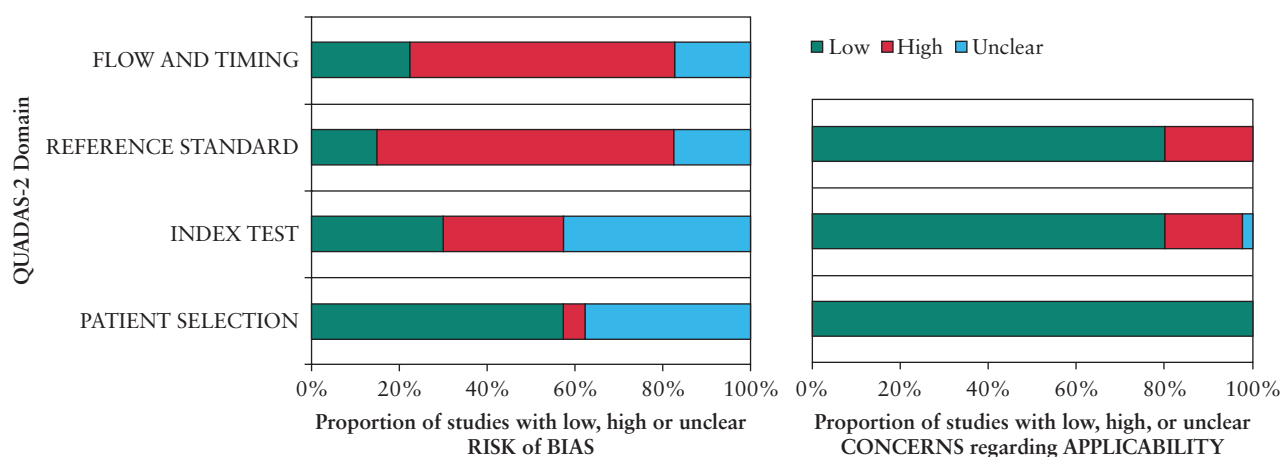
Anti-TNF; infliximab, adalimumab, or golimumab; AZA/6-MP, azathioprine/mercaptopurine; AZA/MTX, azathioprine/methotrexate; biologics, no data on which biologics; BWT, bowel wall thickness; CDS, colour Doppler signal; CRP, C-reactive protein; CS, corticosteroids; FCP, faecal calprotectin; IFX, infliximab; N/A, not available; SCCAI, Simple Clinical Colitis Activity Index; TOF, tofacitinib; UC, ulcerative colitis; UC-DAI, Ulcerative Colitis Disease Activity Index; VEDO, vedolizumab; IUS, intestinal ultrasound; IV, intravenous; CD, Crohn's disease; HBI, Harvey-Bradshaw Index; AUROC, area under receiver operating characteristic curve.

<sup>a</sup>Abstract.

<sup>b</sup>Report data on both Crohn's disease and ulcerative colitis, stratified by disease.

<sup>c</sup>Report data on both Crohn's disease and ulcerative colitis, not stratified by disease.





**Figure 2.** Risk of bias and applicability—studies from the systematic review, stop date February 27, 2020.

10–14 days,<sup>40,45</sup> possibly even earlier.<sup>55</sup> Such rapid rates of improvement have not been reported for biologics or immunomodulators. Two years after treatment initiation with either anti-tumour necrosis factor [TNF] or azathioprine, Castiglione *et al.* showed a significant difference in transmural remission [TR] rates by 25% [17/66] vs. 4% [3/67], respectively.<sup>18</sup> In addition, a pediatric [ $n = 28$ ]<sup>56</sup> and an adult study [ $n = 234$ ],<sup>20</sup> showed no difference in changes of IUS parameters between patients treated with anti-TNF as monotherapy or in combination with azathioprine, 6 and 12 months after treatment initiation, respectively.

In CD patients, a shorter disease duration [ $11 \pm 8$  vs.  $19 \pm 9$  months,  $p = 0.01$ ] is associated with better IUS and endoscopic responses after 2 years of maintenance treatment with biologics or thiopurines.<sup>18</sup> After 3 months of variable treatment, a divergence of treatment effect can be seen; 41% [ $n = 16$ ] with disease duration <2 years exhibited improvement, compared with 20% [ $n = 10$ ] with a disease duration >5 years,  $p < 0.001$ .<sup>20</sup> After 12 months [ $n = 188$ ], the only predictor for higher risk of unchanged/worsened disease was a longer disease duration,  $p = 0.02$  (odds ratio [OR] 3.0, [1.2–7.9]).<sup>34</sup>

Strictures and/or fistulae prognosticate inadequate treatment response, with reported data showing inconsistent results. After 12 weeks of anti-TNF treatment, 33% [3/9] with baseline stenosis or fistulae responded to treatment.<sup>16</sup> After 2 years, 17% [1/6] with stenosis responded.<sup>19</sup> Other studies found no response after 12 and 14 months, respectively [0/5,<sup>21</sup> 0/3<sup>25</sup>]. The presence of stenosis before biologic treatment was associated with worse IUS response after 12 weeks,  $p < 0.001$ .<sup>21</sup> These rates are much lower than uncomplicated luminal inflammation. Taken together, differences in IUS responses are more likely explained by patient phenotype, disease course, and treatment efficacy than by IUS-specific factors.

3.3.2.3. Response time is generally shorter in ulcerative colitis compared with Crohn's disease. [InA. 0, Unc. 1, App. 16]

3.3.2.4. In responders, colonic disease tends to respond faster with respect to reduced bowel wall thickness than small bowel disease. [InA. 0, Unc. 2, App. 15]

follow-up. Thus, our statements are based on limited evidence. Kucharzik *et al.* [ $n = 234$ , variable treatment] showed normalisation of BWT in the colon within 3 months, with only minor improvement thereafter. For terminal ileum, the proportion of patients with normalisation of BWT increased steadily throughout the 12-month follow-up period.<sup>20</sup> These findings were similar to the STARDUST sub-study [ $n = 76$ , ustekinumab], with IUS response for colon and terminal ileum at 40% and 30%, respectively, at Week 16,<sup>57</sup> with a continued difference at Week 48, 63% vs. 40%.<sup>58</sup> A significant reduction of BWT was already observed at Week 4.<sup>57</sup> Early initial response was also documented in a paediatric population with a significant reduction of BWT, CDS, and length of disease 2 weeks after initiation with infliximab [IFX].<sup>56</sup> In adults with UC, a significant and clinically relevant proportion of patients showed normalisation of BWT after only 2 weeks of treatment.<sup>40</sup> Given the anatomical location of disease and the fact that CD is a transmural disease whereas UC is not, response may occur faster in UC than in CD. This claim is further supported by many of the co-authors' clinical observations.

3.3.2.5. Response rate, in general, is different for:  
 3.3.2.5.1. strictures than luminal disease; [InA. 0, Unc. 2, App. 15]  
 3.3.2.5.2. phlegmons than luminal disease; [InA. 0, Unc. 3, App. 14]  
 3.3.2.5.3. abscesses than luminal disease. [InA. 0, Unc. 2, App. 15]

Treatment responsiveness is related to the reversibility of the disease process. In a mixed cohort of patients with inflammatory and stricturing CD, treated with anti-TNF as monotherapy or in combination with azathioprine for 12 weeks, all 33 patients with inflammatory disease responded as determined by reducing BWT, compared with only 6/9 with stricturing disease.<sup>16</sup> After 2 years of treatment, only 17% [1/6] with stricturing disease achieved TR, compared with 23% [9/40] with inflammatory luminal disease.<sup>19</sup> Similarly, Ripollés *et al.* report an IUS response/remission for 56% [29/51] after 1 year, with no improvement documented in the six patients with stricturing disease. Strictureing behaviour was the only sonographic feature associated with a negative predictive value for response [ $p = 0.0001$ ].<sup>21</sup> The same tendency was reported by Moreno *et al.*, with three colonic strictures at baseline turning into four after a median duration of 14 months, whereas a significant luminal improvement in other

Most studies report cross-sectional data on disease location and distribution at baseline but do not report stratified measures during

**Table 3.** RAND/UCLA process results.

3.3. Statements for both Crohn's disease and ulcerative colitis	InA	Unc	App	Total
3.3.1. Machine recommendations				
3.3.1.1. Treatment response can be assessed by intestinal ultrasound	0	0	17	17
3.3.1.2. Response should be assessed with:				
3.3.1.2.1. - the same type of probe [high-frequency vs. abdominal probe]	0	2	15	17
3.3.1.2.2. - constant machine settings [Doppler scale, preset, etc.]	1	1	15	17
3.3.2. Response rate				
3.3.2.1. Response rate detected by intestinal ultrasound is comparable with:				
3.3.2.1.1. - rate of improvement in luminal inflammation, assessed by endoscopy	0	3	14	17
3.3.2.1.2. - rate of magnetic resonance enterography improvement	0	0	17	17
3.3.2.2. Response rate in intestinal ultrasound is depending on:				
3.3.2.2.1. - class of drug [mesalazine vs. steroids vs. immunosuppressants vs. biologics]	1	3	13	17
3.3.2.2.2. - disease duration [new onset vs. long-term established disease]	0	2	15	17
3.3.2.2.3. - histological composition of pathological segment [active inflammation only vs. fibrotic only vs. combined]	0	1	16	17
3.3.2.3. Response time is generally shorter in ulcerative colitis compared with Crohn's disease	0	1	16	17
3.3.2.4. In responders, colonic disease tends to respond faster with respect to bowel wall thickness than small bowel disease	0	2	15	17
3.3.2.5. Response rate in general is different for:				
3.3.2.5.1. - strictures than luminal disease	0	2	15	17
3.3.2.5.2. - phlegmons than luminal disease	0	3	14	17
3.3.2.5.3. - abscesses than luminal disease	0	2	15	17
3.3.3. Length of disease				
3.3.3.1. Length in both Crohn's disease and ulcerative colitis should be reported using involved colonic segment[s] [sigmoid colon, descending colon, transverse colon, ascending colon, caecum]	0	0	18	18
3.3.3.2. For terminal ileum, length should be reported as distance in cm and distance from ileocaecal valve [if possible] or as proximal small bowel	0	0	18	18
3.3.4. Measuring bowel wall thickness				
3.3.4.1. Response depends on baseline thickness and should be reported in:				
3.3.4.2. - absolute [mm] and relative [%] change from baseline	2	1	14	17
3.3.4.3. - continuous measurements and is preferred over categories	0	1	15	16
3.3.4.4. - continuous measurements and should be measured with one decimal for increased precision	0	1	16	17
3.3.4.5. - continuous measurements, as a mean of two measures in cross-section and two measures in longitudinal orientation	1	1	15	17
3.3.5. Defining the worst segment				
3.3.5.1. The worst segment in both Crohn's disease and ulcerative colitis is defined by the most pathological bowel wall thickness; however, if two segments have the same bowel wall thickness, the order of secondary parameters for defining the worst segment should be the grading of colour Doppler signals, bowel wall stratification, and then inflammatory mesenteric fat, respectively	0	1	17	18
3.3.6. Disease activity indices				
3.3.6.1. If a score is used, the score should summarise measures of all individual segments	0	3	14	17
3.3.6.2. Treatment response could be a combined change in one or more activity parameters, specified as a point-reduction from an activity score [present or in the future], bowel wall thickness [continuous], and/or colour Doppler signals [ordinal], and/or bowel wall stratification [ordinal], and/or inflammatory mesenteric fat [ordinal] [IBUS-SAS]	0	3	14	17

**Table 3. Continued**

<b>3.4. Crohn's disease</b>					
Response definition and timing of assessment in Crohn's disease					
3.4.1.	Treatment response is identified by reduction of bowel wall thickness [continues measurements] $>25\%$ or $>2.0$ mm or $>1.0$ mm and one colour Doppler signal reduction]	0	3	15	18
3.4.1.1.	Intestinal ultrasound complications that should be assessed for response:				
3.4.1.2.	- strictures	0	2	15	17
3.4.1.2.1.	- phlegmons	0	3	14	17
3.4.1.2.2.	- abscesses	1	3	13	17
3.4.1.2.3.	Response should initially be assessed in the small and large bowel after treatment initiation [regardless of treatment] at $14 \pm 2$ weeks. However, in a subset of patients, response after steroids or biologics may occur already after 4 weeks. Early intestinal ultrasound assessment may in certain situations be beneficial between Weeks 4 and 8	0	0	17	17
3.4.1.3.	Ideal assessment of intestinal ultrasound response within first year of treatment initiation/escalation/change is at baseline, Week $14 \pm 2$ , and between Weeks 26 and 52 + IUS depending on elevated faecal calprotectin or symptoms or clinical suspicion of flare	1	1	15	17
3.4.1.4.	Transmural remission, definition and timing of assessment in Crohn's disease				
3.4.2.	Transmural remission of terminal ileum, small and large bowel is defined by bowel wall thickness $\leq 3$ mm and normal/0 colour Doppler signal	0	1	17	18
3.4.2.1.	In some patients, sigmoid colon may contain an enlarged muscularis propria [outer hypochoic layer—typical in diverticular disease], allowing for bowel wall thickness up to 4 mm without resembling active inflammation	3	1	13	17
3.4.2.2.	Transmural remission should be assessed after treatment initiation [regardless of treatment] between 26 and 52 weeks.	0	3	14	17
3.4.2.3.	Transmural remission may occur already at Week 12 but with increasing likelihood up to 1 [maybe 2] years	0	0	17	17
3.4.2.4.					
<b>3.5 Ulcerative colitis</b>					
Response definition and timing of assessment in ulcerative colitis					
3.5.1.	Treatment response in ulcerative colitis is identified by reduction of bowel wall thickness [continuous measurements] $>25\%$ or $>2.0$ mm or $>1.0$ mm and one colour Doppler signal reduction]	0	3	15	18
3.5.1.1.	Ideal assessment of intestinal ultrasound response within first year of treatment initiation/escalation/change is at baseline, Week $14 \pm 2$ , and between Weeks 26 and 52 + intestinal ultrasound depending on elevated faecal calprotectin or symptoms or clinical suspicion of flare	0	2	14	16
3.5.1.2.	After treatment initiation, response should be measured in all segments that were affected at baseline	0	0	14	14
3.5.1.3.	Transmural remission, definition, and timing of assessment in ulcerative colitis				
3.5.2.	Transmural remission in ulcerative colitis of the large bowel is defined by bowel wall thickness $\leq 3$ mm and normal/0 colour Doppler signal	0	1	17	18
3.5.2.1.	In some patients, sigmoid colon may contain an enlarged muscularis propria [outer hypochoic layer—typical in diverticular disease], allowing for bowel wall thickness up to 4 mm without resembling active inflammation	3	1	13	17
3.5.2.2.	Transmural remission in ulcerative colitis should be assessed after treatment initiation [regardless of treatment] at Week $14 \pm 2$ .	0	2	16	18
3.5.2.3.	Transmural remission in ulcerative colitis may occur already at Week 4 but with increasing likelihood up to Week 12 [potentially 1 year]	1	3	14	18
3.5.2.4.					
<b>3.6. Adults vs. paediatric population</b>					
3.6.1.	The remission/response statements for Crohn's disease, may be used in both adult and paediatric populations	2	1	14	17
3.6.2.	The remission/response statements for ulcerative colitis, may be used in both adult and paediatric populations Under inappropriate [InA], uncertain [Unc], and appropriate [App], the number of panellists voting as either 1–3, 4–6, or 7–9 is presented.	2	2	12	16

IBUS-SVAS, International Bowel Ultrasound Segmental Activity Score; IUS, intestinal ultrasound.

segments/patients was observed.<sup>25</sup> In a paediatric study by Civitelli *et al.*, 4/32 had stricturing disease at baseline with no significant improvement after 9–12 months.<sup>59</sup> In the large TRUST CD trial [ $n = 134$ ], the presence of strictures at baseline was 25%, followed by 12% [ $p = 0.03$ ], 10% [ $p = 0.001$ ], and 9% [ $p \leq 0.001$ ], at 3, 6, and 12 months respectively. The presence was 5% for abscesses, followed by 2%, 1.5%, and 0.7%, respectively, non-significant [NS]. Both BWT and CDS had higher improvement rates compared with these complications.<sup>20</sup> No study report data on phlegmons. In the RAND/UCLA process, only one study specifically reported on fistula healing response with a transabdominal approach.<sup>31</sup> Consequently, statements regarding fistulae were not included in the RAND/UCLA process. Moreno *et al.* [ $n = 46$ , entero-mesenteric in 70%] recently published a retrospective study, showing that a complete closure of fistulae was achieved in 24/46 [52%] after immunosuppressive treatment, suggesting that IUS could be efficient in monitoring fistulae.<sup>60</sup> However, high-quality studies focusing on strictures, fistulae, phlegmons, and abscesses are warranted.

### 3.3.3. Length of disease

3.3.3.1. Length in both Crohn's disease and ulcerative colitis should be reported using involved colonic segment[s] [sigmoid colon, descending colon, transverse colon, ascending colon, cecum]. [InA. 0, Unc. 0, App. 18]

3.3.3.2. For the terminal ileum, the length should be reported as distance in cm and distance from the ileocaecal valve [if possible] or as proximal small bowel. [InA. 0, Unc. 0, App. 18]

Length of disease is rarely reported in prospective observational trials and almost never included in their IUS response/remission definition. If reported, studies use the extension of disease in centimetres and/or affected bowel segment.<sup>30</sup> Castiglione *et al.* [ $n = 40$  CD patients] showed that small bowel length decreased from  $35 \pm 18$  cm at baseline to  $20 \pm 11$  cm after 2 years of treatment with anti-TNF,  $p \leq 0.01$ . Corresponding data for MRE were  $45 \pm 15$  cm to  $18 \pm 12$  cm,  $p < 0.001$ .<sup>19</sup> Calabrese *et al.* [ $n = 188$  CD patients] showed a decrease of median length [range] of ileal disease from 15 [4–60] cm at baseline, to 10 [0–60] cm after 3 months, 10 [0–60] cm after 6 months, and 10 [0–50] cm after 12 months of treatment with biologics,  $p < 0.05$ . Corresponding values for colonic disease were 40 [20–100] cm, 30 [0–100] cm, 20 [0–100] cm, and 10 [0–100] cm, respectively,  $p < 0.05$ .<sup>34</sup> Three pediatric CD studies used similar ways of reporting extension. After treatment with anti-TNF  $\pm$  immunomodulators, IUS length decreased from  $13 \pm 5$  cm to  $8 \pm 6$  cm after 9–12 months [ $n = 32$ ]<sup>59</sup> and from  $12 \pm 5$  cm to  $9 \pm 5$  cm [2 weeks],  $8 \pm 7$  cm [4 weeks],  $4 \pm 4$  cm [13 weeks], and  $5 \pm 6$  cm [26 weeks],  $p < 0.0001$  [ $n = 28$ ].<sup>56</sup> Only in patients with endoscopic response did the extension decrease significantly.<sup>59</sup> Similar data were reproduced in an abstract [ $n = 13$  children, CD] exhibiting a decrease from  $11.3 \pm 1.4$  cm to  $6.8 \pm 3.8$  cm, 14 weeks after treatment initiation.<sup>61</sup>

Another way of reporting the extent of disease is the number of affected segments before and after treatment. In CD patients, 59 segments containing ulcers were evaluated with IUS and endoscopy after a mean treatment period of 14 months with anti-TNF and/or immunomodulators. Endoscopy showed remission in 42 segments and IUS showed remission

in 37,  $\kappa = 0.76$ ,  $p = 0.001$ . Endoscopy identified 77 affected segments at baseline, and IUS identified 75. During follow-up, the numbers were reduced to 43 and 29, respectively,  $p < 0.001$ .<sup>25</sup> In UC, using X-ray double-contrast barium enema as the reference standard, IUS correctly defined the extension of UC in 74% of patients, 9/11 with left-sided, 4/7 with subtotal, and 7/9 with pancolitis.<sup>41</sup> Further, the two largest studies on UC and CD report their data based on segmental involvement, which gives a good overview of the treatment response and/or remission for different segments and thereby the burden of disease over time.<sup>20,40</sup>

### 3.3.4. Measuring bowel wall thickness

3.3.4.1. Response depends on baseline thickness and should be reported in:

3.3.4.1.1. absolute [mm] and relative [%] change from baseline; [InA. 2, Unc. 1, App. 14]

3.3.4.1.2. continuous measurements, preferred over categories; [InA. 0, Unc. 1, App. 15]

3.3.4.1.3. continuous measurements within 1 decimal for increased precision; [InA. 0, Unc. 1, App. 16]

3.3.4.1.4. continuous measurements, as a mean of two measures in cross-section and two measures in longitudinal orientation. [InA. 1, Unc. 1, App. 15]

The exact method for measuring BWT, number of measures, and values are rarely described in observational studies. A standard mode of measurement has recently been suggested by European Federation of Societies for Ultrasound in Medicine and Biology [EFSUMB] and IUS experts.<sup>6,62</sup> The latter suggest using continuous numbers with one decimal and a mean of two measures in cross-section and two in longitudinal to avoid any limitation of measuring in one scan plane. This allows for high reliability with an intraclass correlation coefficient [ICC] of 0.96 by 12 readers.<sup>62</sup> Further, a reduction as low as  $>0.5$  mm has been reported for 11/17 with a partial clinical response or remission (based on Crohn's Disease Activity Index [CDAI] without BWT decline in non-responders,  $p = 0.001$ ).<sup>17</sup> Uncertainty between 0.5 and 1.0 mm may be allowed, and accuracy of mean measurements down to 0.1 mm can be important when assessing minor changes over time. When using BWT to assess treatment response/remission over time, both an absolute and a relative change from baseline should be reported. If only one of the latter is used, different conclusions might be drawn. Categorisation of BWT has been used in several scores and may be combined with other IUS variables.<sup>63,64</sup> Categorising BWT as a standalone into grades of severity is not sufficient to categorise disease activity and is not recommended. For example, if BWT severity class is defined as 3–5 mm, a reduction of 1 mm might result in different activity category, depending on a baseline value of 4.5 mm or 5.5 mm.

### 3.3.5. Defining the worst segment

3.3.5.1. The worst segment in both Crohn's disease and ulcerative colitis is defined by the most pathological bowel wall thickness; however, if two segments have the same bowel wall thickness, the order of secondary parameters for defining the worst segment should be the grading of colour Doppler signals, bowel wall stratification, and then inflammatory mesenteric fat, respectively. [InA. 0, Unc. 1, App. 17]

BWT is the most widely used, reported, and reliable IUS parameter [ICC = 0.96] in clinical observational trials, closely followed by CDS [ $\kappa = 0.6$ ].<sup>7,12</sup> Increased BWT alone or combined with increased CDS suggests more severe disease.<sup>12,22</sup> Although less reliable,<sup>62</sup> loss of bowel wall stratification [BWS] is associated with ulcers,<sup>65</sup> and inflammatory fat [I-fat] has been shown to be present in endoscopically active disease only.<sup>66</sup> Combined with our clinical experience, we suggest that BWS and I-fat can be used as contributory parameters when assessing the worst segment.<sup>7,12</sup> However, since the interrater reliability of IUS parameters assessed by 12 IUS experts in CD patients was low to moderate for BWS and I-fat,  $\kappa = 0.39$  and  $\kappa = 0.51$ , respectively, assessment of these parameters should be carefully considered in combination with more reliable parameters.<sup>62</sup> In UC, the interrater reliability between two experts was 0.92 for BWT and 0.60–0.79 for CDS [depending on disease location]. No data are reported for I-fat or BWS.<sup>67</sup> In addition, De Voogd *et al.* showed 30 cine-loop cases to six IUS experts, resulting in an ICC of 0.96 for BWT,  $\kappa = 0.63$  for CDS,  $\kappa = 0.36$  for I-fat, and  $\kappa = 0.24$  for BWS,<sup>68</sup> further confirming the high interrater variability between I-fat and BWS.

### 3.3.6. Disease activity indices

- 3.3.6.1. If a score is used, the score should summarise measures of all individual segments. [InA. 0, Unc. 3, App. 14]
- 3.3.6.2. Treatment response could be a combined change in one or more activity parameters, specified as a point reduction from an activity score [present or in the future], bowel wall thickness [continuous] and/or colour Doppler signals [ordinal], and/or bowel wall stratification [ordinal] and/or inflammatory mesenteric fat [ordinal]. [InA. 0, Unc. 3, App. 14]

Empirically, IUS response and remission rates for both CD and UC are prone to considerable variation between patients and can occur segmentally. We therefore recommend measurements from all segments to be included in a future responsive score for the assessment of treatment response. Further, a future validated score should focus on responsiveness and define levels for response and remission, like the validated Maria and simple Maria scores for MRE.<sup>54,69</sup> Most of the current scores that use BWT, CDS, BWS, and I-fat generally correlate well with their respective reference standard. However, two recent systematic reviews both conclude that no current published score is validated.<sup>7,12</sup> After the RAND/UCLA process, several new scores have been published, using different combinations of BWT, CDS, BWS, I-fat, clinical symptoms, contrast IUS, and elastography.<sup>62,64,66,67,70–75</sup> Interestingly, Saevik *et al.* used only BWT and CDS in their score, excluding BWS and I-fat due to poor interobserver agreement.<sup>64</sup> In our opinion, no score using continuous measures of BWT is sufficiently validated for responsiveness, and future extensive validation studies are warranted before any specific score can be recommended.

## 3.4. Crohn's disease

### 3.4.1. Response definition and timing of assessment in Crohn's disease

- 3.4.1.1. Treatment response is identified by reduction of bowel wall thickness [continuous measurements] [ $>25\%$ ] or [ $>2.0$  mm] or [ $>1.0$  mm and one colour Doppler signal reduction]. [InA. 0, Unc. 3, App. 15]
- 3.4.1.2. Intestinal ultrasound complications that should be assessed for response:
- 3.4.1.2.1. strictures; [InA. 0, Unc. 2, App. 15]
- 3.4.1.2.2. phlegmons; [InA. 0, Unc. 3, App. 14]
- 3.4.1.2.3. Abscesses. [InA. 1, Unc. 3, App. 13]
- 3.4.1.3. Response should initially be assessed in the small and large bowel after treatment initiation [regardless of treatment] at  $14 \pm 2$  weeks. However, in a subset of patients, response after steroids or biologics may occur already after 4 weeks. Early intestinal ultrasound assessment may, in certain situations, be beneficial between weeks 4 and 8. [InA. 0, Unc. 0, App. 17]
- 3.4.1.4. Ideal assessment of intestinal ultrasound response within the first year of treatment initiation/escalation/change is at baseline, week  $14 \pm 2$ , AND between week 26–52 + IUS depending on elevated f-Calprotectin OR symptoms OR clinical suspicion of flare. [InA. 1, Unc. 1, App. 15].

Different prospective definitions of IUS treatment response have been proposed in the literature, primarily using BWT alone or in combination with CDS [Table 2, Supplementary Table 2 and 3].<sup>16,17,20–22,32</sup> Few of these definitions are correlated with clinical outcomes.<sup>21,22,34,37</sup> Although not part of the response definition, both strictures, phlegmons, and abscesses should be reported when assessing response, especially if interested in disease prognosis. These complications are identified utilizing the recommendations from the EFSUMB group.<sup>5</sup>

#### 3.4.1.5. Bowel wall thickness

After 2 weeks of variable treatment, absolute and relative reductions in BWT of 0.6–0.9 mm [11–16%] have been reported.<sup>56,61</sup> After 4 weeks the BWT was reduced to 0.3–1.3 mm, [5–23%],<sup>22,30,56</sup> after 12 weeks to 0.01–3.0 mm [0.2–43%],<sup>16,17,21,27,29,30,34,56,76</sup> after 6 months to 1.0–1.9 mm [17–34%],<sup>34,56,76</sup> after 1 year to 1.4–2.35 mm [22–34%],<sup>21,30,34,77</sup> and after 2 years to 2.0–2.2 mm [33–36%].<sup>18,19</sup> Only one study investigated azathioprine monotherapy and found a non-significant reduction of 0.4 mm [6%] after 2 years.<sup>18</sup> Unfortunately, in most of these studies, responders and non-responders were reported together. Consequently, a group treatment effect is seen rather than an isolated effect reflecting endoscopic response. Data heterogeneity may indeed reflect diversity in reporting and patient populations among studies. Both absolute and relative reductions were increased when only focusing on treatment responders [defined by clinical scores].



After 4 weeks of any treatment, BWT decreased by 2.2 mm as opposed to 0.9 mm in the non-response group,  $p < 0.05$ .<sup>78</sup> After 6–18 weeks, BWT decreased by 3.0 mm [43%] as opposed to 1.0 mm [14%],  $p =$  not available [N/A].<sup>29</sup> After 12 weeks, BWT decreased by 1.5 mm [24%]<sup>16</sup> and 1.2 mm [19%] as opposed to 0.1 mm,  $p = 0.01$ , in the non-response group.<sup>17</sup> A median reduction of 1.7 mm in 13 patients after 3 months of treatment, compared with a reduction in Simple Endoscopic Score in CD [SES-CD], showed  $\rho = 0.65$ ,  $p = 0.015$ .<sup>27</sup>

#### 3.4.1.6. Colour Doppler signal

Most studies apply the original or a modified version of the ordinal Limberg score [0–4]<sup>79</sup> and report the number of patients with stable or declined CDS at each time point. CDS response is usually accompanied by a reduction of BWT between 0.5 to 2.0 mm or by 25% in prospective response definitions [see Tables 1 and 2; and Supplementary Tables 2 and 3]. It is therefore difficult to assess the impact of a CDS reduction alone on clinical outcomes. Only two studies investigated this specifically. Ripolles *et al.* showed that 17/28 treated with 5-ASA, or with corticosteroids as monotherapy or combined with azathioprine, experienced relapse or needed surgery during follow-up. At Week 4, 76% had an increased CDS compared with 18% in the non-relapse group,  $p < 0.01$ .<sup>22</sup> A mean reduction of 2.7 CDS points was reported in those achieving long-term remission [1-year follow-up] compared with 1.2 points in non-responders,  $p = 0.014$ .<sup>80</sup> Therefore, a sole reduction of one CDS point without subsequent reduction in BWT is likely insufficient to predict good long-term outcomes. Increased CDS is not always detected at baseline, even with an increase in BWT. In general, one can expect that between 39% and 80% have an elevated baseline CDS [Limberg  $\geq 2$ ].<sup>16,17,20,22,25,59,81,82</sup> Ripolles *et al.* found an early improvement in CDS after 3–8 days of treatment in 23%, followed by 32% with normalised CDS after 4 weeks.<sup>22</sup>

In conclusion, based on this evidence, a reduction in BWT of  $>25\%$  or  $>2.0$  mm or  $>1.0$  mm with one CDS grade reduction] seems to be accurate when defining treatment response.

#### 3.4.1.7. Timing of response assessment

Kucharzik *et al.* [ $n = 182$ ] observed a 10% or 25% reduction of BWT in 95% and 80% of patients after 3 months, respectively. Like BWT, a reduction of CDS mainly occurs within the first 3 months. However, continuous improvement is seen for ileal disease as previously outlined.<sup>20</sup> Ripolles *et al.* showed that 22/26 patients with a prospectively defined sonographic improvement [BWT normalisation or decrease of  $\geq 2$  mm with a decrease of one CDS grade] after 12 weeks continued with further improvement at 52 weeks; data were not stratified for type of segment. Further, the response at 12 weeks seems to predict response at 52 weeks with a sensitivity of 76% and a specificity of 82%, odds ratio of 14.<sup>21</sup> Dillman *et al.* [ $n = 28$ , paediatrics] performed a regression analysis and found that a mean daily reduction in BWT after infliximab [IFX] treatment was 0.004 mm after adjustment for covariates. It took 2 weeks for BWT and CDS to reach a significant reduction, which was maintained at follow-up visits after 1, 3, and 6 months.<sup>56</sup>

### 3.4.2. Transmural remission, definition, and timing of assessment in Crohn's disease

- 3.4.2.1. Transmural remission of the small and large bowel is defined by bowel wall thickness  $\leq 3$  mm with normal/0 colour Doppler signal. [InA. 0, Unc. 1, App. 17]
- 3.4.2.2. In some patients, sigmoid colon may contain an enlarged muscularis propria [outer hypoechoic layer typical in diverticular disease], allowing for bowel wall thickness up to 4 mm without resembling active inflammation. [InA. 3, Unc. 1, App. 13]
- 3.4.2.3. Transmural remission should be assessed after treatment initiation [regardless of treatment] between 26 and 52 weeks. [InA. 0, Unc. 3, App. 14]
- 3.4.2.4. Transmural remission may occur already at Week 12 but with increasing likelihood up to 1 year [maybe 2 years]. [InA. 0, Unc. 0, App. 17]

No expert consensus on the definition of TR has previously existed.<sup>8</sup> We recognise that a BWT  $\leq 4$  mm of the sigmoid can be normal for some patients, especially if diverticula are present. However, based on the studies from Castiglione *et al.*<sup>18,19,83</sup> and Moreno *et al.*<sup>25</sup> combined with our own expert opinion, a majority of the panel recommend defining TR as BWT  $\leq 3$  mm with normal CDS for both small and large bowel. This definition is consistent with the definition previously suggested in the article by Geyl *et al.*<sup>84</sup> and with the recommendation from Goodsall *et al.* for clinical trials.<sup>85</sup> Based on cross-sectional studies, a BWT cut-off value of 3 mm gives a sensitivity of 89% and a specificity of 96% in detecting inflammation.<sup>5</sup> Further, a recent systematic review and meta-analysis, based on both CD and UC, concluded that a colorectal segment  $< 3$  mm is highly likely to be present in segments achieving endoscopic remission [ER] [negative predictive value 92.7%].<sup>86</sup> With this definition, one can expect that between 20% and 30% will achieve TR after 12 weeks,<sup>16,17</sup> with 30–50% achieving TR after 1 year on biologics.<sup>16,25</sup>

#### 3.4.2.5. BWT and its association with transmural remission

The most used definition of IUS TR in prospective observational trials is BWT  $\leq 3$  mm alone or in combination with other IUS parameters [Table 1; Supplementary Tables 2 and 3].<sup>8,84</sup> BWT  $\leq 3$  mm alone has a substantial association with endoscopic remission [ER] [defined as the absence of ulcerations, SES-CD  $< 2$ ,  $\kappa = 0.63$ ,  $p = 0.01$ ]<sup>18,19</sup> and an almost perfect agreement with TR assessed by MRE [defined as BWT  $\leq 3$  mm without signs of hypervascularisation],  $\kappa = 0.9$ ,  $p \leq 0.01$ .<sup>19</sup> As expected,<sup>9</sup> BWT  $\leq 3$  mm alone has a fair association with clinical remission [CDAI  $< 150$ ],  $\kappa = 0.27$ ,  $p \leq 0.01$ , and a substantial association with C-reactive protein [CRP],  $\kappa = 0.79$ ,  $p = 0.02$ .<sup>18,19</sup> These data are derived from two studies which, combined, focused on TR rates in 173 patients 2 years after treatment with anti-TNF. The same research group compared 1-year clinical outcomes with three different groups: TR combined with ER [ $n = 68$ ], ER alone [ $n = 60$ ], and without objective evidence of remission [ $n = 90$ ]. TR



**Table 4.** Crohn's disease – proportion of patients achieving transmural remission at each assessment.

Transmural remission definition	Treatment	Week 4	Week 8	Week 8 - 12	Weeks 12–16	6 months	9–12 months	2 years	3 years
BWT ≤3 mm	Anti-TNFAZA/6-MP				27% <sup>26</sup> 30% <sup>87</sup>		30% <sup>26</sup>	25% <sup>19</sup> 26% 5% <sup>18</sup>	
BWT ≤3 mm and CDS 0 to 1	Anti-TNF								
BWT ≤3 mm small bowel, ≤4 mm colon <sup>a</sup>	Anti-TNF			21% <sup>16</sup> 29% <sup>17</sup>			42% <sup>16</sup>		
BWT <3 mm small bowel, <4 mm large bowel, CDS 0 <sup>b</sup>	Biologics				16% <sup>34</sup>	2.5% <sup>34</sup>	28% <sup>34</sup>	50% <sup>25</sup> 32% <sup>33</sup>	
BWT ≤2 mm small bowel, ≤3 mm colon, CDS score ≤1 <sup>c</sup>	UST	2% <sup>57</sup>	6% <sup>57</sup>		11% <sup>57</sup>				
BWT ≤3 mm, normalisation of CDS <sup>d</sup>	Anti-TNF						14% <sup>59</sup> 17% <sup>88</sup>	20% <sup>88</sup>	24% <sup>88</sup>
BWT ≤3 mm, normalisation of CDS <sup>e</sup>	Anti-TNF					32% <sup>36</sup>			
BWT Ileum ≤ 2 mm, sigmoid ≤ 4 mm, rest of colon ≤ 3 mm, normalization of CDS	±AZA/6-MP, 5-ASA AZA/MTX ± Anti-TNF, Anti-integrin, systemic CS			32% <sup>37</sup>					
BWT ileum ≤2 mm, sigmoid ≤4 mm, rest of colon ≤3 mm, normalisation of CDS, restored BWS and no I-fat [minus one factor that could not be assessed]	AZA/MTX ± Anti-TNF, Anti-integrin, systemic CS			37% <sup>37</sup>					
BWT ileum ≤2 mm, sigmoid ≤4 mm, rest of colon ≤3 mm, normalisation of CDS [Limberg 1/2], restored BWS and no I-fat	AZA/MTX ± Anti-TNF, Anti-integrin, systemic CS			24% <sup>37</sup>					

5-ASA, mesalazine; anti-TNF, infliximab; adalimumab; AZA/6-MP, azathioprine/mercaptopurine; biologics, infliximab, adalimumab, ustekinumab, vedolizumab; BWS, bowel wall stratification; BWT, bowel wall thickness; CDS, colour Doppler signals; I-fat, inflammatory fat; UST, ustekinumab; CS, corticosteroid.

<sup>a</sup>No length of disease, absence of fistulae, phlegmons, or abscesses.

<sup>b</sup>No length of disease, normal bowel wall stratification, no inflammatory fat, no active inflammation or fistulising disease.

<sup>c</sup>Normal bowel wall stratification and absence of inflammatory fat.

<sup>d</sup>Normal five-layer bowel wall stratification, no inflammatory fat, no lymph node enlargement or presence of strictures or pre-stenotic dilation.

<sup>e</sup>Normal bowel wall stratification, absence of inflammatory fat, abscesses, and fistulae.

[BWT  $\leq 3$  mm] was associated with higher rates of steroid-free clinical remission (96%, hazard ratio [HR] 0.87,  $p < 0.01$ ), lower rates of hospitalization [9%, HR 0.88,  $p < 0.01$ ], need for surgery [0%, HR 0.94,  $p < 0.01$ ] compared with ER. Even for patients discontinuing anti-TNF treatment, TR predicted better clinical outcomes compared with ER,  $p < 0.01$ .<sup>83</sup> Defining TR as BWT  $\leq 3$  mm for small bowel,  $\leq 4$  mm for large bowel, no length of disease, and absence of fistulae, phlegmons, or abscess, showed that no patient achieving TR [13/41] underwent surgery, required corticosteroid treatment, or needed hospitalisation during 1-year follow-up.<sup>33</sup> A greater BWT at baseline [ $n = 188$ ] was associated with a lower chance of TR at 3 months,  $p = 0.018$ , OR 0.69,– and 12 months,  $p = 0.006$ , OR 0.65.<sup>34</sup>

#### 3.4.2.6. CDS and its relationship with transmural remission

No study uses CDS alone to define TR. Moreno *et al.* [ $n = 30$ ] defined TR as a combination of BWT  $\leq 3$  mm together with no CDS [Limberg grade 0–1] and low perfusion (assessed with contrast-enhanced ultrasound [CEUS]). After a median duration of 14 months [anti-TNF  $\pm$  azathioprine], TR demonstrated a good correlation with ER (total CD endoscopic index of severity [CDEIS]  $< 6$  points),  $\kappa = 0.73$ ,  $p < 0.001$ . BWT showed the best correlation,  $\kappa = 0.86$ ,  $p < 0.001$ , and CDS showed an almost equally good correlation,  $\kappa = 0.85$ ,  $p < 0.001$ . The variable with the best prognostic value for predicting endoscopic remission was BWT  $\leq 3$  mm [96%].<sup>25</sup>

#### 3.4.2.7. When does transmural remission occur?

The definition of TR varies among studies. Depending on disease severity, the treatment used, disease location, and the IUS parameters included, remission rates vary Table 4. While Castiglione *et al.* showed a significant difference in TR rates between anti-TNF and thiopurines, 26% [17/66] vs. 5% [3/67],<sup>18</sup> no significant differences exist between biologic treatments.<sup>18,19,34</sup> However, a newly published study by Calabrese *et al.* found that ustekinumab had a lower chance of achieving TR. Authors acknowledge that ustekinumab is offered for refractory diseases, which may influence their findings.<sup>34</sup> Further, TR often occurs within the first 3 months of treatment, followed by a minor increase thereafter.<sup>26,34,87</sup> Paredes *et al.* showed that all patients with TR at Week 12 remained TR at 1 year.<sup>16</sup> At Week 8, BWT had normalised in 29% [5/24], and CDS had normalised in 33% [8/24].<sup>17</sup> This is further supported by the STARDUST study, where BWT and CDS started to normalise at Week 8, and BWS and I-fat first normalised at Week 16.<sup>57</sup>

In two paediatric studies, after 9–12 months of treatment, TR was achieved in 14% [4/32]<sup>59</sup> and 17% [8/48], respectively.<sup>88</sup> After 24 and 36 months, the rates were 20% [9/46] and 24% [8/33], respectively.<sup>88</sup> While CDS, I-fat, and lymph node enlargement improved significantly in the endoscopic response group, strictures and pre-stenotic dilation together with BWS did not. Disruption of BWS was not related to changes in BWT or vascularisation.<sup>59</sup>

These paediatric findings are supported by Orlando *et al.* [ $n = 30$ ], showing that CDS or BWS did not influence variations in BWT and TR at 14 and 52 weeks during follow-up in adults.<sup>26</sup> However, BWS may reflect longitudinal ulcers.<sup>65</sup> In a study by Wilkens *et al.*, segments with histologically proven ulcers were thicker than non-ulcerated segments,  $p < 0.01$ .<sup>89</sup> Orlando *et al.* is the only study published to date that has not found CDS influential regarding BWT or TR.<sup>26</sup>

#### 3.4.3. Other important intestinal ultrasound parameters that are not included in the definition of response and transmural remission

BWT and CDS appear to be the most important parameters when assessing IUS response and remission, based on their relationship

with clinical outcomes. Although deemed important by experts,<sup>62</sup> I-fat and BWS are not included in our current definition of response or remission/TR. Current data on BWS suggest that up to 53% with active CD will have a loss of BWS,<sup>9</sup> with gradual restoration of BWS after 3 months of treatment to 29%, followed by 22% at both 6 and 12 months,  $p < 0.001$ .<sup>20</sup> Other studies have not reported a significant restoration of BWS over time.<sup>59</sup> In active CD, I-fat might be present in up to half of the patients before treatment initiation, with a more apparent decline after 3 months of treatment to 22% followed by 17–18% at 6 and 12 months, respectively,  $p < 0.001$ .<sup>20</sup> Currently, no study has correlated BWS or I-fat with clinical outcomes. However, mesenteric adipose tissue proliferation correlates with increased BWT [OR 7.6] and internal fistulae [OR 13.5].<sup>90</sup> We believe that the maintained presence of extra-mural inflammation [e.g. I-fat] can be a sign of chronic disease. BWS and I-fat might be included in future definitions of response/remission. However, we suggest that these parameters are mainly contributory to disease activity assessment and could be integrated with more important parameters [BWT/CDS] in an IUS activity score. In patients with strictures, only 6% [1/16]<sup>18</sup> to 16% [1/6],<sup>19</sup> and no patient with penetrating disease, achieved TR.<sup>18,19</sup> This suggests that normalisation of stricturing or penetrating disease is less likely to occur, and TR may only be achievable for predominantly inflammatory disease.

### 3.5. Ulcerative colitis

#### 3.5.1. Response definition and timing of assessment in ulcerative colitis

- |          |   |
|----------|---|
| 3.5.1.1. | Treatment response in ulcerative colitis is identified by reduction of bowel wall thickness [continues measurements] [ $>25\%$ ] or [ $>2.0$ mm] or [ $>1.0$ mm and one colour Doppler signal reduction]. [InA. 0, Unc. 3, App. 15]   |
| 3.5.1.2. | Ideal assessment of intestinal ultrasound response within the first year of treatment initiation/escalation/change is at baseline, Week 14 $\pm$ 2, and between Weeks 26–52 + intestinal ultrasound depending on elevated faecal calprotectin or symptoms or clinical suspicion of flare. [InA. 0, Unc. 2, App. 14] |
| 3.5.1.3. | After treatment initiation, response should be measured in all segments that were affected at baseline. [InA. 0, Unc. 0, App. 14]   |

There are currently only a few studies, most with high risk of bias, examining the relationship between IUS response over time with a reference standard such as clinical scores or endoscopy in UC trials [Table 2; Supplementary Figure 2]. Our recommendations are, therefore, primarily based on our clinical experience and expert opinion. After 2–3 weeks of steroid/cytapheresis treatment, 42% [11/26] showed a BWT reduction by  $\geq 2.5$  mm. One-year clinical relapse was found in 9% [1/11] in the response group, compared with 47% [9/15] in the non-response group,  $p < 0.05$ .<sup>42</sup> After 2 months of treatment with steroids, Maconi *et al.* [ $n = 30$ ] showed a significant decrease in BWT by 2.3 mm [31%] in the response group alone.<sup>41</sup> Already after 10 days of steroid treatment, a significant decrease in BWT meant no risk of surgery at 3 months,  $n = 32$  [25 moderate/severe based on the Truelove–Witts score].<sup>45</sup> In clinical experience, patients receiving steroids tend to respond faster than patients receiving biologics. It is still unclear if transabdominal IUS response

can be measured earlier than at 2 weeks. This doubt reflects the lack of consensus for statements on early response in acute severe ulcerative colitis [Supplementary Material 2, second round voting results, 44.2]. However, a recent pilot study [ $n = 10$ ] on steroid treatment in severe acute UC showed that IUS performed within the first 48 h of hospitalization potentially predicts treatment outcome.<sup>91</sup>

Focusing on anti-TNF in UC, a BWT reduction in 34% [15/44] is shown after 6 weeks in the sigmoid and descending colon. Further, patients with an increased CDS at Weeks 6 and 12 had a significantly higher simple clinical colitis activity index [SCCAI], compared with no CDS signal,  $p \leq 0.001$ .<sup>44</sup> After 14 weeks of vedolizumab treatment, 57% [4/7] achieved BWT reduction of 1.0 mm,  $p = \text{N/A}$ , in the response group alone. CDS significantly decreased from 1.3 to 0.5 in responders and increased from 1.3 to 2.7 in non-responders,  $p \leq 0.05$ .<sup>28</sup>

After the RAND/UCLA process, De Voogd *et al.* [ $n = 29$ ] published an abstract showing a mean BWT reduction of  $2.6 \pm 1.4$  mm for the sigmoid and  $1.8 \pm 1.0$  mm for the descending colon in patients achieving ER on tofacitinib treatment.<sup>46</sup> Further, Helwig *et al.* showed that 76% [100/171] achieved a greater than 25% BWT reduction after 12 weeks of mixed treatment.<sup>37</sup>

This limited available evidence suggests using the exact definition of treatment response in UC as for CD. However, more studies are needed, and no pediatric studies were identified.

### 3.5.2. Transmural remission, definition, and timing of assessment in ulcerative colitis.

- 3.5.2.1. Transmural remission in ulcerative colitis of the large bowel is defined by bowel wall thickness  $\leq 3$  mm with normal/0 colour Doppler signal. [InA. 0, Unc. 1, App. 17]
- 3.5.2.2. In some patients, sigmoid colon may contain an enlarged muscularis propria [outer hypoechoic layer—typical in diverticular disease], allowing for bowel wall thickness up to 4 mm without resembling active inflammation. [InA. 3, Unc. 1, App. 13]
- 3.5.2.3. Transmural remission in ulcerative colitis should be assessed after treatment initiation [regardless of treatment] at Week  $14 \pm 2$ . [InA. 0, Unc. 2, App. 16]
- 3.5.2.4. Transmural remission in ulcerative colitis may occur already at Week 4 but with increasing likelihood up to Week 12 [potentially 1 year]. [InA. 1, Unc. 3, App. 14]

Before the RAND/UCLA process, no study had explicitly defined TR for UC. Given the common understanding that UC is not considered a transmural disease, one could argue that no definition of TR is needed [Table 2]. However, numerous examples of extra-mural inflammation, like I-fat and enlarged lymph nodes, in moderate and severe UC challenges the classification of UC as a disease limited to the mucosa only.<sup>40</sup> As a consequence, we believe that a definition of TR is valid and vital for future studies examining the role of IUS remission and its' relationship with clinical outcomes during follow-up for UC patients. After 2 weeks of variable treatment [ $n = 224$ ], the proportion of patients with increased BWT in the sigmoid colon was reduced from 89% to 39%,  $p < 0.001$ . A further improvement at Weeks 6 and 12 were shown, at 35% and 32%, respectively,

$p \leq 0.001$ . A thickened bowel wall was present in 83% at baseline in the descending colon, followed by a significant decrease to 43% at both Weeks 2 and 6. Endoscopy was not routinely performed during follow-up. However, the IUS findings had a moderate association with SCCAI and faecal calprotectin [FC]. In sigmoid colon, baseline CDS was increased by 35%, followed by 23%, 16%, and 13% at Weeks 2, 6, and 12,  $p < 0.001$ . The proportion of patients with an increased CDS in the descending colon were 15% at baseline, followed by 7%, 5%, and 7%,  $p < 0.001$ .<sup>40</sup> In 5/6 patients with ER and clinical remission, BWT was  $\leq 4$  mm after 2 months of various treatments. BWT was significantly higher in the pre-treatment group with moderate/severe clinical and endoscopic activity compared with the mild endoscopic group.<sup>41</sup> These findings report a considerable improvement in BWT and CDS within the first 12 weeks of treatment. By combining BWT and CDS in a 0–3 score and comparing it with the 0–3 Baron endoscopic score, Paredes *et al.* showed substantial reliability,  $\kappa = 0.76$ , at 3 months, and almost perfect  $\kappa = 0.88$ –0.90 at 9 months and 15 months, respectively.<sup>39</sup> After 8 weeks of treatment with tofacitinib, de Voogd *et al.* [ $n = 29$ ] showed that all patients in the ER group had a BWT cut-off value of  $\leq 2.9$  mm (area under the receiver operating characteristic curve [AUROC] 0.91 [0.83–0.99], sensitivity 83%, and specificity 100%) in the sigmoid colon and  $\leq 2.8$  mm (AUROC 0.98 [0.94–1.00], sensitivity 91%, and specificity 92%) for descending colon.<sup>46</sup> Helwig *et al.* [ $n = 171$ ] examined three different definitions of TR. Focusing on the definition containing BWT and CDS, 12-week TR rates were 53%. This high rate could be explained by a BWT cut-off value of 4 mm in the sigmoid and a CDS score of 1–2 defined as normal.<sup>37</sup> A recent systematic review of cross-sectional studies concluded that the most often used criteria to define disease activity were BWT and CDS. The evidence also suggests that BWT in combination with CDS or BWS gives a more accurate correlation with other markers of disease activity.<sup>4</sup>

Although based upon limited evidence, most of the experts in our panel believe that the same definition for TR in CD is applicable in UC.

### 3.5.3. Additional relevant IUS parameters

The TRUSTandUC study showed that 40%, 23%, and 57% have a presence of I-fat, loss of BWS, and loss of haustration at baseline, respectively. All parameters significantly improved 12 weeks later. These parameters are contributory in the assessment of UC activity by IUS. However, there are no current data on their relationship with clinical outcomes over time and consequently they are not included in our definition. However, they might be included in a validated future score for response and remission, as previously discussed.

## 3.6. Adults vs. paediatric population

- 3.6.1. The remission/response statements for Crohn's disease may be used in both adult and paediatric populations. [InA. 2, Unc. 1, App. 14]
- 3.6.2. The remission/response statements for ulcerative colitis may be used in both adult and paediatric populations. [InA. 2, Unc. 2, App. 12]

There was only one paediatrician involved in our RAND/UCLA process. However, based on the limited available evidence from paediatric studies presented throughout this article [Supplementary Table 3],<sup>36,59,61,88,92,93</sup> we find that our recommendations may be used in both populations. Future studies are needed to validate or refute this assumption.

## 4. Discussion

Cross-sectional imaging, an objective biomarker, currently gains increasing attention and incorporation into clinical trials as a proposed treatment target.<sup>84</sup> IUS is an accurate, reliable, cost-effective, patient-friendly, non-invasive imaging modality performed by clinicians in a point-of-care setting.<sup>2</sup> However, definitions for imaging response and transmural remission/healing and optimal assessment timing currently lack international consensus. This systematic review demonstrates the diversity in the current literature of IUS response definitions and reporting. Using a robust methodology, the eligible studies included patients with different disease characteristics [severity and location], treatments, times to follow-up, reference standards, aims, and outcomes. This further highlights the need for an international expert consensus on IUS response assessment and reporting. We now provide clear international expert consensus defining optimal timing and cut-offs for transmural response and remission for CD and UC, using IUS. We also establish consensus recommendations on imaging acquisition, expected transmural response time, disease length, measuring and reporting bowel wall thickness, defining worst bowel segment, the composition of disease activity indices, and paediatric applicability.

Our study has several strengths. Not only did we perform a comprehensive systematic review, we also added a novel and robust RAND/UCLA process, with a panel including many of the world's leading IBD IUS researchers. Using this methodology, panelists are not forced into a majority agreement but individual rating statements on an appropriateness scale. Indeed, statements reached agreement on appropriate definitions for IUS response reporting, preceded by high-level and intense discussions. Not all researchers voted on all statements, and one additional expert was added during the second round. This is reflected by the different total vote counts, especially between CD and UC statements. Due to the small amount of data and the experts' area of expertise limitations, UC statements received fewer votes.

Limitations of this study include the limited amount of high-quality prospective evidence, leaving the panel with an agreement based upon the available literature and expert experience. The applicability of the included research to answer our study questions was high, but so was the risk of bias. A large proportion of the uncertain or unknown biases comes from the included abstracts. Due to the expected low number of full-text studies, the inclusion of abstracts was deemed necessary. Another high risk of bias is the large proportion of clinical scores used as a reference standard. Clinical scores are a subjective rather than an objective measure of inflammation, and results should therefore be considered carefully.<sup>94,95</sup> With only six studies using ER and/or MRE as a reference standard, definitions of response were influenced by all included studies. In addition, a couple of pivotal studies were published after the first literature search. Since they were aligned with our voting, we chose to add them to the supporting text, although they were not part of the systematic review itself. We aimed at rating individual statements by the Grading of Recommendations, Assessment, Development, and Evaluations [GRADE] terminology. However, observational studies per se are considered low certainty evidence, potentially further downgraded to very low certainty by the limitations reported by the risk of bias. In the absence of any randomised controlled trials using IUS in IBD patients, all our recommendations are considered weak.

The definitions regarding response, TR, and assessment time points need further validation, and more studies regarding IUS's ability to assess and predict treatment response are warranted.

However, we hope these consensus definitions and recommendations will guide future high-quality prospective therapeutic trials using IUS as a secondary or primary endpoint, eventually leading to broad adoption of intestinal ultrasound as the standard of care in objective disease monitoring in IBD striving towards achieving TR.

In conclusion, an agreement was reached on 43 different appropriate statements, including clear definitions on IUS treatment response, transmural remission, optimal timing of follow-up, and general considerations for using transabdominal intestinal ultrasound in inflammatory bowel disease. To ensure a unified approach in routine care and clinical trials, we provide recommendations and definitions for incorporation in future prospective studies.

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## Authors Contributions

JFKF: conceptualisation, methodology, validation, formal analysis, investigation, data curation, writing—original draft, writing—review and editing, visualization, project administration. TH: validation, investigation, data curation, writing—review and editing. TMG: validation, investigation, data curation, writing—review and editing. JBS: data curation, writing—original draft, writing—review and editing, supervision. HA-F: data curation, writing—review and editing. MA: data curation, writing—review and editing. JB: data curation, writing—review and editing. RVB: data curation, writing—review and editing. DC: data curation, writing—review and editing. BC: data curation, writing—review and editing. MCD: data curation, writing—review and editing. KBG: data curation, writing—review and editing. TK: data curation, writing—review and editing. CL: data curation, writing—review and editing. CM: data curation, writing—review and editing. GM: data curation, writing—review and editing. KN: data curation, writing—review and editing. CP: data curation, writing—review and editing. SRW: data curation, writing—review and editing. KN: conceptualization, methodology, data curation, writing—original draft, writing—review and editing, supervision. RW: conceptualisation, methodology, validation, data curation, writing—original draft, writing—review and editing, visualisation, supervision, project administration.

## Supplementary Data

Supplementary data are available at ECCO-JCC online.

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