International expert guidance for defining and monitoring small bowel strictures in Crohn's disease on intestinal ultrasound: a consensus statement

Cathy Lu, Ryan Rosentreter, Claire E Parker, Julie Remillard, Stephanie R Wilson, Mark E Baker, Gauraang Bhatnagar, Jakob Begun, David H Bruining, Robert V Bryant, Britt Christensen, Brian G Feagan, Joel G Fletcher, Ilyssa Gordon, Gaylyn Henderson, Vipul Jairath, John Knudsen, Torsten Kucharzik, Kyle Lesack, Christian Maaser, Giovanni Maconi, Kerri Novak, Jordi Rimola, Stuart A Taylor, Rune Wilkens, Florian Rieder, on behalf of the Stenosis Therapy and Anti-Fibrotic Research (STAR) consortium

Summary

Background Diagnostic imaging using CT enterography, magnetic resonance enterography, and intestinal ultrasound are important tools in evaluating stricturing Crohn's disease. Definitions of strictures have been developed for CT enterography and magnetic resonance enterography. However, expert recommendations for definitions and treatment response of strictures on intestinal ultrasound are not available. The aim of this study was to standardise definitions, diagnosis, and treatment response criteria in small bowel stricturing Crohn's disease on intestinal ultrasound.

Methods Using modified RAND–University of California Los Angeles Appropriateness Method, a diverse expert panel of 13 gastroenterologists, seven radiologists, and two patient representatives was assembled. A total of 466 statements on definitions and response to therapy of stricturing Crohn's disease on intestinal ultrasound were generated from a systematic review and from expert opinion, with subsequent rating for appropriateness. Two rounds of voting with an interposed survey result discussion were performed. Statements were classified as inappropriate, uncertain, or appropriate based on the median panel rating and degree of disagreement. Appropriateness was rated using a nine-point Likert scale (1 being inappropriate, 9 being highly appropriate).

Findings A naive or anastomotic small bowel Crohn's disease stricture on intestinal ultrasound is defined by the combination of bowel wall thickening, luminal narrowing, and pre-stenotic dilation. Bowel wall thickness is defined as being more than 3 mm. Luminal narrowing is defined as either a luminal diameter reduction of more than 50% in the narrowest area and relative to a normal adjacent bowel loop, or a luminal diameter of less than 1 cm. Pre-stenotic dilation is defined as more than 2·5 cm or an increase in bowel diameter relative to a normal adjacent bowel loop. Definitions for grading hyperaemia, inflammatory fat, wall stratification, intestinal ultrasound machine technical parameters, and image acquisition were also devised. Treatment response of strictures was defined as reduction in stricture length, bowel wall thickening, luminal narrowing, pre-stenotic dilation, and motility abnormalities.

Interpretation To our knowledge, this is the first intestinal ultrasound appropriateness rating exercise conducted for defining, diagnosing, and measuring response to therapy in small bowel stricturing Crohn's disease and informs future clinical use and intestinal ultrasound index development for clinical trials.

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Introduction

CT enterography and magnetic resonance enterography readily evaluate transmural complications of Crohn's disease, including stricture formation. Strictures are narrowings most commonly found in the terminal ileum. CT enterography, magnetic resonance enterography, and intestinal ultrasound have similar sensitivity and specificity for stricture diagnosis.[1] Strictures are known to contain both inflammation and fibrosis in varying degrees, thus making it challenging to classify them dichotomously as inflammatory or fibrotic.[2] Definitions, diagnostic modalities, and treatment targets for anti-fibrotic stricture therapies in Crohn's disease using CT enterography and magnetic resonance enterography were rated for appropriateness by an expert panel.[3,4] A comparative exercise has not been undertaken for intestinal ultrasound.

The use of point-of-care intestinal ultrasound in managing Crohn's disease is growing worldwide, probably because it is non-invasive, well tolerated, cost effective, and is an easily repeatable imaging technique.[5] Contrast enhanced intestinal ultrasound and elastography further evaluate disease activity, but their use to distinguish the inflammatory and fibrotic composition of

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Division of Gastroenterology and Hepatology, Department of Medicine (C Lu MD, R Rosentreter MSc, Prof S R Wilson MD, K Lesack PhD, K Novak MD) **and Department of Radiology** (Prof S R Wilson), **University of Calgary, Calgary, AB, Canada; Alimentiv, London, ON, Canada** (C E Parker MLIS, J Remillard MSc, Prof B G Feagan MD, Prof V Jairath MD); **Imaging Institute** (Prof M E Baker MD) **and Program for Global Translational Inflammatory Bowel Disease** (F Rieder MD), **Cleveland Clinic, Cleveland, OH, USA; Centre for Medical Imaging, University College London, London, UK** (G Bhatnagar MD, Prof S A Taylor MD); **Frimley Health NHS Foundation Trust, Surrey, UK** (G Bhatnagar); **Mater Research Institute, University of Queensland-Translational Research Institute, Brisbane, QLD, Australia** (J Begun MD, R V Bryant MD); **Department of Gastroenterology, The Queen Elizabeth Hospital, Adelaide, SA, Australia** (J Begun, R V Bryant); **Division of Gastroenterology and Hepatology** (D H Bruining MD) **and Department of Radiology** (Prof J G Fletcher MD, J Knudsen MD), **Mayo Clinic, Rochester, MN, USA; Department of Gastroenterology, Royal Melbourne Hospital and University of Melbourne, Melbourne, VIC, Australia** (B Christensen MD); **Department of Medicine, Western University, London, ON, Canada** (Prof B G Feagan,

Prof V Jairath); **Department of Pathology, Robert J Tomsich Pathology and Laboratory Medicine Institute, Cleveland Clinic Foundation, Cleveland, OH, USA** (I Gordon MD); **Gutless and Glamourous, Atlanta, GA, USA** (G Henderson MPH); **Department of Epidemiology and Biostatistics, Department of Medicine, Western University, London, ON, Canada** (Prof V Jairath); **Department of General Internal Medicine and Gastroenterology, University Teaching Hospital Lüneburg, Lüneberg, Germany** (Prof T Kucharzik MD); **Outpatients' Department of Gastroenterology, University Teaching Hospital Lüneburg, Lüneberg, Germany** (Prof C Maaser MD); **Gastroenterology Unit, Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy** (Prof G Maconi MD); **IBD unit, Radiology Department, Hospital Clinic Barcelona, IDIBAPS, Barcelona, Spain** (Prof J Rimola MD); **Copenhagen University Hospital—Bispebjerg, Digestive Disease Center, Copenhagen, Denmark** (R Wilkens MD); **Copenhagen Intestinal Ultrasound, Bispebjerg Hospital, Copenhagen, Denmark** (R Wilkens MD); **Department of Inflammation and Immunity, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA** (F Rieder); **Department of Gastroenterology, Hepatology and Nutrition, Digestive Disease Institute, Cleveland Clinic, Cleveland, Ohio, USA** (F Rieder)

Correspondence to: Dr Cathy Lu, Division of Gastroenterology and Hepatology, Department of Medicine, University of Calgary, Calgary T2N 4Z6, AB, Canada
luc@ucalgary.ca

Research in context

Evidence before this study

Intestinal ultrasound is a comparable modality to CT enterography and magnetic resonance enterography for evaluating Crohn's disease. Definitions and diagnosis of Crohn's disease small bowel strictures have been established for CT enterography and magnetic resonance enterography, but not for intestinal ultrasound. A thorough systematic review of the intestinal ultrasound literature was conducted with a risk of bias assessment before this consensus. There was heterogeneity with the definitions of small bowel Crohn's disease strictures, with most studies incorporating all three parameters of bowel wall thickness, luminal narrowing, and pre-stenotic dilation.

Added value of this study

As intestinal ultrasound is easily repeatable, well-tolerated, and accurate in diagnosing and monitoring strictures, it is poised as an informative tool for not only clinical practice, but also clinical trials. The definition of naive and anastomotic small bowel Crohn's disease strictures on intestinal ultrasound matches the criteria for CT enterography and magnetic resonance enterography and includes the same three features: bowel wall thickness, luminal narrowing, and pre-stenotic dilation. None of the current adjunctive tools or novel intestinal ultrasound techniques, such as intravenous contrast, and strain or shear wave elastography are sufficiently accurate to differentiate inflammatory and fibrotic components of strictures. As stricture drug development has been constrained by absence of well-defined endpoints, this consensus provides guidance for intestinal ultrasound features that indicate improvement in strictures following therapy. Overall, this study provides expert guidance for the definition, diagnosis, and measurement of response to treatment of small bowel Crohn's disease strictures using intestinal ultrasound.

Implications of the available evidence

This study lays the foundation to validate definitions of strictures on intestinal ultrasound and to develop a reliable and responsive intestinal ultrasound index. In the future, this index could be used in both clinical practice and trials to study anti-fibrotic therapies.

strictures requires further exploration.[6,7] Intestinal ultrasound disease activity was evaluated in the STARDUST trial,[8] a phase 3b, randomised controlled trial that assessed ustekinumab in Crohn's disease. The study showed that intestinal ultrasound can measure transmural response and remission as early as week 4 and up to week 48, and suggested that intestinal ultrasound is of value and complementary to endoscopy in those with terminal ileum and colonic inflammation.[8]

In addition, despite increasing numbers of anti-inflammatory agents and one anti-fibrotic agent (Agomab-129) currently in a phase 2a clinical trial, the use of intestinal ultrasound in clinical trials has been limited due to the absence of lack of validated definitions and properly developed clinical trial endpoints.[9] To facilitate future drug development in stricturing small bowel Crohn's disease, the Stenosis Therapy and Anti-Fibrotic Research (STAR) consortium assembled a global panel of expert gastroenterologists and radiologists to complete a two-round evaluative process using an appropriateness method developed by the University of California at Los Angeles (UCLA) and the research organisation RAND, the RAND–UCLA Appropriateness Method.[4,10]

Topics of consideration included intestinal ultrasound-based diagnostic criteria, outcome definitions, and treatment targets. Technical parameters, elastography, and oral and intravenous contrast were also appraised. The aim of this study was to standardise definitions, diagnosis, and treatment response criteria in small bowel stricturing Crohn's disease on intestinal ultrasound. The resulting statements provide a framework to formally develop and validate an intestinal ultrasound index for future clinical trials of stricturing Crohn's disease.

Methods

The RAND–UCLA Appropriateness Method

The RAND–UCLA Appropriateness Method is an evidence-based, modified Delphi technique in which an expert panel rates a series of statements for appropriateness across at least two rounds of voting.[10] A moderated group discussion occurs between voting rounds in which no attempt is made to force consensus. Based on this discussion, the initial statement list could be modified in subsequent voting rounds.

Statement generation

A previously published systematic literature review and expert opinion were used to generate the initial statement list.[11] Subsections were: (1) defining naive and anastomotic small bowel strictures on intestinal ultrasound; (2) defining inflammatory and fibrotic strictures on intestinal ultrasound; (3) specific parameters and scoring conventions; (4) treatment response; (5) technical considerations; and (6) current intestinal ultrasound indices.

Panel recruitment

A global panel of 13 gastroenterologists, seven radiologists, and two patients (one patient from the USA and one patient from Canada) from Australia, Canada, Denmark, Germany, Italy, UK, and USA were recruited according to their experience in stricturing Crohn's disease, publication record, international reputation in the diagnosis or treatment of stricturing Crohn's disease, and previous participation in the development and validation of evaluative imaging indices. The final selection of panelists were then determined by CL and FR.

Appropriateness rating process

Before voting, panelists were allowed to provide feedback on the draft round one survey. Panelists then anonymously rated statement appropriateness on a nine-point Likert scale (1 being inappropriate and 9 being highly appropriate). After round one of voting, results were circulated to the panelists and a moderated group discussion was conducted via teleconference. Statements were revised following the group discussion, and a second round of appropriateness voting was done. Surveys were developed and completed using SurveyMonkey (San Mateo, California, USA).

Statistical analysis

The median appropriateness rating for each statement and rating distribution, as expressed by the IQR, were calculated. Statements were classified as inappropriate, uncertain, or appropriate based on the median panel rating and degree of disagreement (median 1–3 without disagreement was classed as inappropriate, median 4–6 or any median with a disagreement was classed as uncertain, and median 7–9 without a disagreement was classed as appropriate). A disagreement was considered present when two or more panelists rated appropriateness in each extreme three-point region (1–3 and 7–9).[4]

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The round one survey consisted of 394 statements. In total, 178 (45%) of statements were rated as appropriate, 27 (7%) as inappropriate, and 188 (48%) as uncertain. Following the group discussion, 69 new statements were added to the survey (one stand-alone and 19 multiple-part statements) and eight statements were revised (one stand-alone and seven multiple-part statements; appendix pp 7–19). Thus, 463 statements were included in round two of the survey (142 stand-alone and 324 multiple-part statements).

When diagnosing anastomotic and naive small bowel strictures on the intestinal ultrasound, the panel determined that increased bowel wall thickness, luminal narrowing, and pre-stenotic dilation must be present (table 1). The panel was uncertain whether motility abnormalities, loss of bowel wall stratification, and lack of compressibility must be present, whereas the presence of eight parameters (mesenteric inflammatory fat, mesenteric lymphadenopathy, echogenic submucosa, enlarged lymph nodes, penetrating disease, ulceration, mural or peri-enteric hyperaemia, and comb sign) were rated as inappropriate. In the case of a fixed narrowing (ie, a rigid segment of bowel with a narrowed lumen), it was felt that pre-stenotic dilation is not necessary, provided that bowel wall thickness was greater than 3 mm for naive strictures, and that bowel wall thickness was greater than 3 mm, and there were motility abnormalities for anastomotic strictures (appendix pp 20–21). The panel felt that obstructive symptoms were not required to diagnose a stricture on the intestinal ultrasound.

For inflammatory and fibrotic strictures, the panel rated the following stricture features as likely to be

See Online for appendix

	Median rating (IQR)	Appropriateness
When diagnosing a naive small bowel stricture on intestinal ultrasound, the following items must be present		
Bowel wall thickening	9 (8–9)	Appropriate
Luminal narrowing	9 (8–9)	Appropriate
Pre-stenotic dilation	7 (6–8)	Appropriate
Motility abnormalities	6 (4–8)	Uncertain
Loss of bowel wall layer stratification	4·5 (3–5)	Uncertain
Lack of compressibility	4 (2–6)	Uncertain
Mesenteric inflammatory fat	3·5 (2–5)	Inappropriate
Mesenteric lymphadenopathy	2·5 (1–3)	Inappropriate
Echogenic submucosa	3 (2–5)	Inappropriate
Enlarged lymph nodes	2 (1–3)	Inappropriate
Penetrating disease	3 (1–3)	Inappropriate
Ulceration	2 (1–3)	Inappropriate
Mural or peri-enteric hyperaemia	2·5 (1–3)	Inappropriate
Comb sign	3 (2–3)	Inappropriate
When diagnosing an anastomotic naive small bowel stricture on intestinal ultrasound, the following items must be present		
Bowel wall thickening	8·5 (8–9)	Appropriate
Luminal narrowing	8·5 (8–9)	Appropriate
Pre-stenotic dilation	7 (6–9)	Appropriate
Motility abnormalities	6 (5–7)	Uncertain
Loss of bowel wall layer stratification	5 (3–6)	Uncertain
Lack of compressibility	4 (2–5)	Uncertain
Mesenteric inflammatory fat	3 (2–5)	Inappropriate
Mesenteric lymphadenopathy	3 (1–3)	Inappropriate
Echogenic submucosa	3 (2–5)	Inappropriate
Enlarged lymph nodes	3 (1–3)	Inappropriate
Penetrating disease	3 (1–3)	Inappropriate
Ulceration	2 (1–3)	Inappropriate
Mural or peri-enteric hyperaemia	2·5 (1–3)	Inappropriate
Comb sign	3 (2–3)	Inappropriate
Obstructive symptoms are required for the diagnosis of stricture on intestinal ultrasound	3·5 (2–5)	Inappropriate
A naive small bowel stricture can be diagnosed in the absence of pre-stenotic dilation if there is internal penetrating disease (eg, abscess, inflammatory mass [phlegmon], or fistula)	6 (4–8)	Uncertain
An anastomotic small bowel stricture can be diagnosed in the absence of pre-stenotic dilation if there is internal penetrating disease (eg, abscess, inflammatory mass [phlegmon], or fistula)	6 (4–8)	Uncertain
A naive small bowel stricture can be diagnosed in the absence of pre-stenotic dilation if there is a fixed narrowing (ie, a rigid segment of bowel with a narrowed lumen)	6 (5–8)	Uncertain
An anastomotic small bowel stricture can be diagnosed in the absence of pre-stenotic dilation if there is a fixed narrowing (ie, a rigid segment of bowel with a narrowed lumen)	5 (5–7)	Uncertain

Table 1: **Consensus statements for diagnosis of naive and anastomotic small bowel Crohn's disease strictures on intestinal ultrasound**

	Median rating (IQR)	Appropriateness
Inflammation of a stricture is likely when the following features are present		
Bowel wall thickening	7 (6–8)	Appropriate
Luminal narrowing	5·5 (4–7)	Uncertain
Pre-stenotic dilation	4·5 (3–6)	Uncertain
Motility abnormalities	5 (4–6)	Uncertain
Loss of bowel wall layer stratification	7 (6–8)	Appropriate
Lack of compressibility	5 (3–5)	Uncertain
Mesenteric inflammatory fat	7·5 (7–9)	Appropriate
Mesenteric lymphadenopathy	5 (4–7)	Uncertain
Echogenic submucosa	4·5 (3–6)	Uncertain
Enlarged lymph nodes	5·5 (4–7)	Uncertain
Penetrating disease	6·5 (5–8)	Appropriate
Ulceration	8 (7–9)	Appropriate
Mural or peri-enteric hyperaemia	9 (8–9)	Appropriate
Comb sign	8 (7–9)	Appropriate
Fibrosis of a stricture is likely present when the following features are present		
Bowel wall thickening	7 (5–7)	Appropriate
Luminal narrowing	6 (5–7)	Uncertain
Pre-stenotic dilation	7 (5–8)	Appropriate
Motility abnormalities	6 (4–7)	Uncertain
Loss of bowel wall layer stratification	5 (4–7)	Uncertain
Lack of compressibility	5·5 (5–7)	Uncertain
Mesenteric inflammatory fat	4 (2–5)	Uncertain
Mesenteric lymphadenopathy	3·5 (2–5)	Inappropriate
Echogenic submucosa	6 (5–7)	Uncertain
Enlarged lymph nodes	3 (2–4)	Inappropriate
Penetrating disease	4·5 (2–5)	Uncertain
Ulceration	2·5 (1–4)	Inappropriate
Mural or peri-enteric hyperaemia	3 (2–4)	Inappropriate
Comb sign	3 (2–5)	Inappropriate
The following features should be used to distinguish a predominantly inflammatory stricture from a predominantly fibrotic stricture		
Bowel wall thickening	5 (2–7)	Uncertain
Luminal narrowing	4·5 (2–5)	Uncertain
Pre-stenotic dilation	5 (4–6)	Uncertain
Motility abnormalities	3·5 (2–5)	Inappropriate
Loss of bowel wall layer stratification	7 (5–8)	Appropriate
Lack of compressibility	5 (3–5)	Uncertain
Mesenteric inflammatory fat	7·5 (5–8)	Appropriate
Mesenteric lymphadenopathy	5 (3–6)	Uncertain
Echogenic submucosa	6·5 (5–8)	Appropriate
Penetrating disease	5·5 (5–8)	Uncertain
Ulceration	8 (6–8)	Appropriate
Mural or peri-enteric hyperaemia	8 (8–9)	Appropriate
Comb sign	8 (6–8)	Appropriate
Luminal narrowing in Crohn's disease can be due to inflammation or fibrosis	9 (8–9)	Appropriate
The amount of pre-stenotic dilation correlates with the degree of fibrosis in the stricture	5 (5–7)	Uncertain

Table 2: **Consensus statements for diagnosing inflammation and fibrosis in small bowel Crohn's disease strictures on intestinal ultrasound**

reflective of inflammation: bowel wall thickness, loss of bowel wall layer stratification, mesenteric inflammatory fat, penetrating disease, ulceration, mural or peri-enteric hyperaemia, and comb sign. Presence of inflammation was deemed uncertain if luminal narrowing, pre-stenotic dilation, motility abnormalities, lack of compressibility, mesenteric lymphadenopathy, echogenic submucosa, or enlarged lymph nodes were present (table 2).

Stricture features that were likely to be indicative of fibrosis included bowel wall thickness and pre-stenotic dilation. It was considered inappropriate for mesenteric lymphadenopathy, ulceration, mural or peri-enteric hyperaemia, or comb sign to be a criterion for defining the presence of fibrosis. The panel was uncertain whether luminal narrowing, motility abnormalities, loss of bowel wall layer stratification, lack of compressibility, mesenteric inflammatory fat, echogenic submucosa, and penetrating disease should be considered markers of fibrosis (table 2).

For bowel wall thickness, the panel considered it appropriate to define bowel wall thickness as a maximally thickened area of greater than 3 mm. It was also considered appropriate to score bowel wall thickness continuously (recorded in mm to one decimal place) using the mean of two measurements in a cross-sectional orientation, and two measurements in a longitudinal orientation. The panel determined that bowel wall thickness should be measured from the air or intestinal content interface and hypoechoic mucosa to the hyperechoic serosa of the area with the smallest luminal diameter. It was not considered appropriate for bowel wall thickness to be defined as a percentage increase in wall thickness (>25%, 50%, 75% or 100%, measured in the maximally thickened area relative to a normal adjacent bowel loop). Although the panel was uncertain whether bowel wall thickness should be scored on a four-category ordinal scale, the following cutoffs were considered acceptable if this method was employed: absent as less than 3·0 mm, mild as 3·1 to 5·0 mm, moderate as 5·1 to 8·0 mm, and severe as greater than 8·0 mm (table 3).

The panel considered it appropriate to define luminal narrowing as a luminal diameter (in the narrowest area, relative to a normal adjacent bowel loop) of less than 50%, or a luminal diameter of less than 1 cm. Grading luminal narrowing was also deemed appropriate as either absent (luminal diameter equivalent to the luminal diameter of a normal adjacent bowel loop), mild (luminal diameter reduction >25%), moderate (luminal diameter reduction >50%), or severe (luminal diameter reduction >75%; table 3).

The panel considered it appropriate to define pre-stenotic dilation as an increase in bowel diameter (in the maximally dilated area, relative to a normal adjacent bowel loop) of more than 50%, or a bowel diameter of more than 2·5 cm or an unequivocal increase in bowel diameter relative to a normal adjacent bowel loop with bowel wall thickness of less than 3 mm. The panel

determined that pre-stenotic dilation should be scored as a continuous measurement (in cm within 1 decimal place). It was uncertain whether pre-stenotic dilation should be scored using an ordinal scale (table 3).

In terms of motility, the panel felt that absence of peristalsis at the stricture site and luminal content squirting through the stricture should be used to define motility abnormalities at the stricture site. When defining motility abnormalities at the site of pre-stenotic dilation, the panel determined that absence of peristalsis at the stricture site, to-and-fro (oscillating), non-linear bowel content motion, and excess peristalsis proximal to the stricture should be used to define motility abnormalities at the site of pre-stenotic dilation. The panel acknowledged that motility abnormalities can occur before pre-stenotic dilation is present. In addition, motility abnormalities can occur when there is a fixed, rigid, thickened bowel wall with luminal narrowing in the absence of pre-stenotic dilation. Concerning scoring, the panel determined that motility abnormalities should be scored as absent or present. If present, motility abnormalities can be further scored as reduced or increased. The panel determined that motility abnormalities should be scored at both the stricture and pre-stenotic dilation sites (appendix p 7).

Definitions for individual stricture parameters were queried for naive and anastomotic small bowel strictures. The panel found that the same definitions were appropriate for both forms of strictures (figure 1). Appropriateness ratings for mural and peri-enteric hyperaemia, mesenteric inflammatory fat, bowel wall stratification, submucosa, compressibility, mesenteric lymphadenopathy, and peri-enteric complications can be found in the appendix (p 8).

The panel felt that when measuring stricture length, taking the measurement (in cm) from the bowel segment with luminal narrowing is appropriate (appendix p 11). It was also deemed appropriate to take the measurement (in cm) from the bowel segment with the smallest luminal diameter at the beginning and end of the area of abnormality (appendix p 21).

The panel considered it appropriate to detect multiple strictures per patient using grey scale intestinal ultrasound with Doppler imaging, and uncertain with grey scale intestinal ultrasound with oral contrast (appendix p 12). The use of grey scale intestinal ultrasound with elastography and grey scale intestinal ultrasound with intravenous contrast and elastography were deemed uncertain (appendix p 12).

For treatment response, the panel determined that the following intestinal ultrasound features will improve with successful anti-inflammatory stricture treatment: stricture length, bowel wall thickness, luminal narrowing, pre-stenotic dilation, motility abnormalities, loss of bowel wall layer stratification, mesenteric inflammatory fat, penetrating disease, ulceration, mural or peri-enteric hyperaemia, and comb sign (table 4, figure 2). Concerning successful anti-fibrotic treatment, the panel concluded that stricture length, bowel wall thickness, luminal narrowing, pre-stenotic dilation, and motility abnormalities will improve. Enlarged lymph nodes, ulceration,

	Median rating (IQR)	Appropriateness
Bowel wall thickness should be scored as a continuous measurement (in mm within 1 decimal place)	8·5 (8–9)	Appropriate
Bowel wall thickness should be scored as a continuous measurement using the mean of two measures in cross-sectional orientation and two measures in longitudinal orientation	8 (7–9)	Appropriate
Bowel wall thickness should be scored as absent, mild, moderate, or severe	4 (2–7)	Uncertain
Bowel wall thickness should be scored using the following cutoffs*		
Absent: <3·0 mm; mild: 3·1–6·0 mm; moderate: 3·1–6·0 mm; severe: >6·0 mm	4·5 (1–6)	Uncertain
Absent: <3·9 mm; mild: 4·0–6·0 mm; moderate: 6·1–8·0 mm; severe: >8·1 mm	4 (2–5)	Uncertain
Absent: <3·0 mm; mild: 3·1–5·0 mm; moderate: 5·1–8·0 mm; severe: >8·0 mm	7 (5–8)	Appropriate
None of the above	5 (1–7)	Uncertain
Bowel wall thickening should be defined as a measurement in the maximally thickened area of		
>2·0 mm	3 (2–5)	Inappropriate
>3·0 mm	8·5 (8–9)	Appropriate
>4·0 mm	5 (3–7)	Uncertain
>5·0 mm	4 (2–7)	Uncertain
Bowel wall thickening should be defined as an increase in wall thickness (in the maximally thickened area, relative to a normal adjacent bowel loop) of		
>25%	4·5 (3–6)	Uncertain
>50%	5 (3–7)	Uncertain
>75%	3 (2–7)	Inappropriate
100%	3 (2–5)	Inappropriate
The same definition of bowel wall thickening can be used for both naive and anastomotic small bowel strictures	8 (7–9)	Appropriate
Luminal narrowing should be defined as a luminal diameter (in the narrowest area, relative to a normal adjacent bowel loop) of		
<25%	5 (3–5)	Uncertain
<50%	7 (5–8)	Appropriate
<75%	5 (3–7)	Uncertain
100%	3 (2–6)	Inappropriate
Luminal narrowing should be defined as a luminal diameter of		
<2·0 cm	3 (2–5)	Inappropriate
<1·5 cm	4 (2–6)	Uncertain
<1·0 cm	6·5 (5–8)	Appropriate
<0·5 cm	6 (5–8)	Uncertain
Complete obstruction	3 (2–7)	Inappropriate
The same definition of luminal narrowing can be used for both naive and anastomotic small bowel strictures	8 (7–9)	Appropriate
Luminal narrowing should be scored as absent (luminal diameter equivalent to the luminal diameter of a normal adjacent bowel loop); mild (luminal diameter reduction >25% of luminal diameter of a normal adjacent bowel loop); moderate (luminal diameter reduction >50% of luminal diameter of a normal adjacent bowel loop); or severe (luminal diameter reduction >75% of luminal diameter of a normal adjacent bowel loop)	6·5 (3–8)	Appropriate
Pre-stenotic dilation should be defined as an unequivocal increase in bowel diameter relative to a normal adjacent bowel loop with bowel wall thickness <3 mm*	7 (6–8)	Appropriate

(Table 3 continues on next page)

	Median rating (IQR)	Appropriateness
(Continued from previous page)		
Pre-stenotic dilation should be defined as an increase in bowel diameter (in the maximally dilated area, relative to a normal adjacent bowel loop) of		
>25%	4 (2–6)	Uncertain
>50%	6·5 (2–8)	Appropriate
>75%	5 (2–6)	Uncertain
100%	5 (2–7)	Uncertain
Pre-stenotic dilation should be defined as a bowel diameter of		
>2·0 cm	3 (2–5)	Inappropriate
>2·5 cm	7 (4–8)	Appropriate
>3·0 cm	8 (6–8)	Appropriate
>3·5 cm	4 (3–7)	Uncertain
>4·0 cm	3·5 (2–6)	Inappropriate
The same definition of pre-stenotic dilation can be used for both naive and anastomotic small bowel strictures	8 (8–9)	Appropriate
Pre-stenotic dilation should be scored as a continuous measurement (in cm within 1 decimal place)	8 (7–8)	Appropriate
Pre-stenotic dilation should be scored as absent, mild, moderate, severe, or unclear (due to bowel gas shadowing of the posterior wall)	6 (2–8)	Uncertain

*Indicates questions that were modified following round one of the UCLA–RAND Consensus process.

Table 3: **Consensus statements for defining individual stricture parameters in small bowel Crohn's disease strictures on intestinal ultrasound**

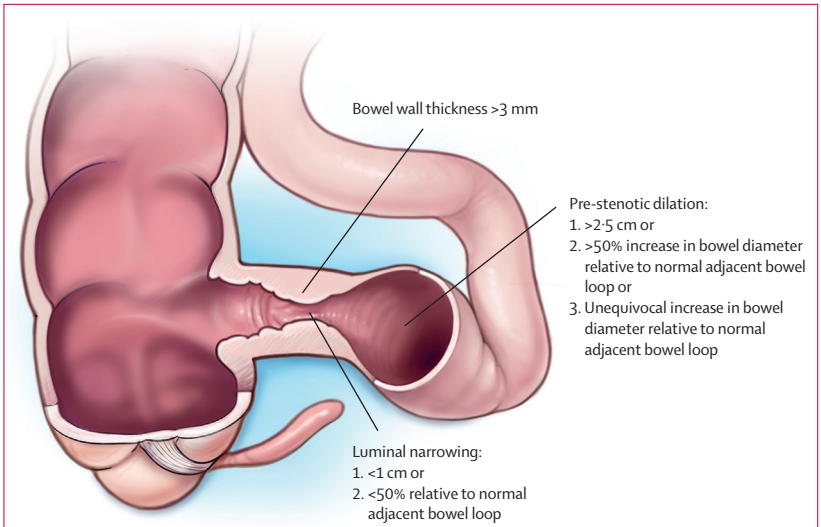

Figure 1: **Anastomotic and naive small bowel Crohn's disease strictures on intestinal ultrasound defined by the combination of bowel wall, luminal narrowing, and pre-stenotic dilation**
Items defining motility abnormalities are described in the Results and the appendix (p 7).

mural or peri-enteric hypaeremia, and comb sign were rated as inappropriate indicators of successful anti-fibrotic therapy (table 5). With respect to failure of anti-fibrotic treatment, stricture length, bowel wall thickness, luminal narrowing, pre-stenotic dilation, motility abnormalities, ulceration, and mural or peri-enteric hyperaemia in addition to penetrating disease were also considered as features appropriate for detecting treatment failure of a small bowel stricture (table 6).

	Median rating (IQR)	Appropriateness
Stricture length	7 (5–8)	Appropriate
Bowel wall thickening	8 (8–9)	Appropriate
Luminal narrowing	8 (6–9)	Appropriate
Pre-stenotic dilation	7 (6–9)	Appropriate
Motility abnormalities	7 (5–8)	Appropriate
Loss of bowel wall layer stratification	8 (7–8)	Appropriate
Lack of compressibility	5·5 (5–7)	Uncertain
Mesenteric inflammatory fat	8 (7–9)	Appropriate
Mesenteric lymphadenopathy	6 (4–8)	Uncertain
Echogenic submucosa	5 (4–7)	Uncertain
Enlarged lymph nodes	6 (3–7)	Uncertain
Penetrating disease	7 (5–8)	Appropriate
Ulceration	8 (8–9)	Appropriate
Mural or peri-enteric hyperaemia	8 (8–9)	Appropriate
Comb sign	8 (6–8)	Appropriate

Table 4: **Consensus statements for improved features from successful anti-inflammatory treatment of small bowel Crohn's disease strictures on intestinal ultrasound**

In terms of treatment response for stricture length, in the first round of voting, the panel determined that it is appropriate to define improvement in stricture length as a reduction in length of more than 25%. However, this definition was rated as uncertain in the second round of voting. All the other improvement benchmarks (a reduction of greater than 0·5–3·0 cm and a reduction >10–75%) were rated as uncertain across both rounds of voting (appendix p 13).

Of the definitions queried, only an improvement of more than 25% in bowel wall thickness was considered appropriate (appendix p 13).

Of the definitions queried, only an improvement of more than 50% in luminal narrowing was considered appropriate (appendix p 13).

Two definitions were deemed appropriate for improvement in pre-stenotic dilation: (1) a reduction in the absolute diameter of more than 25%; and (2) a bowel diameter of less than 2·5 cm (appendix p 14). If the stricture has a fixed narrowing (ie, a rigid segment of bowel with a narrowed lumen) without pre-stenotic dilation, the panel determined that treatment response can be defined as an improvement in stricture length, bowel wall thickness, luminal narrowing, motility abnormalities, loss of bowel wall layer stratification, ulceration, or mural or peri-enteric hyperaemia (appendix p 15).

It was considered appropriate to measure improvement in mural and peri-enteric hyperaemia (using colour Doppler signal) as a one-point or two-point reduction in the Limberg score[12] and modified Limberg score (appendix p 14).[13] A one-point decrease with or without a bowel wall thickness by more than 25% in the International Bowel Ultrasound Segmental Activity Score Colour Doppler imaging signal sub-score was also considered appropriate.[13]

The panel considered it appropriate to assess treatment response on intestinal ultrasound as the primary outcome at three time points: weeks 12, 24, and 52 (appendix p 15).

Voting on reporting, intestinal ultrasound machine settings, make, model, pre-sets, fasted state, and image and video capture parameters have been described in the appendix (pp 17–18).

The results for using conventional intestinal ultrasound with Doppler imaging, grey scale intestinal ultrasound with oral contrast, or the addition of intravenous contrast or elastography for diagnosing and assessing strictures can be found in the appendix (pp 12, 19). In brief, conventional intestinal ultrasound with Doppler imaging or intravenous contrast was considered appropriate to assess the inflammatory component of a small bowel stricture, but uncertain for elastography. For evaluating the fibrotic component of a stricture, it was uncertain if grey scale intestinal ultrasound with oral or intravenous contrast, or elastography was ideal. Only grey scale intestinal ultrasound with Doppler imaging was considered appropriate for assessing the fibrotic component of a small bowel stricture.

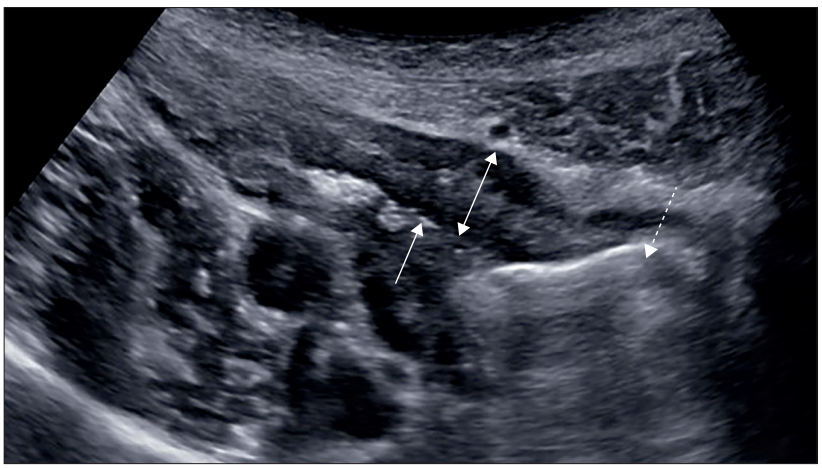

Figure 2: **Longitudinal view of terminal ileal stricture with bowel wall thickness at 9·3 mm (double-headed solid arrow), luminal apposition at 1·3 mm (solid arrow), and pre-stenotic dilation (dashed arrow)**
Echogenic mesenteric inflammatory fat is present around the stricture with loss of bowel wall layer stratification. Treatment response of strictures is defined as reduction in stricture length, bowel wall thickening, luminal narrowing, pre-stenotic dilation, mesenteric inflammatory fat, mural or peri-enteric hyperaemia as measured by colour Doppler signal, comb sign, motility abnormalities, and improved loss of bowel wall layer stratification.

	Median rating (IQR)	Appropriateness
Stricture length	8 (7–8)	Appropriate
Bowel wall thickening	8 (7–8)	Appropriate
Luminal narrowing	8 (8–9)	Appropriate
Pre-stenotic dilation	8 (7–9)	Appropriate
Motility abnormalities	7·5 (7–8)	Appropriate
Loss of bowel wall layer stratification	5 (5–8)	Uncertain
Lack of compressibility	6 (5–7)	Uncertain
Mesenteric inflammatory fat	5 (2–5)	Uncertain
Mesenteric lymphadenopathy	4 (2–5)	Uncertain
Echogenic submucosa	5 (2–7)	Uncertain
Enlarged lymph nodes	3 (2–5)	Inappropriate
Penetrating disease	5 (2–5)	Uncertain
Ulceration	3·5 (2–5)	Inappropriate
Mural or peri-enteric hyperaemia	3·5 (2–5)	Inappropriate
Comb sign	3·5 (2–5)	Inappropriate

Table 5: **Consensus statements for improved features from successful anti-fibrotic treatment of small bowel Crohn's disease strictures on intestinal ultrasound**

Discussion

Although CT enterography and magnetic resonance enterography are the most commonly used diagnostic imaging modalities to assess Crohn's disease strictures, the use of intestinal ultrasound is growing worldwide.[14,15] The accuracy of CT enterography, magnetic resonance enterography, and intestinal ultrasound for stricture diagnosis is high when using histopathology as a reference standard.[1] A systematic review[1] has reported sensitivities for CT from 85%[16] to 100%,[17] MRI from 75%[18] to 100%,[19] and intestinal ultrasound from 80%[20] to 100%,[21] and specificities from 38·9%[22] to 100%[17] for CT, 91%[19] to 96%[18] for MRI, and 63%[21] to 100%[20] for intestinal ultrasound. Given that intestinal ultrasound has unique differences to conventional cross-sectional imaging, it is unclear if the global Crohn's disease anti-fibrotic stricture therapies (CONSTRICT) consensus criteria[3] for small bowel stricture diagnosis and treatment response apply to intestinal ultrasound. We conducted a modified RAND–UCLA Appropriateness Method exercise to assess the appropriateness of a comprehensive list of items from a systematic review for definitions and treatment targets for small bowel Crohn's disease strictures.[11] Compiling these statements creates the foundation for the continuing creation and validation of a stricture intestinal ultrasound index for clinical trials.

The definition of small bowel strictures on intestinal ultrasound matches the CONSTRICT criteria for CT enterography and magnetic resonance enterography,[3] and includes the same three features: bowel wall thickness, luminal narrowing, and pre-stenotic dilation. Similarly, the specific criteria for each feature match, except for the CONSTRICT criteria that specify a percent increase in bowel wall thickness compared with normal adjacent bowel. Two notable differences for stricture definitions from this intestinal ultrasound consensus compared with CT enterography and magnetic resonance enterography criteria are the addition of a definition for luminal narrowing of less than 1 cm, and a pre-stenotic dilation of more than 2·5 cm instead of only more than 3·0 cm. Our systematic review, conducted before this consensus, identified that most intestinal ultrasound studies used a pre-stenotic dilation cutoff of 2·5 cm,[11] which could be explained by the fact that in

	Median rating (IQR)	Appropriateness
Stricture length	7 (5–8)	Appropriate
Bowel wall thickening	8 (7–8)	Appropriate
Luminal narrowing	8 (7–9)	Appropriate
Pre-stenotic dilation	8 (8–9)	Appropriate
Motility abnormalities	7 (5–8)	Appropriate
Loss of bowel wall layer stratification	5·5 (5–7)	Uncertain
Lack of compressibility	5 (3–6)	Uncertain
Mesenteric inflammatory fat	5·5 (5–7)	Uncertain
Mesenteric lymphadenopathy	5 (3–5)	Uncertain
Echogenic submucosa	5 (4–6)	Uncertain
Enlarged lymph nodes	5 (2–6)	Uncertain
Penetrating disease	6·5 (5–8)	Appropriate
Ulceration	7 (5–8)	Appropriate
Mural or peri-enteric hyperaemia	7·5 (7–9)	Appropriate
Comb sign	5·5 (5–7)	Uncertain

Table 6: **Consensus statements for features of treatment failure or re-obstruction of small bowel Crohn's disease strictures on intestinal ultrasound**

distinction to CT enterography and magnetic resonance enterography, intestinal ultrasound does not routinely use oral contrast. Absence of oral contrast is likely to result in less bowel dilation. Of note, a stricture on intestinal ultrasound can be diagnosed without pre-stenotic dilation if there is fixed narrowing and bowel wall thickness of more than 3 mm. The diagnosis of a stricture in the absence of pre-stenotic dilation has been controversial on magnetic resonance enterography or CT enterography[23,24] as other stricture criteria, such as bowel wall thickness and luminal narrowing could be caused by inflammation alone. Importantly, intestinal ultrasound can assess motility, but its use in clinical trials is hampered by absence of standard methodology and correlation with fibrosis or inflammation. The reliability of intestinal ultrasound motility assessment has not been established. Developing reliable methods to detect motility abnormalities in Crohn's disease strictures is required. This goal is part of the Crohn's disease stricture intestinal ultrasound index development programme of the STAR consortium.

An important finding of this consensus was that the criteria for definitions and monitoring of naive and anastomotic strictures were highly similar. This result contrasts with opinions that naive and anastomotic strictures are due to distinct pathological processes with anastomotic strictures being more related to ischaemia,[25] which is a notion that remains unproven. It was the consensus' view that the same intestinal ultrasound criteria should be used for both naive and anastomotic small bowel Crohn's disease strictures, and in both clinical practice and trials.

None of the novel intestinal ultrasound techniques such as intravenous contrast and elastography are sufficiently accurate to differentiate inflammatory and fibrotic components of strictures. Elastography lacks standardised methodology, and challenges include the heterogeneous pattern of fibrosis along a stricture, the selection of the optimal region of interest, and empiric evidence of reliability.[26] Only colour Doppler imaging is considered sufficient for assessment of transmural inflammatory activity of strictures with the Limberg score, modified Limberg score, or the International Bowel Ultrasound colour Doppler Imaging score.

Of importance, standards for stricture assessment, including cine loop videos, measurement, grading parameters, machine settings, fasting states, or oral contrast are currently available. Implementation of these standards will probably improve accuracy and reproducibility between investigations, similar to the evolution that has occurred for endoscopic and histopathology assessments.[27,28]

As the absence of well-defined endpoints has constrained stricture drug development, this consensus provides guidance for intestinal ultrasound features that indicate improvement in strictures following therapy. After 12 weeks, 24 weeks, and 52 weeks, stricture length, bowel wall thickness, luminal narrowing, pre-stenotic dilation, and motility abnormalities can be used. In the only randomised controlled trial in stricturing Crohn's disease, the STRIDENT trial, intestinal ultrasound endpoints included a decrease in bowel wall thickness by at least 25%, normalisation of pre-stenotic dilation (<2·5 cm), and reduction in stricture hyperaemia (Limberg score ≤1).[29] It has to be noted, however, that strictures did not require the presence of pre-stenotic dilation for inclusion. We speculate that a high number of patients could have had inflammatory disease predominance, rather than a more fixed stricture.

Limitations of our study include recommendations that are based on expert opinion and mainly observational data that preclude strong recommendations in several areas. For example, in round one, the panel agreed that stricture length improvement was defined as reduction in length of more than 25%. However, in the second round, the panel was uncertain about this statement. As a result, our unbiased approach was to report the discrepancy between both rounds. Secondly, our study did not thoroughly query how to define multifocal strictures. The panel agreed that intestinal ultrasound can be used to evaluate multifocal strictures. We propose to measure the length of a segment with multifocal strictures as one single long segment if the strictures are less than or equal to 3 cm from each other with active disease in between them. Multifocal strictures in close proximity to each other are often treated as one stricture when resected. Furthermore, there is no data on the effect of anti-fibrotic treatment on small bowel strictures. This RAND–UCLA Appropriateness Method survey assumed that effective anti-fibrotic therapy will reverse the severity of the stricture, but future therapies could only be able to prevent

progression. Additionally, the panel agreed that a stricture could be diagnosed without proximal dilation if a fixed narrowing is present. However, there remains an absence of clarity whether this description should also consider the quantity of hyperaemia, and wall layer echo stratification pattern to maximise the likelihood of a stricture diagnosis. Also, this definition could lead to false positive diagnoses as inflammation alone can alter intestinal motility. The accuracy of this definition and other definitions would need to be evaluated in future prospective studies. Strengths of our study include the use of rigorous methodology to minimise bias while including international experts in inflammatory bowel disease, strictures, and diagnostic imaging. The greatest strength is that our study addresses a critical unmet need in Crohn's disease clinical care and research. This study is a necessary step to provide guidance to define and diagnose strictures on intestinal ultrasound for future trial design.

In summary, this RAND–University of California Los Angeles consensus makes clear recommendations on definitions, treatment response, and technical parameters for intestinal ultrasound imaging and video capture using existing evidence and expert opinion. Based on the items considered appropriate, an intestinal ultrasound index will be developed and validated for responsiveness to therapy. This initiative allows for the use of intestinal ultrasound as a cost-effective, accurate, and well-tolerated tool for patients in routine clinical use and in anti-fibrotic drug development.

Contributors

CL and FR worked on the conception and design of the manuscript. CL, SRW, MEB, GB, JB, DHB, RVB, BC, BGF, JGF, GH, VJ, JK, TK, KL, CM, GM, KN, JR, SAT, RW, and FR were members of the panel for the RAND–University of California Los Angeles Appropriateness Method. CL, RR, CEP, JR, SRW, MEB, GB, JB, DHB, RVB, BC, BGF, JGF, IG, GH, VJ, JK, TK, KL, CM, GM, KN, JR, SAT, RW, and FR contributed to the drafting of the article or revising it critically for important intellectual content, and approved the final version to be submitted. All authors approved the final version of the Article. CL and FR directly accessed and verified the underlying data reported in the manuscript.

Declaration of interests

CL has received speaker fees from AbbVie, Celltrion, Janssen, and Fresenius Kabi, and advisory board fees from AbbVie, Janssen, Lilly, Pfizer, Takeda, Fresenius Kabi, Pendopharm, and Ferring. CEP is an employee of Alimentiv. JR is an employee of Alimentiv. SRW has received partial research support from Samsung for an unrelated project, and equipment support from Samsung, Siemens, and Philips. MEB receives grant support to his institution from Siemens Healthineers, the Leona M and Harry B Helmsley Charitable Trust, and Pfizer, and provides informal consulting to Agomab. JB has received speaker and advisory board fees from Abbvie. DHB has received advisory board fees from Janssen. RVB has received speaker and advisory board fees from AbbVie, BiomeBank, Ferring, Janssen, Shire, and Takeda, and is a shareholder in BiomeBank. BC has received research support and speaker fees from AbbVie, Janssen, Takeda, Celltrion, Sandoz, and Falk. BGF has received speaker and advisory board fees from AbbVie, AbolerIS, AgomAB Therapeutics, Allianthera, Amgen, AnaptysBio, Applied Molecular Transport, Arena Pharma, Avoro Capital Advisors, Atomwise, BioJamp, Biora Therapeutics, Boehringer-Ingelheim, Boxer, Celsius Therapeutics, Celgene or Bristol Myers Squibb, Connect BioPharma, Cytoki, Disc Medicine, Duality, EcoR1, Eli Lilly, Equillium, Ermium, First Wave, First Word Group, Galapagos, Galen Atlantica, Genentech or Roche, Gilead, Gossamer Pharma, GSK, Hinge Bio, Hot Spot Therapeutics, Index Pharma, Imhotex, Immunic Therapeutics, JAK Academy, Janssen, Japan Tobacco, Kaleido Biosciences, Landos Biopharma, Leadiant, LEK Consulting, Lenczner Slaght, LifeSci Capital, Lument AB, Millennium, MiroBio, Morgan Lewis, Morphic Therapeutics, Mylan, OM Pharma, Origo BioPharma, Orphagen, Pandion Therapeutics, Pendopharm, Pfizer, Prometheus Therapeutics and Diagnostics, Play to Know AG, Progenity, Protagonist, PTM Therapeutics, Q32 Bio, Rebiotix, REDX, Roche, Sandoz, Sanofi, Seres Therapeutics, Silverback Therapeutics, Surrozen, Takeda, Teva, Thelium, Tigenix, Tillotts, Ventyx Biosciences, VHSquared, Viatris, Ysios, Ysopia, and Zealand Pharma, and is a shareholder in Gossamer Bio. JGF has received grant support from Siemens Healthineers. VJ has received speaker and advisory board fees from AbbVie, Alimentiv, Arena pharmaceuticals, Asahi Kasei Pharma, Asieris, Astra Zeneca, Avoro Capital, Boehringer Ingelheim, Bristol Myers Squibb, Celltrion, Eli Lilly, Endpoint Health, Ferring, Flagship Pioneering, Fresenius Kabi, Galapagos, Gilde Healthcare, GlaxoSmithKline, Genentech, Gilead Sciences, Innomar, JAMP Pharma, Janssen, Merck, Metacrine, Mylan, Pandion, Pendopharm, Pfizer, Protagonist, Prometheus Biosciences, Reistone Biopharma, Roche, Sandoz, SCOPE, Second Genome, Sorriso pharmaceuticals, Takeda, Teva, Tigenix, Topivert, Ventyx, and Vividion, and research support from Abbvie, Boehringer Ingelheim, Celgene/BMS, Eli Lilly, Gilead Sciences, Janssen, Pfizer, and Tigenix. TK has received advisory board and speaker fees from AbbVie, Amgen, Boehringer Ingelheim, Biogen, Celltrion, Celgene, Bristol-Myers Squibb, Hospira, Mundipharma, Dr Falk Pharma GmbH, Ferring Arzneimittel GmbH, Galapagos, Gilead, Janssen, Merck Sharp & Dohme GmbH, Novartis, Pfizer, Roche, Takeda Pharma GmbH, and UCB Pharma. CM has received speaker or honoraria fees AbbVie, Astra Zeneca, Biogen, Bristol-Myers Squibb, Dr Falk Pharma GmbH, Ferring Arzneimittel, Galapagos, Gilead, Janssen, Lilly, Merck Sharp & Dohme, Pfizer, Roche, Samsung, Takeda Pharma, and Vifor Pharma. GM has received speaker and advisory board fees from Alfa Sigma, Fresenius Kabi, and Gilead. KN has received speaker and advisory board fees from AbbVie, Amgen, Bristol Myers Squibb, Janssen, Lily, Organon, Pendopharm, Pfizer, Ferring, Takeda, and Fresenius Kabi, research support from Pfizer and Janssen, and equipment support from Samsung. JR has received speaker and advisory board fees from Alimentiv, Boehringer Ingelheim, Gilead, Janssen Pharmaceuticals, Takeda, TiGenix, Ferring, and Origo, and research support from AbbVie and Genentech. SAT has received speaker and advisory board fees from Alimentiv and AstraZeneca, and is a shareholder in Motilent. RW has received speaker and advisory board fees from AbbVie, Alimentiv, Janssen, Pfizer, and Takeda. FR is consultant to Adiso, Adnovate, Agomab, Allergan, AbbVie, Arena, Astra Zeneca, Boehringer-Ingelheim, Celgene/BMS, Celltrion, Clinical Data Interchange Standards Consortium, Celsius, Cowen, Ferring, Galapagos, Galmed, Genentech, Gilead, Gossamer, Granite, Guidepoint, Helmsley, Horizon Therapeutics, Image Analysis, Index Pharma, Landos, Jannsen, Koutif, Mestag, Metacrine, Mopac, Morphic, Organovo, Origo, Palisade, Pfizer, Pliant, Prometheus Biosciences, Receptos, RedX, Roche, Samsung, Sanofi, Surmodics, Surrozen, Takeda, Techlab, Teva, Theravance, Thetis, UCB, Ysios, and 89Bio. All other authors declare no competing interests.

Data sharing

All data has been presented in this Article and appendix.

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