



STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD

Dan Turner,^{1,*} Amanda Ricciuto,^{2,*} Ayanna Lewis,^{3,*} Ferdinando D'Amico,^{4,*} Jasbir Dhaliwal,^{5,*} Anne M. Griffiths,² Dominik Bettenworth,⁶ William J. Sandborn,⁷ Bruce E. Sands,⁸ Walter Reinisch,⁹ Jürgen Schölmerich,¹⁰ Willem Bemelman,¹¹ Silvio Danese,⁴ Jean Yves Mary,¹² David Rubin,¹³ Jean-Frederic Colombel,¹⁴ Laurent Peyrin-Biroulet,¹⁵ Iris Dotan,¹⁶ Maria T. Abreu,³ and Axel Dignass,¹⁷ on behalf of the International Organization for the Study of IBD

¹ Shaare Zedek Medical Center, the Hebrew University of Jerusalem, Jerusalem, Israel; ²Hospital for Sick Children, Toronto, Canada; ³Division of Gastroenterology, Department of Medicine, University of Miami Miller School of Medicine, Miami, Florida; ⁴Humanitas Clinical and Research Center – IRCCS, Rozzano and Humanitas University, Department of Biomedical Sciences, Pieve Emanuele, Milan, Italy; ⁵Cincinnati Children's Hospital, University of Cincinnati, Cincinnati, Ohio; ⁶Department of Medicine B for Gastroenterology and Hepatology, University Hospital Münster, Münster, Germany; ⁷Division of Gastroenterology, University of California San Diego, La Jolla, California; ⁸Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, New York; ⁹Medical University of Vienna, Department of Internal Medicine III, Division Gastroenterology and Hepatology, Vienna, Austria; ¹⁰(Private Practice), Hofheim, Germany; ¹¹Department of Surgery, Amsterdam UMC, University of Amsterdam, Locatie AMC, The Netherlands; ¹²Inserm UMR1153 CRESS, équipe ECSTRRA, Université de Paris, Paris, France; ¹³Section of Gastroenterology, Hepatology and Nutrition, University of Chicago Medicine, Chicago, Illinois; ¹⁴Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, New York; ¹⁵Department of Gastroenterology and Inserm NGERE U1256, University Hospital of Nancy, University of Lorraine, Vandoeuvre-lès-Nancy, France; ¹⁶Division of Gastroenterology, Rabin Medical Center, Petah Tikva, Israel and the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; and ¹⁷Department of Medicine I, Agaplesion Markus Hospital, Goethe University, Frankfurt/Main, Germany

See Covering the Cover synopsis on page 1435.

BACKGROUND: The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative of the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) has proposed treatment targets in 2015 for adult patients with inflammatory bowel disease (IBD). We aimed to update the original STRIDE statements for incorporating treatment targets in both adult and pediatric IBD. **METHODS:** Based on a systematic review of the literature and iterative surveys of 89 IOIBD members, recommendations were drafted and modified in 2 surveys and 2 voting rounds. Consensus was reached if $\geq 75\%$ of participants scored the recommendation as 7 to 10 on a 10-point rating scale. **RESULTS:** In the systematic review, 11,278 manuscripts were screened, of which 435 were included. The first IOIBD survey identified the following targets as most important: clinical response and remission, endoscopic healing, and normalization of C-reactive protein/erythrocyte sedimentation rate and calprotectin. Fifteen recommendations were identified, of which 13 were endorsed. STRIDE-II confirmed STRIDE-I long-term targets of clinical remission and endoscopic healing and added absence of disability, restoration of quality of life, and normal growth in children. Symptomatic relief and normalization of serum and fecal markers have been determined as short-term targets. Transmural healing in Crohn's disease and histological healing in ulcerative colitis are not formal targets but should be assessed as measures of the remission depth. **CONCLUSIONS:** STRIDE-II

encompasses evidence- and consensus-based recommendations for treat-to-target strategies in adults and children with IBD. This framework should be adapted to individual patients and local resources to improve outcomes.

Keywords: Treat-to-Target; Endoscopic Healing; Biologics; Patient-Reported Outcomes; Biomarkers.

Knowledge of clinically relevant targets of individual treatments is important for improving management of patients with inflammatory bowel diseases (IBD). The Selecting Therapeutic Targets in IBD (STRIDE) program was initiated by the International Organization for the Study of IBD (IOIBD) in 2013 using an evidence-based expert consensus process. It subsequently led to a

*Authors share co-first authorship.

Abbreviations used in this paper: AUC, area under the curve; CD, Crohn's disease; CDAI, Crohn's disease activity index; CRP, C-reactive protein; EH, endoscopic healing; ESR, erythrocyte sedimentation rate; FC, fecal calprotectin; IBD, inflammatory bowel diseases; IOIBD, International Organization for the Study of Inflammatory Bowel Disease; MES, Mayo endoscopic subscore; PRO, patient-reported outcome; QoL, quality of life; SF, stool frequency; STRIDE, Selecting Therapeutic Targets in IBD; TNF, tumor necrosis factor; UC, ulcerative colitis.

Most current article

© 2021 by the AGA Institute
0016-5085/\$36.00

<https://doi.org/10.1053/j.gastro.2020.12.031>

WHAT YOU NEED TO KNOW**BACKGROUND AND CONTEXT**

Timely introduction and adjustment of appropriate medications according to well-defined treatment goals is the fundamental basis of managing Crohn's disease and ulcerative colitis.

NEW FINDINGS

The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE-II) group, has updated the 2015 STRIDE recommendations and has developed 13 updated and new recommendations for treating to target in Crohn's disease and ulcerative colitis, in both adults and pediatrics.

LIMITATIONS

These consensus recommendations are based on a systematic review of the literature in a rapidly evolving medical field, but often the available evidence was insufficient to make firm conclusions.

IMPACT

STRIDE-II presents the accumulating data on available treatment targets in an intuitive and time-dependent clinically-useful algorithm in order to facilitate treatment of IBD and improving long term disease outcomes.

position statement determining therapeutic targets for IBD to be used for a "treat-to-target" clinical management strategy.¹ Since then, the rapid advent of novel biologics and small molecules has increased our ability and aspirations in reaching beyond the conventional treatment goals of STRIDE-I. In parallel, advanced diagnostic tools are becoming widely available, such as bedside bowel ultrasound and home-based measurement of fecal inflammatory biomarkers, introducing new opportunities to improve disease outcomes. Nonetheless, these have also introduced further complexity into management algorithms, such as which drugs should be used in which particular sequence, when to start, when to dose-modify, when to stop, and when to consider surgery. This complexity is inevitably associated with discussions on new treatment goals and targets, such as histological healing, transmural healing, and molecular-based measures.

The overall goal of this position statement is to update the previous STRIDE guidance on treatment outcomes by providing contemporary consensus recommendations for using the different targets over the treatment course. Specifically, we aimed to review and discuss existing and potential endpoints on the basis of recently published new evidence data and to extend the previous recommendations also to pediatric IBD. Finally, we aimed to tabulate the reviewed endpoints in an escalating algorithm along the timeline of specific treatments. Importantly, the STRIDE recommendations are focused on clinical practice rather than the clinical trial setting.

Methods

This project has been developed as part of the IOIBD endpoints cluster initiative and followed several stages to reach consensus among international IBD experts after careful review of existing evidence. A flow diagram of the various consensus procedures including the Delphi-like process and the systematic literature review is depicted in [Figure 1](#). A steering committee of 10 IOIBD members formulated the search questions and scope. A systematic review of the literature was performed in July 2019 by the informatician of Shaare Zedek Medical Center in Jerusalem using an identical search strategy as in STRIDE-I¹ and starting from the end date of the previous search, which reviewed the literature until the end of 2013. Similar to STRIDE-I, the following potential targets were explored separately in ulcerative colitis (UC) and in Crohn's disease (CD): clinical, endoscopic, histologic, imaging, biomarkers, and patient-reported outcomes (PROs). Four bibliographic fellows (2 for CD and 2 for UC) reviewed all identified abstracts and potentially eligible studies were retrieved in full text. The fellows drafted summary reports of the evidence of each potential target addressing both accuracy and time to achieving the target following initiation of treatment. These reports were circulated to all IOIBD members before voting.

In parallel, a survey was sent to all IOIBD members asking them to state the most important targets in UC and separately in CD. The derived list was re-sent to the group to rank by order of importance on a 5-grade scale (1 as most important, 5 as least important) until no new inputs were obtained following a Delphi-like process. At each round, responses were tabulated and summarized before re-sending to the group. The participants were also asked to comment on anticipated time to achieving the different potential targets after starting specific treatments. Finally, the group was asked to comment on which specific index or measure should be used for each potential target and to recommend optimal cutoff to define achieving the target (eg, cutoff of fecal calprotectin). Two face-to-face meetings were held to discuss the concepts: one at the initiation of the project (in Rio de Janeiro, Brazil) and another after the completion of the first draft (in Havana, Cuba).

Based on the preceding, consensus statements were drafted by the steering committee, and then sent to all IOIBD members for voting along with the literature review. Identical to the methodology used in STRIDE-I, agreement was achieved if at least 75% of participants scored the statement as 7 to 10 on a 10-point rating scale (1, do not agree at all; 10, agree completely). For those statements, where no consensus was achieved, the statements were revised based on the voters' comments, followed by a second round of voting. If no agreement was reached after 2 rounds of voting, then the statement was excluded.

Results

In total, 11,278 abstracts were screened in duplicate (6223 in CD and 5055 in UC), 1005 were reviewed as full text (413 in CD and 592 in UC) and 435 manuscripts (297 in CD and 138 in UC) were eventually included in the summary of evidence (Appendices under [Supplementary Material](#)). The following reasons for exclusion included among others: inappropriate follow-up period, reviews, irrelevant targets, small case series, and language other than English.

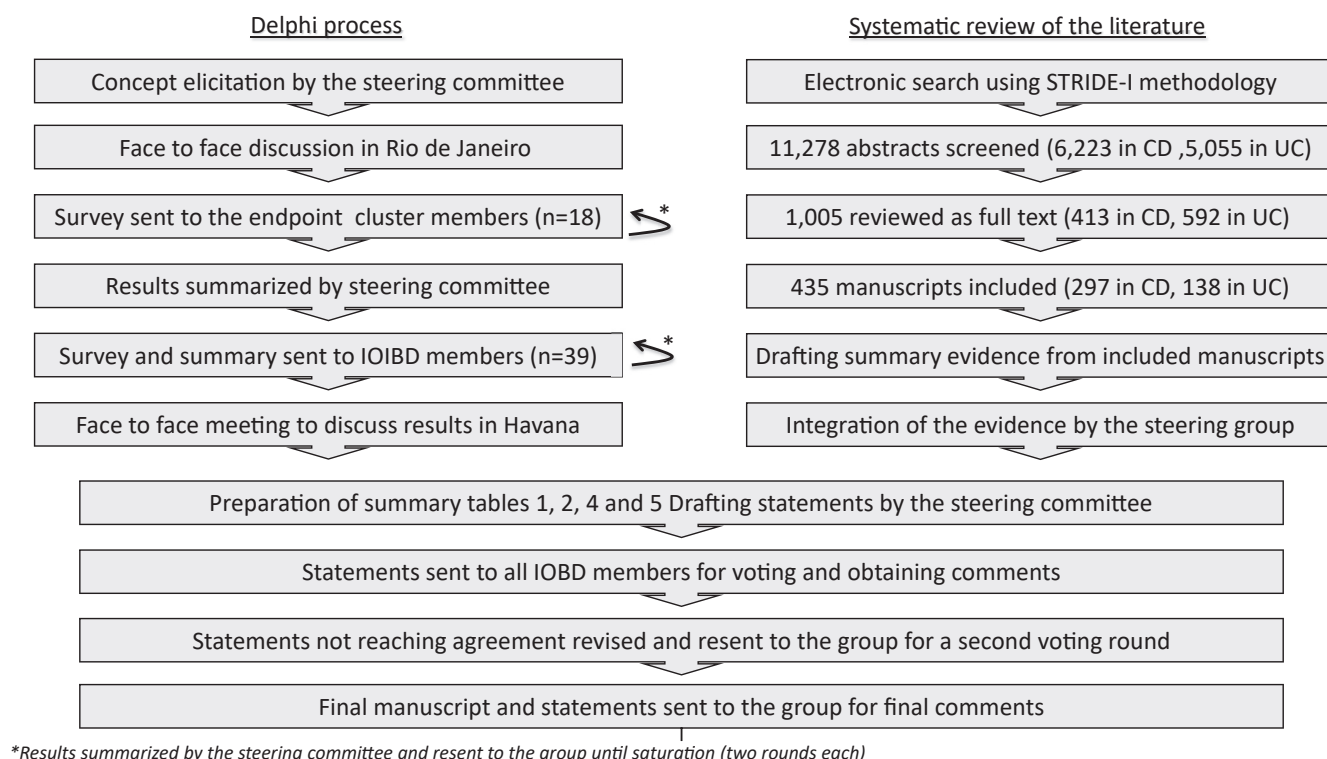


Figure 1. Flow diagram of the various consensus steps including Delphi-like process and systemic literature review.

The Delphi group suggested and ranked the potential targets (Table 1) and identified the preferred tools for capturing the identified targets with its recommended cutoff values. Supplementary Table 1 summarizes the most frequent cutoff scores suggested by the Delphi group and in the systematic review, as judged by the steering group that reviewed the evidence summaries.

Of the 89 IOIBD members, 39 (44%) participated in this concept elicitation stage. Based on the systematic review of the evidence and the Delphi-like process, recommendations were tabulated, along with the agreement rate obtained during 2 voting rounds returned by 70 (79%) of 89 IOIBD members (Table 2). Table 3 highlights the main new items in STRIDE-II

compared with STRIDE-I. Those not responding were most often members who felt they do not have enough clinical experience to vote (including pathologists, a statistician, and surgeons). In addition, 3 members who participated in the voting procedures did not vote on the pediatric statements.

Abbreviated Supportive Text

Comprehensive review of the evidence may be found in the Supplementary Material. Tables of evidence according to outcomes along with risk of bias and quality of individual included studies are included as supplementary material both in CD (Supplementary Table 2) and in UC

Table 1. Ranking of Importance of Short-Term Treatment Goals in IBD (1, Most Important; 5, Least Important) (Mean Values)

Crohn's disease (n = 39)		Ulcerative colitis (n = 36)	
Goals (order of importance)	Score	Goals (order of importance)	Score
Clinical remission	1.8	Clinical remission	2.3
Endoscopic response	2.1	Clinical response	2.4
Clinical response	2.2	Endoscopic response	2.4
Normalization of CRP/ESR	2.2	Normalization of CRP/ESR	2.7
Normalization of calprotectin	2.6	Normalization of calprotectin	2.7
Transmural healing	3.1	Histological healing	2.7
Histological healing	3.4	Transmural healing	4.2

Table 2. Recommendations for Treating to Target in CD and UC by the IOIBD (70 Participated of 89 Invited)

Recommendations	Voting results	
	Strength of recommendation ^c	% votes 7–10
<i>Clinical</i>		
1. Clinical response is an immediate treatment target. Consider changing treatment if this target has not been achieved. ^a	9.0	94
2. Clinical response should be defined as: a) <u>CD</u> : decrease of at least 50% in PRO2 (abdominal pain and stool frequency), and in children decrease in PCDAI of at least 12.5 points and in wPCDAI at least 17.5 points b) <u>UC</u> : decrease of at least 50% in PRO2 (rectal bleeding and stool frequency), and in children decrease in PUCAI of at least 20 points	8.3	84
3. Clinical remission is an intermediate (ie, medium-term) treatment target. Consider changing treatment if this target has not been achieved. ^a	8.7	94
4. Clinical remission should be defined as: a) <u>CD</u> : PRO2 (abdominal pain ≤ 1 and stool frequency ≤ 3) or HBI < 5 ; in children by PCDAI (< 10 points or < 7.5 excluding the height item) or wPCDAI (< 12.5 points) b) <u>UC</u> : PRO2 (rectal bleeding = 0 and stool frequency = 0) or partial Mayo (< 3 and no score > 1), and in children PUCAI < 10 points	8.5	81
5. Clinical response or remission are insufficient to be used as long term treatment targets	8.3	80
6. In children, restoration of normal growth is a long-term treatment target. Consider changing treatment if this target has not been achieved.	9.3	98
<i>Endoscopic and transmural assessment</i>		
7. Endoscopic healing is a long-term target. Consider changing treatment if this target has not been achieved.	8.7	87
8. Assessment of endoscopic healing can be achieved by sigmoidoscopy or colonoscopy. When not feasible, alternatives in CD can be capsule endoscopy or balloon enteroscopy.	8.3	86
9. Endoscopic healing should be measured by: a) <u>CD</u> : SES-CD < 3 points or absence of ulcerations (e.g. SES-CD ulceration subscores = 0) b) <u>UC</u> : Mayo endoscopic subscore = 0 points, or UCEIS ≤ 1 points	8.5	85
10. Histologic remission is not a treatment-target in either CD or UC. Nonetheless, in UC it could be used as an adjunct to endoscopic remission to represent a deeper level of healing.	7.7	80
11. Transmural healing (assessed by CTE, MRE, or bowel ultrasound) is not a treatment-target in either CD or UC. Nonetheless, in CD it should be used as an adjunct to endoscopic remission to represent a deeper level of healing.	7.5	77
<i>Biomarkers</i>		
12. Normalization of CRP (to values under the upper limit of normal) and fecal calprotectin (to 100–250 $\mu\text{g/g}$)^b is an intermediate treatment target in UC and CD. Consider changing treatment if this target has not been achieved.	8.2	80

(Supplementary Table 3). The following represents a succinct summary.

Crohn's Disease

Endoscopic healing. It is widely accepted that treating to the target of endoscopic healing (EH) is associated with

improved long-term outcomes and may reduce the risk of bowel damage.² Mucosal inflammation, even in the presence of clinical remission, is associated with long-term disease-related complications, flares, and surgeries.³ Indeed, EH was selected as the primary treatment target in the original STRIDE initiative and was also scored highest in our Delphi-like process as a

Table 2. Continued

Recommendations	Voting results	
	Strength of recommendation ^c	% votes 7–10
<i>Quality of life and disability</i>		
13. Absence of disability and normalized health-related quality of life are long-term treatment targets. Consider changing treatment if this target has not been achieved.	7.7	75

^aTime to achieving the target vary based on therapy and mechanism of action (Table 3).

^bThe cutoff value of fecal calprotectin is dependent on the desired outcome. Lower thresholds (eg, <100 µg/g) have been proposed for reflecting deep healing (both endoscopic and transmural healing) or histological healing, whereas higher values (eg, <250 µg/g) reflect less stringent outcomes (eg, MES of 0 or 1 in UC).

^cCalculated as the mean score of all responders (on a scale of 1–10 where “10” demotes complete agreement and “1” complete disagreement).

NOTE. The following 2 statements were removed after the second voting given low endorsement: “Absence of health-related fatigue is a long-term treatment target” (47% agreement) and “Absence of health-related anxiety and depression is a long-term treatment target” (37% agreement).

CTE, computerized tomography enterography; MRE, magnetic resonance enterography; PRO, patient reported outcome; PUCAL, pediatric UC activity index; SES-CD, simple endoscopic score in CD; UCEIS, endoscopic index of severity; wPCDAI, weight pediatric CD activity index.

long-term target (Table 1). It has been emphasized by the Delphi group that EH is suitable for the longer term, whereas in the short term, endoscopic response may suffice. There is a lack of consistency in defining thresholds for endoscopic response and remission. In the systematic review and the Delphi group, the following definitions prevailed: for endoscopic response a >50% decrease in the SES-CD (simple endoscopic score in CD) or CDEIS (endoscopic index of severity) and for endoscopic remission SES-CD ≤2 points or CDEIS <3 and lack of ulcerations (ie, any ulcerations, including aphthous ulcers) (Supplementary Table 1).

Clinical indices. Clinical symptoms are poorly correlated with degree of mucosal inflammation in CD and it is not infrequent to discover significant mucosal inflammation during complete clinical remission.⁴ The CALM trial demonstrated that treatment escalation based on symptoms alone led to a lower rate of EH than guiding treatment by a composite strategy of clinical and biochemical activity assessment (fecal calprotectin [FC] and C-reactive protein [CRP]).⁵ On the other hand, and not surprisingly, patients

identify clinical symptoms as the most important parameters to treat. Accordingly, most experts in the Delphi group considered symptom relief (clinical response and then clinical remission) as important short-term and intermediate treatment goal in IBD (Table 1). Taken together, clinical remission should be considered as a mandatory intermediate target but in addition, objective improvement in measures of inflammation must subsequently be shown.

When considering signs and symptoms, PROs are becoming the standard of measure. Different perceptions of patients and their physicians on the condition often lead to misalignment in estimating health concerns.⁶ Due to the strong correlation of PROs with patient well-being, this target should be assessed early and frequently throughout the disease course. Empirically derived PROs have been developed to satisfy regulatory requirements. The most commonly used PRO in adult CD is the PRO2, which is the sum of the weighted daily stool frequency (SF) and abdominal pain items from the CDAL.⁷ PRO2 is the only currently available PRO measures that is simple enough for

Table 3. What Is New in STRIDE-II?

- The STRIDE group, under the auspices of the IOIBD, has updated the 2015 first reported STRIDE recommendations and has developed 13 updated and new recommendations for treating to target in CD and UC (STRIDE-II recommendations).
- Time to expected response, remission, and endoscopic healing with the different treatments have been introduced for incorporating the treatment targets.
- STRIDE-II added clinical response and remission as well as normalization of CRP as immediate and short-term targets.
- Reduction of FC to an acceptable range has been added as a formal intermediate treatment target.
- Pediatric targets, reflected by different measuring scales and the addition of restoration of normal growth as a formal treatment target have been added.
- Restoration of QoL and absence of disability have been added to EH as long-term targets.
- Transmural healing in CD and histological healing in UC have been newly recognized as important adjunctive measures but were not endorsed as formal new treatment targets.

clinical use and has been explored in several studies. Once more clinically oriented tools will be developed the recommendations may be adapted. Cutoff values of remission are suggested in [Supplementary Table 1](#) based on the review of the literature and the Delphi results.

Serum and fecal inflammatory biomarkers. FC and CRP are the 2 most widely used biomarkers in IBD, with FC generally outperforming CRP. A recent meta-analysis summarized the performance of FC when using all available data, whatever the cutoff values used, showed pooled sensitivity of 82%, specificity of 72% and area under the curve (AUC) of 0.84 for FC in reflecting endoscopic disease activity in CD.⁸ The evidence (detailed in the [Supplementary Material](#)) suggests that a reduction in FC, as well as a target below a certain threshold, have clear prognostic significance, justifying utilization of this biomarker as a treatment target. FC predicted long-term clinical outcomes when measured 12 weeks after initiating medical treatment.⁹ A meta-analysis of 6 studies indicated that patients with elevated FC had 53% to 83% probability of relapse during the subsequent 2 to 3 months.¹⁰ Our systematic review of the evidence and the Delphi-like process both supported using an FC cutoff value of 150 $\mu\text{g/g}$ to identify EH ([Supplementary Table 4](#)). Nonetheless, given the low reliability of FC, the range of 100 to 250 $\mu\text{g/g}$ is considered a gray zone, whereas even values <600 $\mu\text{g/g}$ can still be associated with minimal inflammation. FC determined at time of anti-tumor necrosis factor (TNF) discontinuation predicted subsequent relapse at cutoff values 50 to 150 $\mu\text{g/g}$.^{11–13} In a small anti-TNF study, FC <300 $\mu\text{g/g}$ or 50% decrease at week 12 was associated with corticosteroid-free remission at 1 year.¹⁴ A pediatric study showed that FC <500 or decrease >50% had predictive value for inactive endoscopic disease.¹⁵ Other studies support that FC at week 12 to 14 following anti-TNF initiation is predictive of clinical remission, as well as EH, with cutoff values of 82 to 168 $\mu\text{g/g}$.^{16,17}

Whereas FC has high sensitivity and lower specificity in identifying mucosal inflammation, CRP has the opposite characteristics: it has higher specificity but low sensitivity.¹⁸ Thus, normal CRP after initiating treatment should be considered as a minimal obligatory short- to medium-term target but insufficient for the longer term. Low CRP values are associated with reduced risk of clinical relapse, with AUC of 0.70 to 0.72.^{19–22} On the other side, high CRP values determined at time of anti-TNF discontinuation are associated with higher risk of relapse.^{23,24} CRP normalization at 8 to 14 weeks after treatment predicts remission at 1 year,^{14,25,26} as well as anti-TNF success at 2 years.²⁷ In a post hoc analysis of the ACCENT trial, week 14 CRP decrease by $\geq 60\%$ predicted durable sustained response to infliximab with AUC 0.75.²⁸ Similarly, CRP >5 mg/dL at week 22 has been shown to predict secondary loss of response to anti-TNF.²⁹

Transmural healing. Ileocolonoscopy has a limited role in tight monitoring strategies because it cannot be performed repeatedly. In addition, mucosal assessments may not be feasible in certain scenarios, such as in proximal small bowel disease and, as shown in the prospective ImageKids study of 240 children with CD, mismatch

between endoscopic healing and transmural healing is not uncommon.³⁰ Given the complementary nature of both modalities, cross-sectional imaging, using ultrasound, contrast-enhanced computed tomography, and magnetic resonance enterography, has been increasingly used in addition to endoscopic assessments. The use of bedside bowel ultrasound has revolutionized our ability to assess the degree of inflammation in IBD.³¹ It allows frequent assessments and has the advantage of assessing the entire gastrointestinal tract, including transmural healing. Numerous studies have confirmed the usefulness of cross-sectional imaging modalities in detecting therapy-related changes, a feature mandatory for any treatment target (see [Supplementary Material](#)). However, given the limited ability of the currently available treatments to achieve transmural healing, the IOIBD Delphi group agreed that the use of imaging should be considered as an adjuvant assessment rather than a formal treatment target.

Histology. Histologic remission has been increasingly studied in recent years with the assumption that the deeper the remission, the better the outcomes. However, the Delphi-like survey rated histology low, indicating that it should not be included as a formal treatment target in CD. Some of the reasons mentioned are lack of well-validated, reliable, and accepted measuring tool (a notion that became evident in our systematic review), and insufficient data to justify intensified immunosuppressant medications to reach this expanded goal. Another reason is that currently available treatments have limited effectiveness in inducing histologic remission, especially in CD. Indeed, in one study, only 13% of patients with CD treated with long-term anti-TNF regimens had achieved histologic remission.³²

Well-being (relevant to both CD and UC section later in this article). Health-related well-being concepts correlate only modestly with markers of disease activity, such as fecal calprotectin,³³ as they tap a separate aspect of the disease. Supporting the notion that “the patient is at the center,” well-being domains must thus be frequently assessed during the disease course, independently of objective markers of inflammation, even when not considered formal targets. The recent LIRIC trial, which compared surgical resection with anti-TNF in CD used quality of life (QoL) as its primary outcome, highlighting the increasing importance attributed to this endpoint.³⁴ Unexpressed illness perceptions of IBD are strongly associated with the patients’ QoL.⁶ Higher QoL was found in patients undergoing laparoscopic surgery compared with open surgery, and patients with a stoma have worse health-related QoL.^{35,36} Sustained poor QoL is associated with increased risk of opiate use in UC.³⁷ Restoration of QoL at week 14 after initiation of therapy was associated with sustained remission at 1 year.³⁸

Patients with CD showed overall reduced disability compared with patients with UC.³⁹ Mood disorders are of major concern in IBD, as they appear to be associated with disability. In a cross-sectional study of 200 patients with IBD, 105 of whom had UC, 27% had anxiety or depression, which was associated with worse scores on the IBD

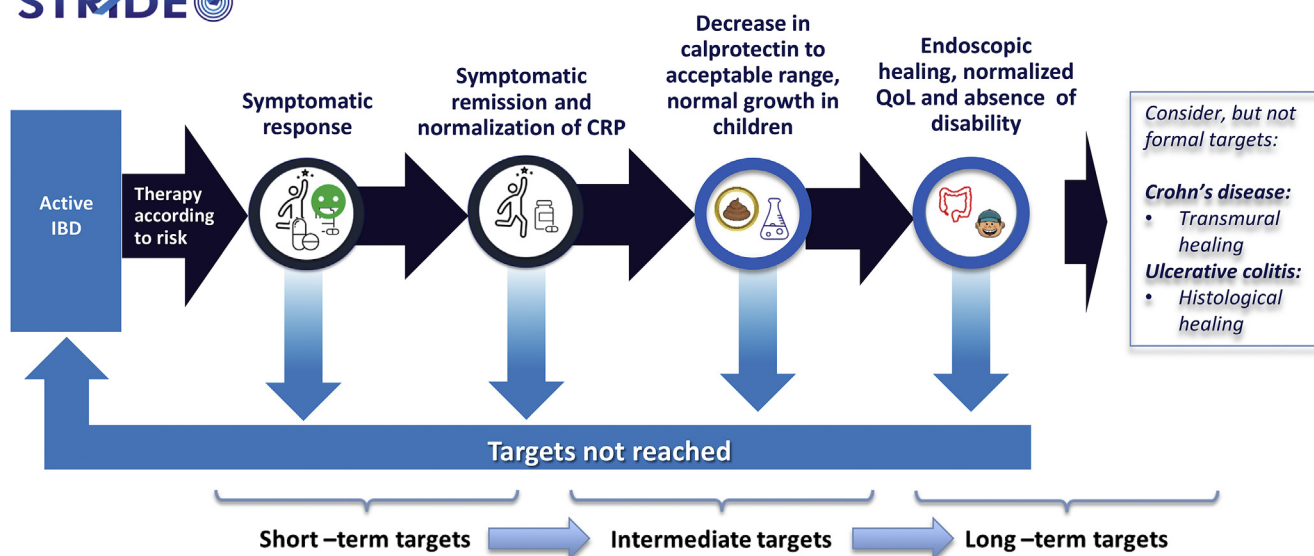


Figure 2. Treatment targets in CD and UC.

disability index (IBD-DI).⁴⁰ In the PRO Measurement Information System (PROMIS) study of Internet-based collection of PROs, 6689 patients with CD and 3945 with UC reported more depression, anxiety, fatigue, sleep disturbance, and pain interference than the general population, as well as less social satisfaction.⁴¹ A Japanese study looking at sexual function after ileal pouch anal anastomosis found relatively poor sexual activity postoperatively, whereas another study did not.^{42,43} Fatigue was reported in 26% of 220 patients with IBD and associated with poor QoL, disability, and depression, even when controlling for disease activity.⁴⁴

The IOIBD Delphi group voted to include restoration of QoL and reduction in disability as formal long-term treatment targets irrespective of other objective markers of inflammation. One possible implication of this statement is that a given treatment impairing QoL should be revisited even if deep healing has been achieved with this treatment. Because EH is also a treatment target, shared decision making with the patient is of utmost importance to balance the different targets, as not always all can be achieved. Nonetheless, QoL (including food-related QoL), disability, fatigue, depression, anxiety, sexual dysfunction, and body image must all be heavily factored in the regular assessment of patients with IBD (see [Supplementary Material](#) for details).

“The more the merrier”: Combining targets as a strategy to improve patient outcomes. The individual merit of each of the aforementioned targets can be further enhanced by the development and use of composite endpoints involving several targets instead of individual ones. A post hoc analysis of the CALM trial demonstrated that the combination of CRP with FC is superior to FC alone in predicting endoscopic healing after 48 weeks of adalimumab treatment.⁴⁵ This has also been shown in the pediatric

ImageKids cohort using the MINI (Mucosal-Inflammation-Non-Invasively)-index.⁴⁶ The MINI index performed better in reflecting endoscopic inflammation when it included CRP in addition to FC alone, especially in the gray FC values zone of 100 to 600 $\mu\text{g/g}$. A similar study in adults showed that adding CRP to FC to the Utrecht Activity Index had a superior performance than using FC alone.⁴⁷ Another retrospective study reported improved accuracy in diagnosing CD among 128 children with elevated FC levels by considering also erythrocyte sedimentation rate (ESR), CRP, and albumin.⁴⁸ In a small pediatric study, FC <500 $\mu\text{g/g}$, CRP <5 mg/dL, and pediatric CDAI (PCDAI) <10 had excellent negative likelihood ratio (0.2) for endoscopically inactive disease.¹⁵

In other studies, the addition of CDAI to FC improved area under the receiver operating characteristic curve for detecting mucosal inflammation from 0.88 to 0.96,⁴⁹ and the addition of CRP to FC improved specificity from 87% to 100%.²⁰ Similarly, one study showed that a CDAI-based PRO plus FC and CRP (ie, PRO+) performed better than PRO alone (area under the receiver operating characteristic curve 0.81 vs 0.56 for SES-CD ≥ 7).⁵⁰ A pediatric prospective study showed that the combination of weighted PCDAI (wPCDAI) with FC was superior to either alone in predicting long-term deep healing following infliximab treatment.⁵¹ Additional studies support the notion that the combination of multiple targets improves the overall test performance.^{52–54} Indeed, in a post hoc analysis of the EXTEND trial, achieving combined endpoint of lack of ulcerations on endoscopic evaluation and clinical remission (ie, deep remission) was associated with fewer treatment adjustments, hospitalizations, surgeries, and better QoL, compared with achieving EH alone.⁵⁵ Voiosu et al⁵⁶ showed prospectively that the combination of FC >30 $\mu\text{g/g}$ and low QoL

Table 4. Time (Mean Number of Weeks) Required for Achieving the Goal After Starting Treatment for CD (n = 39) and UC (n = 36), Based on the Delphi-like Process and the Systematic Review of the Evidence

	Clinical response	Clinical remission	Norm of CRP/ESR	Decrease of FC ^a	EH
Crohn's disease					
Oral steroids/EEN	2	4	5	8	13
Budesonide	3	6	8	10	15
Thiopurines	11	15	15	17	24
Methotrexate	9	14	14	15	24
Anti-TNF	2–4	4–6	9	11	17
Vedolizumab	11	17	15	17	24
Ustekinumab	7	13	11	14	19
Ulcerative colitis					
Oral 5-ASA	4	8	8	10	13
Oral Steroids	2	2	5	8	11
Locally active steroids ^b	3	8	8	9	13
Thiopurines	11	15	15	15	20
Adalimumab	6	11	10	12	14
Infliximab	5	10	9	11	13
Vedolizumab	9	14	14	15	18
Tofacitinib	6	11	9	11	14

NOTE. Given the paucity of high-quality scientific data, the data in this table should be considered merely as a rough estimate of experts' opinion.

5ASA, 5-aminosalicylic acid; EEN, exclusive enteral nutrition.

^aBelow a desired threshold outlined in the text and [Supplementary Table 4](#).

^bBeclomethasone Dipropionate (BDP), Budesonide MMX.

(Short Inflammatory Bowel Disease Questionnaire [SIBDQ] >6) had greater specificity for active endoscopic disease than FC alone in patients who were in clinical remission. This increasing body of evidence supports the multiple targets approach as adopted in the new STRIDE-II recommendations ([Figure 1](#)).

Ulcerative Colitis

Clinical indices. Unlike in CD, clinical symptoms are well correlated with endoscopic degree of inflammation. Normal SF and absence of rectal bleeding are the main clinical targets in patients with UC. The absence of diarrhea and blood is an independent predictor of relapse-free survival, colectomy-free survival, and long-term outcomes.⁵⁷ The Mayo score and the partial Mayo score are the most frequently used clinical scores in adult clinical trials,¹ but clinical remission by the Mayo scores allows streaks of blood in the stool, which cannot be considered as complete remission. Complete clinical remission with normal SF and no blood or abdominal pain is associated with EH or near EH (Mayo Endoscopic Subscore [MES] of 0 or 1) in

approximately 80% to 90% of patients (see [Supplementary Material](#)). In children, the most widely used index is the pediatric UC activity index (PUCAI), a 6-item clinical index, highly correlated with endoscopic appearance and predicts clinically important outcomes.^{58–61} Thus, clinical response and remission are valuable short-term targets in UC, much more than in CD. In adults, the PRO2 has become the current standard for assessing symptoms in UC. It is composed of the 2 subjective items of the Mayo score, namely SF and rectal bleeding. Although it is now widely used, its correlation with endoscopic healing is moderate to high and thus being used in conjunction with an objective measure of inflammation.^{62,63} The absence of rectal bleeding is more sensitive than normalization of SF.⁶³

Endoscopic healing. In STRIDE-I, EH was the preferred long-term treatment goal in UC.¹ The current Delphi-like survey and the systematic review of the literature performed since STRIDE-I did not identify new evidence to change this conclusion. Several endoscopic scores have been explored in UC but the MES and Ulcerative Colitis Endoscopic Index of Severity are the most studied.⁶⁴ EH is commonly defined as MES ≤1, but complete endoscopic

Table 5. Gaps in Knowledge and Areas for Future Research

- PROs
 - o Gap: PRO2 for both CD and UC have been formulated from existing measures as a temporary measure to meet the regulatory agencies' requirement in clinical trials. They were not a product of stringent psychometric development and evaluation.
 - o Future research: PROs should be developed aiming at use in clinical practice, with high reliability, face validity, construct validity, responsiveness, and feasibility.
- HRQOL
 - o Gap: Current measuring tools were developed as research tools and are too cumbersome for using in routine clinical practice.
 - o Future research: Development and validation of a shorter measuring tool for everyday use.
- Histology and transmural healing
 - o Gap: It is still unclear whether these are significant enough to justify the increased utilization of medical treatment to achieve these extended endpoints. This is the reason why they were not selected as formal treatment target for STRIDE-II.
 - o Future research: More prospective studies, preferably randomized-controlled, are needed to explore the number-needed-to treat to these targets for achieving superior clinical outcomes.
- Endoscopic healing
 - o Gap: The thresholds to define remission or response remain un-validated.
 - o Future research: More studies are needed to link the optimal thresholds with specific outcomes

HRQOL, health related quality of life.

healing (ie, MES 0) is associated with superior disease outcomes (see [Supplementary Material](#) for details).

Serum and fecal inflammatory biomarkers. The ease and low cost of noninvasive biomarkers, nicely position CRP and FC to be performed post induction and regularly throughout patients' disease course. CRP, ESR, and FC can predict endoscopic activity, although FC appears to be much more sensitive than either CRP or ESR in UC.^{1,65,66} CRP and ESR levels modestly correlate with endoscopic activity in UC ($r \sim 0.5$ for CRP and ~ 0.4 for ESR); the sensitivity/specificity values are 51% to 53%/69% to 71% and 85% to 87%/63% to 66%, respectively⁶⁷).

The high correlation of FC with clinical disease activity, endoscopic, and histological indices has been described in children and in adults.⁶⁸⁻⁷³ Few studies have indicated that calprotectin can be useful in predicting relapses in UC,^{70,74,75} but its added predictive value while in complete clinical remission is less clear. Two measurements of FC, 1 month apart, may best predict flares before clinical symptoms.⁷⁶ In the post induction phase of therapy, FC has been associated with 83% sensitivity and 74% specificity (cutoff ≤ 168 $\mu\text{g/g}$) for predicting a sustained clinical response at 1 year and a 79% sensitivity and a 57% specificity (cutoff ≤ 121 $\mu\text{g/g}$) for predicting endoscopic healing in UC.^{17,77}

Histology. Histologic activity has emerged as an aspirational therapeutic goal in the prevention of long-term complications.⁷⁸ Indeed, the added benefit of histological remission over macroscopic EH in predicting long-term remission⁷⁸⁻⁸² and cancer prevention⁸³ has been well presented in UC. However, histologic remission is a high hurdle to achieve, while the number needed to treat for achieving one clinically significant outcome over EH alone or even FC is unknown and likely quite high. This must be balanced

against the cost and risks of the required therapies to achieve this extended goal. Indeed, only one-third of patients with UC with EH in the ACT trials had histologic remission.⁸⁴ Furthermore, a large study showed concordance between macroscopic and microscopic degree of inflammation in UC only for the extreme groups of those in remission and those with severe disease, alluding to poor interobserver reliability.⁸⁵ It is for these reasons and for lack of standardized reporting methods, that histologic healing is still limited in its clinical utility and rated low by the Delphi group as an independent treatment target.⁸⁶

Cross-sectional assessment. Bowel ultrasound is a noninvasive tool to assess disease activity in UC with fair interrater reliability. Colonic wall thickening, Doppler blood flow, hypoechogenic wall pattern, and the presence of lymph nodes were all associated with endoscopic activity of disease according to Mayo score.⁸⁷ Although not a formal target, the increasing use of bedside ultrasound makes this tool a valuable means to assess the bowel inflammation intuitively also in UC.

Treat-to-Target Suggested Algorithm

Based on the systematic review of the literature and the results of the IOIBD survey, we have suggested a simple algorithm for using the selected short-, medium-, and long-term targets, while endorsing also the 2 outlined in STRIDE-1: EH with clinical remission ([Figure 2](#)). For the first time, QoL and disability have been selected as formal long-term targets and inflammatory biomarkers as intermediate practical measures. The timing of reaching the goals is dependent on the specific treatment and, to that end, the Delphi group and the systematic review determined how many weeks should be allowed between the onset of

treatments and assessing these targets. The systematic review of the literature was done while a priori focusing also on this question (Supplementary Material). The steering committee tabulated estimated time to response based on judgmental estimation of the results obtained from both the IOIBD survey and the systematic review (Table 4). The table was not voted on, as it portrays cumulative evidence and expert opinion rather than practice recommendations.

Conclusion

STRIDE-II confirms that the most important long-term achievable treatment targets for patients with IBD are clinical remission, EH, restoration of QoL, and absence of disability. Symptomatic relief has been determined as an immediate goal, acknowledging that this is rated highest by patients in studies. With the accumulating clinical evidence, serum and fecal biomarkers are endorsed as intermediate medium-term feasible treatment goals, meaning that at times treatment could be revisited solely based on these tests, to facilitate care in the clinic setting (Table 3).

Although the ultimate target may be complete deep healing (ie, clinical remission + complete endoscopic and histological healing + transmural healing), more research is needed to determine the incremental gain derived from this goal, and whether this gain is worth the therapy-related risks and the costs. Moreover, this ultimate expanded target is not achievable in most patients using currently available treatments. Nonetheless, transmural healing in CD and histological healing in UC are becoming important in adjuvant assessment of the depth of treatment response. For instance, bedside bowel ultrasound performed as point of care is gradually changing the landscape of repeated assessment of treatment response, given its noninvasive character and high feasibility. It should be emphasized that the algorithm is a general scheme and the scientific evidence on which it is based has major gaps (Table 5). Clinical decisions involve a complex analysis of the patient's condition and available courses of action and thus clinical considerations may require decisions that vary from the suggested algorithm. For instance, elevated serum or fecal biomarkers at times may suffice to revise treatment and at other times require endoscopic confirmation to document the extent and severity of the disease before major treatment changes. Nonetheless, STRIDE-II has attempted to collate the accumulating data on available treatment targets in an intuitive and clinically useful algorithm to facilitate long-term outcome of IBD.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online, version of *Gastroenterology* at www.gastrojournal.org, and at <https://doi.org/10.1053/j.gastro.2020.12.031>.

References

1. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): determining therapeutic goals for treat-to-target. *Am J Gastroenterol* 2015;110:1324–1338.
2. Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. *Gut* 2012;61:1619–1635.
3. Ungaro RC, Yzet C, Bossuyt P, et al. Deep remission at 1 year prevents progression of early Crohn's disease. *Gastroenterology* 2020;159:139–147.
4. Laterza L, Piscaglia AC, Minordi LM, et al. Multi-parametric evaluation predicts different mid-term outcomes in Crohn's disease. *Dig Dis* 2018;36:184–193.
5. Colombel JF, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. *Lancet* 2019;390:2779–2789.
6. Rochelle TL, Fidler H. The importance of illness perceptions, quality of life and psychological status in patients with ulcerative colitis and Crohn's disease. *J Health Psychol* 2013;18:972–983.
7. Khanna R, Zou G, D'Haens G, et al. A retrospective analysis: the development of patient reported outcome measures for the assessment of Crohn's disease activity. *Aliment Pharmacol Ther* 2015;41:77–86.
8. Rokkas T, Portincasa P, Koutroubakis IE. Fecal calprotectin in assessing inflammatory bowel disease endoscopic activity: a diagnostic accuracy meta-analysis. *J Gastrointest Liver Dis* 2018;27:299–306.
9. Haisma SM, Verkade HJ, Scheenstra R, et al. Time-to-reach Target calprotectin level in newly diagnosed patients with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2019;69:466–473.
10. Heida A, Park KT, van Rhee PF. Clinical utility of fecal calprotectin monitoring in asymptomatic patients with inflammatory bowel disease: a systematic review and practical guide. *Inflamm Bowel Dis* 2017;23:894–902.
11. Bortlik M, Duricova D, Machkova N, et al. Discontinuation of anti-tumor necrosis factor therapy in inflammatory bowel disease patients: a prospective observation. *Scand J Gastroenterol* 2016;51:196–202.
12. Molander P, Farkkila M, Ristimäki A, et al. Does fecal calprotectin predict short-term relapse after stopping TNF α -blocking agents in inflammatory bowel disease patients in deep remission? *J Crohn's Colitis* 2015;9:33–40.
13. Kennedy NA, Warner B, Johnston EL, et al. Relapse after withdrawal from anti-TNF therapy for inflammatory bowel disease: an observational study, plus systematic review and meta-analysis. *Aliment Pharmacol Ther* 2016;43:910–923.
14. Sollelis E, Quinard RM, Bouguen G, et al. Combined evaluation of biomarkers as predictor of maintained remission in Crohn's disease. *World J Gastroenterol* 2019;25:2354–2364.
15. Zubin G, Peter L. Predicting endoscopic Crohn's disease activity before and after induction therapy in children: a comprehensive assessment of PCDAI, CRP, and fecal calprotectin. *Inflamm Bowel Dis* 2015;21:1386–1391.

16. Boschetti G, Garnero P, Moussata D, et al. Accuracies of serum and fecal S100 proteins (calprotectin and calgranulin C) to predict the response to TNF antagonists in patients with Crohn's disease. *Inflamm Bowel Dis* 2015; 21:331–336.
17. Guidi L, Marzo M, Andrisani G, et al. Faecal calprotectin assay after induction with anti-tumour necrosis factor alpha agents in inflammatory bowel disease: prediction of clinical response and mucosal healing at one year. *Dig Liver Dis* 2014;46:974–979.
18. Nakarai A, Kato J, Hiraoka S, et al. Slight increases in the disease activity index and platelet count imply the presence of active intestinal lesions in C-reactive protein-negative Crohn's disease patients. *Intern Med* 2014;53:1905–1911.
19. Diederer K, Hoekman DR, Leek A, et al. Raised faecal calprotectin is associated with subsequent symptomatic relapse, in children and adolescents with inflammatory bowel disease in clinical remission. *Aliment Pharmacol Ther* 2017;45:951–960.
20. Kostas A, Siakavellas SI, Kosmidis C, et al. Fecal calprotectin measurement is a marker of short-term clinical outcome and presence of mucosal healing in patients with inflammatory bowel disease. *World J Gastroenterol* 2017;23:7387–7396.
21. Poncin M, Reenaers C, Van Kemseke C, et al. Depth of remission in Crohn's disease patients seen in a referral centre : associated factors and impact on disease outcome. *Acta Gastroenterol Belg* 2014; 77:41–46.
22. Foster AJ, Smyth M, Lakhani A, et al. Consecutive fecal calprotectin measurements for predicting relapse in pediatric Crohn's disease patients. *World J Gastroenterol* 2019;25:1266–1277.
23. Gisbert JP, Marin AC, Chaparro M. Systematic review: factors associated with relapse of inflammatory bowel disease after discontinuation of anti-TNF therapy. *Aliment Pharmacol Ther* 2015;42:391–405.
24. Meuwis MA, Vernier-Massouille G, Grimaud JC, et al. Serum calprotectin as a biomarker for Crohn's disease. *J Crohns Colitis* 2013;7:e678–e683.
25. Stallmach A, Langbein C, Atreya R, et al. Vedolizumab provides clinical benefit over 1 year in patients with active inflammatory bowel disease - a prospective multicenter observational study. *Aliment Pharmacol Ther* 2016;44:1199–1212.
26. Levine A, Turner D, Pfeffer Gik T, et al. Comparison of outcomes parameters for induction of remission in new onset pediatric Crohn's disease: evaluation of the porto IBD group "growth relapse and outcomes with therapy" (GROWTH CD) study. *Inflamm Bowel Dis* 2014;20:278–285.
27. Echarri A, Ollero V, Barreiro-de Acosta M, et al. Clinical, biological, and endoscopic responses to adalimumab in antitumor necrosis factor-naïve Crohn's disease: predictors of efficacy in clinical practice. *Eur J Gastroenterol Hepatol* 2015;27:430–435.
28. Cornillie F, Hanauer SB, Diamond RH, et al. Post-induction serum infliximab trough level and decrease of C-reactive protein level are associated with durable sustained response to infliximab: a retrospective analysis of the ACCENT I trial. *Gut* 2014;63:1721–1727.
29. Roblin X, Marotte H, Leclerc M, et al. Combination of C-reactive protein, infliximab trough levels, and stable but not transient antibodies to infliximab are associated with loss of response to infliximab in inflammatory bowel disease. *J Crohns Colitis* 2015;9:525–531.
30. Nakar I, Focht G, Church P, et al. The association of mucosal healing (MH), transmural healing (TH) and calprotectin in paediatric Crohn's disease: a report from the ImageKids study. *J Pediatr Gastroenterol Nutr* 2018; 16:1089–1097.e4.
31. Kucharzik T, Wittig BM, Helwig U, et al. Use of intestinal ultrasound to monitor crohn's disease activity. *Clin Gastroenterol Hepatol* 2017;15:535–542.e2.
32. Tursi A, Elisei W, Picchio M, et al. Effectiveness and safety of infliximab and adalimumab for ambulatory Crohn's disease patients in primary gastroenterology centres. *Eur J Intern Med* 2014;25:485–490.
33. Gauss A, Geib T, Hinz U, et al. Quality of life is related to fecal calprotectin concentrations in colonic crohn disease and ulcerative colitis, but not in ileal Crohn disease. *Medicine (Baltimore)* 2016;95:e3477.
34. Ponsioen CY, de Groof EJ, Eshuis EJ, et al. Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: a randomised controlled, open-label, multicentre trial. *Lancet Gastroenterol Hepatol* 2017;2:785–792.
35. Dowson HM, Ballard K, Gage H, et al. Quality of life in the first 6 weeks following laparoscopic and open colorectal surgery. *Value Health* 2013;16:367–372.
36. Tajti J, Látos M, Farkas K, et al. Effect of laparoscopic surgery on quality of life in ulcerative colitis. *J Laparoendosc Adv Surg Tech A* 2018;28:833–838.
37. Anderson A, Click B, Ramos-Rivers C, et al. The association between sustained poor quality of life and future opioid use in inflammatory bowel disease. *Inflamm Bowel Dis* 2018;24:1380–1388.
38. Herrera-deGuise C, Casellas F, Robles V, et al. Predictive value of early restoration of quality of life in Crohn's disease patients receiving antitumor necrosis factor agents. *J Gastroenterol Hepatol* 2015;30:286–291.
39. Argyriou K, Kapsoritakis A, Oikonomou K, et al. Disability in patients with inflammatory bowel disease: correlations with quality of life and patient's characteristics. *Can J Gastroenterol Hepatol* 2017;2017:6138105.
40. Chan W, Shim HH, Lim MS, et al. Symptoms of anxiety and depression are independently associated with inflammatory bowel disease-related disability. *Dig Liver Dis* 2017;49:1314–1319.
41. Kappelman MD, Long MD, Martin C, et al. Evaluation of the patient reported outcomes measurement information system in a large cohort of patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2014; 12:1315–1323.e2.
42. Yoshida K, Araki T, Uchida K, et al. Sexual activity after ileal pouch-anal anastomosis in Japanese patients with ulcerative colitis. *Surg Today* 2014;44:73–79.
43. Kjaer MD, Laursen SB, Qvist N, et al. Sexual function and body image are similar after laparoscopy-assisted and

- open ileal pouch–anal anastomosis. *World J Surg* 2014; 38:2460–2465.
44. Cohen BL, Zoëga H, Shah SA, et al. Fatigue is highly associated with poor health-related quality of life, disability and depression in newly-diagnosed patients with inflammatory bowel disease, independent of disease activity. *Aliment Pharmacol Ther* 2014;39:811–822.
 45. Reinisch W, Panaccione R, Bossuyt P, et al. Biomarker correlation with endoscopic outcomes in patients with Crohn's disease: data from CALM. *J Crohn Colitis* 2018; 12:S011.
 46. Cozijnsen MA, Ben Shoham A, Kang B, et al. Development and validation of the mucosal inflammation noninvasive index for pediatric Crohn's disease. *Clin Gastroenterol Hepatol* 2020;18:133–140.e1.
 47. Minderhoud IM, Steyerberg EW, van Bodegraven AA, et al. Predicting endoscopic disease activity in Crohn's disease: a new and validated noninvasive disease activity index (The Utrecht Activity Index). *Inflamm Bowel Dis* 2015;21:2453–2459.
 48. Daniluk U, Daniluk J, Krasnodebska M, et al. The combination of fecal calprotectin with ESR, CRP and albumin discriminates more accurately children with Crohn's disease. *Adv Med Sci* 2019;64:9–14.
 49. Chen JM, Liu T, Gao S, et al. Efficacy of noninvasive evaluations in monitoring inflammatory bowel disease activity: a prospective study in China. *World J Gastroenterol* 2017;23:8235–8247.
 50. Morris MW, Stewart SA, Heisler C, et al. Biomarker-based models outperform patient-reported scores in predicting endoscopic inflammatory disease activity. *Inflamm Bowel Dis* 2018;24:277–285.
 51. D'Arcangelo G, Oliva S, DiIillo A, et al. Predictors of long-term clinical and endoscopic remission in children with Crohn disease treated with infliximab. *J Pediatr Gastroenterol Nutr* 2019;68:841–846.
 52. Ma C, Lumb R, Walker EV, et al. Noninvasive fecal immunochemical testing and fecal calprotectin predict mucosal healing in inflammatory bowel disease: a prospective cohort study. *Inflamm Bowel Dis* 2017;23:1643–1649.
 53. Puolanne AM, Kolho KL, Alftan H, et al. Rapid fecal calprotectin test and symptom index in monitoring the disease activity in colonic inflammatory bowel disease. *Dig Dis Sci* 2017;62:3123–3130.
 54. Zittan E, Kabakchiev B, Kelly OB, et al. Development of the Harvey-Bradshaw Index-pro (HBI-PRO) score to assess endoscopic disease activity in Crohn's disease. *J Crohns Colitis* 2017;11:543–548.
 55. Colombel JF, Rutgeerts PJ, Sandborn WJ, et al. Adalimumab induces deep remission in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2014;12:414–422.e5.
 56. Voiosu T, Bengus A, Dinu R, et al. Rapid fecal calprotectin level assessment and the SIBDQ score can accurately detect active mucosal inflammation in IBD patients in clinical remission: a prospective study. *J Gastrointest Liver Dis* 2014;23:273–278.
 57. Arias MT, Vande Casteele N, Vermeire S, et al. A panel to predict long-term outcome of infliximab therapy for patients with ulcerative colitis. *Clin Gastroenterol Hepatol* 2015;13:531–538.
 58. Turner D, Otley AR, Mack D, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. *Gastroenterology* 2007;133:423–432.
 59. Turner D, Hyams J, Markowitz J, et al. Appraisal of the pediatric ulcerative colitis activity index (PUCAI). *Inflamm Bowel Dis* 2009;15:1218–1223.
 60. Turner D, Seow CH, Greenberg GR, et al. A systematic prospective comparison of noninvasive disease activity indices in ulcerative colitis. *Clin Gastroenterol Hepatol* 2009;7:1081–1088.
 61. Turner D, Griffiths AM, Veerman G, et al. Endoscopic and clinical variables that predict sustained remission in children with ulcerative colitis treated with infliximab. *Clin Gastroenterol Hepatol* 2013; 11:1460–1465.
 62. Colombel J-F, Keir ME, Scherl A, et al. Discrepancies between patient-reported outcomes, and endoscopic and histological appearance in UC. *Gut* 2017;66:2063–2068.
 63. Restellini S, Chao CY, Martel M, et al. Clinical parameters correlate with endoscopic activity of ulcerative colitis: a systematic review. *Clin Gastroenterol Hepatol* 2019; 17:1265–1275.e8.
 64. Mohammed Vashist N, Samaan M, Mosli MH, et al. Endoscopic scoring indices for evaluation of disease activity in ulcerative colitis. *Cochrane Database Syst Rev* 2018;1:CD011450.
 65. Sands BE. Biomarkers of inflammation in inflammatory bowel disease. *Gastroenterology* 2015;149:1275–1285.e2.
 66. Stragier E, Van Assche G. The use of fecal calprotectin and lactoferrin in patients with IBD. Review. *Acta Gastro-Enterologica Belgica* 2013;76:322–328.
 67. Yoon JY, Park SJ, Hong SP, et al. Correlations of C-reactive protein levels and erythrocyte sedimentation rates with endoscopic activity indices in patients with ulcerative colitis. *Dig Dis Sci* 2014;59:829–837.
 68. Canani RB, Terrin G, Rapacciuolo L, et al. Faecal calprotectin as reliable non-invasive marker to assess the severity of mucosal inflammation in children with inflammatory bowel disease. *Dig Liver Dis* 2008;40:547–553.
 69. Schoepfer AM, Beglinger C, Straumann A, et al. Ulcerative colitis: correlation of the Rachmilewitz endoscopic activity index with fecal calprotectin, clinical activity, C-reactive protein, and blood leukocytes. *Inflamm Bowel Dis* 2009;15:1851–1858.
 70. Tibble JA, Sigthorsson G, Bridger S, et al. Surrogate markers of intestinal inflammation are predictive of relapse in patients with inflammatory bowel disease. *Gastroenterology* 2000;119:15–22.
 71. Roszak D, Galecka M, Cichy W, et al. Determination of faecal inflammatory marker concentration as a noninvasive method of evaluation of pathological activity in

children with inflammatory bowel diseases. *Adv Med Sci* 2015;60:246–252.

72. Komraus M, Wos H, Wiecek S, et al. Usefulness of faecal calprotectin measurement in children with various types of inflammatory bowel disease. *Mediators Inflamm* 2012; 2012:608249.
73. Ashorn S, Honkanen T, Kolho KL, et al. Fecal calprotectin levels and serological responses to microbial antigens among children and adolescents with inflammatory bowel disease. *Inflamm Bowel Dis* 2009; 15:199–205.
74. Yamamoto T, Shiraki M, Bamba T, et al. Fecal calprotectin and lactoferrin as predictors of relapse in patients with quiescent ulcerative colitis during maintenance therapy. *Int J Colorectal Dis* 2014;29:485–491.
75. Sipponen T, Kolho KL. Faecal calprotectin in children with clinically quiescent inflammatory bowel disease. *Scand J Gastroenterol* 2010;45:872–877.
76. Ferreira-Iglesias R, Barreiro-de Acosta M, Lorenzo-Gonzalez A, et al. Accuracy of consecutive fecal calprotectin measurements to predict relapse in inflammatory bowel disease patients under maintenance with anti-TNF therapy: a prospective longitudinal cohort study. *J Clin Gastroenterol* 2018;52:229–234.
77. Theede K, Holck S, Ibsen P, et al. Fecal calprotectin predicts relapse and histological mucosal healing in ulcerative colitis: inflammatory bowel diseases 2016; 22:1042–1048.
78. Mojtahed A, Khanna R, Sandborn WJ, et al. Assessment of histologic disease activity in Crohn's disease: a systematic review. *Inflamm Bowel Dis* 2014;20:2092–2103.
79. Korelitz BI. Mucosal healing as an index of colitis activity: back to histological healing for future indices. *Inflamm Bowel Dis* 2010;16:1628–1630.
80. Peyrin-Biroulet L, Bressenot A, Kampman W. Histologic remission: the ultimate therapeutic goal in ulcerative colitis? *Clin Gastroenterol Hepatol* 2014;12:929–934.e2.
81. Riley SA, Mani V, Goodman MJ, et al. Microscopic activity in ulcerative colitis: what does it mean? *Gut* 1991; 32:174–178.
82. Isaacs KL. How rapidly should remission be achieved? *Dig Dis* 2010;28:548–555.
83. Ullman TA, Itzkowitz SH. Intestinal inflammation and cancer. *Gastroenterology* 2011;140:1807–1816.
84. Geboes K, Rutgeerts P, Olson A, et al. Infliximab results in reduction of inflammation and inflammatory markers in the mucosa of ulcerative colitis patients: the ACT 1 trial (abstr). *Am J Gastroenterol* 2005;100:S287.
85. Lemmens B, Arijis I, Van Assche G, et al. Correlation between the endoscopic and histologic score in assessing the activity of ulcerative colitis. *Inflamm Bowel Dis* 2013;19:1194–1201.
86. Guardioli J, Arjol C, Armuzzi A. Is histologic remission in ulcerative colitis ready for prime time? *Dig Liver Dis* 2017;49:1334–1335.
87. Allocca M, Fiorino G, Bonovas S, et al. Accuracy of humanitas ultrasound criteria in assessing disease activity and severity in ulcerative colitis: a prospective study. *J Crohns Colitis* 2018;12:1385–1391.

Received June 9, 2020. Accepted December 15, 2020.

Correspondence

Address correspondence to: Dan Turner, MD, PhD, The Juliet Keidan Institute of Pediatric Gastroenterology and Nutrition, Shaare Zedek Medical Center, The Hebrew University, POB 3235, Jerusalem 91031, Israel. e-mail: turnerd@szmc.org.il; fax: +972-2-6555756; or Axel Dignass, MD, PhD, Department of Medicine I, Agaplesion Markus Hospital, Wilhelm-Epstein-Str. 4, D-60431 Frankfurt/Main, Germany. e-mail: axel.dignass@fdk.info.

Acknowledgments

The authors thank the informatician Ms Iris Arad for performing the systematic electronic search of the evidence, Ms Tamar Altaraz for administrative assistance, and all IOIBD members for providing their input via the multiple surveys and Delphi-like process.

CRedit Authorship Contributions

Dan Turner, MD, PhD (Conceptualization: Lead; Data curation: Lead; Formal analysis: Lead; Methodology: Lead; Project administration: Lead; Supervision: Lead; Writing – original draft: Lead; Writing – review & editing: Lead). Amanda Ricciuto, MD, PhD (Data curation: Lead; Formal analysis: Supporting; Writing – review & editing: Equal). Ayanna Lewis, MD (Data curation: Lead; Formal analysis: Supporting; Writing – review & editing: Equal). Ferdinando D'Amico, MD (Data curation: Lead; Formal analysis: Supporting; Writing – review & editing: Equal). Jasbir Dhaliwal, MD (Data curation: Lead; Formal analysis: Supporting; Writing – review & editing: Equal). Anne M. Griffiths, MD (Investigation: Equal; Methodology: Equal; Writing – review & editing: Equal). Dominik Bettenworth, MD (Conceptualization: Equal; Investigation: Equal; Methodology: Equal; Writing – review & editing: Equal). William J. Sandborn, MD (Conceptualization: Equal; Formal analysis: Supporting; Investigation: Equal; Methodology: Equal; Writing – review & editing: Equal). Bruce E. Sands, MD (Conceptualization: Equal; Investigation: Equal; Methodology: Equal; Writing – review & editing: Equal). Walter Reinisch, MD, PhD (Conceptualization: Equal; Data curation: Equal; Formal analysis: Equal; Writing – review & editing: Equal). Jürgen Schölmerich, MD, PhD (Conceptualization: Equal; Data curation: Equal; Formal analysis: Equal; Writing – review & editing: Equal). Willem Bemelman, MD, PhD (Conceptualization: Equal; Data curation: Equal; Formal analysis: Equal; Writing – review & editing: Equal). Silvio Danese, MD, PhD (Conceptualization: Equal; Data curation: Equal; Formal analysis: Equal; Writing – review & editing: Equal). Jean Yves Mary, PhD (Conceptualization: Equal; Formal analysis: Equal; Methodology: Equal; Writing – review & editing: Equal). David Rubin, MD (Conceptualization: Equal; Data curation: Equal; Formal analysis: Equal; Methodology: Equal; Writing – review & editing: Equal). Jean-Frederic Colombel, MD, PhD (Conceptualization: Equal; Data curation: Equal; Formal analysis: Equal; Writing – review & editing: Equal). Laurent Peyrin-Biroulet, MD, PhD (Conceptualization: Equal; Data curation: Equal; Formal analysis: Equal; Methodology: Equal; Writing – original draft: Supporting; Writing – review & editing: Equal). Iris Dotan, MD, PhD (Conceptualization: Equal; Data curation: Equal; Formal analysis: Equal; Methodology: Equal; Project administration: Equal; Writing – review & editing: Equal). Maria T. Abreu, MD, PhD (Conceptualization: Equal; Data curation: Equal; Formal analysis: Equal; Investigation: Equal; Methodology: Equal; Project administration: Equal; Writing – original draft: Supporting; Writing – review & editing: Equal). Axel Dignass, MD, PhD (Conceptualization: Lead; Data curation: Lead; Formal analysis: Lead; Investigation: Lead; Methodology: Lead; Writing – original draft: Lead; Writing – review & editing: Lead).

Conflict of Interest

These authors disclose the following: Axel Dignass has received research support or acted as a principal investigator for AbbVie, Dr. Falk Pharma, Celgene, Gilead, Janssen and Takeda; has acted as a consultant for AbbVie, Amgen, BMS, Boehringer Ingelheim, Celgene, Dr. Falk Pharma, Ferring, Fresenius Kabi, Celltrion, Janssen, MSD, Pfizer, Roche, Takeda, Tillotts, and Vifor; and has participated in speaker bureaus for AbbVie, Falk Foundation, Ferring, Janssen, Med Update, MSD, Pfizer, Roche, Takeda, Tillotts, and Vifor. David T. Rubin has received research funding from Takeda, and has served as a consultant to AbbVie, Abgenomics, Allergan, Inc., Arena Pharmaceuticals, Biomica, Bristol-Myers Squibb, Dical Pharmaceuticals, Ferring Pharmaceuticals, Inc., Genentech/Roche, Janssen Pharmaceuticals, Lilly, Mahana Therapeutics, Medtronic, Merck & Co., Inc, Napo Pharmaceuticals, Pfizer, Prometheus Laboratories, Shire, Takeda, and Target PharmaSolutions, Inc and is a co-founder of Cornerstones Health, Inc. Dan Turner received consultation fee, research grant, royalties, or honorarium from Janssen, Pfizer, Hospital for Sick Children, Ferring, Abbvie, Takeda, Atlantic Health, Shire, Celgene, Lilly, Roche, ThermoFisher, and BMS. Dominik Bettenworth is on the advisory board or consultant for Amgen, AbbVie, Dr. Falk Foundation, Ferring, MSD, Pfizer, Pharmacosmos, Roche, Takeda, Tillotts Pharma, and Vifor. Silvio Danese has served as a speaker, consultant, and advisory board member for Schering-Plough, AbbVie, Actelion, Alphawasserman, AstraZeneca, Cellerix, Cosmo Pharmaceuticals, Ferring, Genentech, Grünenthal, Johnson and Johnson,

Millenium Takeda, MSD, Nikkiso Europe GmbH, Novo Nordisk, Nycomed, Pfizer, Pharmacosmos, UCB Pharma and Vifor. Laurent Peyrin-Biroulet has received personal fees from AbbVie, Janssen, Genentech, Ferring, Tillots, Pharmacosmos, Celltrion, Takeda, Boehringer Ingelheim, Pfizer, Index Pharmaceuticals, Sandoz, Celgene, Biogen, Samsung Bioepis, Alma, Sterna, Nestle, Enterome, Allergan, MSD, Roche, Arena, Gilead, Hikma, Amgen, BMS, Vifor, Norgine, Mylan, Lilly, Fresenius Kabi, Oppilan Pharma, Sublimity Therapeutics, Applied Molecular Transport, OSE Immunotherapeutics, Entera, Theravance; grants from AbbVie, MSD, and Takeda; and stock options from CTMA. Iris Dotan has served as a speaker, consultant, and advisory board member for Takeda, Janssen, AbbVie, Pfizer, Ferring, Roche/Genentech, Celgene/BMS, Falk Pharma, Rafa Laboratories, Neopharm, Nestle, Arena, Gilead, MSD, DSM, Celltrion, Sublimity, Sandoz, Abbott, and Athos therapeutics. Maria T. Abreu has served as a scientific advisory board member for Boehringer Ingelheim Pharmaceuticals, Gilead, AbbVie, Seres Therapeutics, Shire, and Landos Biopharma; served as a trainer or lecturer for Imedex, Focus Medical Communications, and Cornerstones Health, Inc.; has served as a consultant for Ferring Pharmaceuticals, Allergan, Amgen, Celltrion Healthcare CO, Millennium Pharmaceuticals, Theravance Biopharma Inc., and UCB Biopharma SRL; and has funded projects by Prometheus Laboratories and Pfizer. Walter Reinisch has served as a speaker for Abbott Laboratories, AbbVie, Aesca, Aptalis, Astellas, Centocor, Celltrion, Danone Austria, Elan, Falk Pharma GmbH, Ferring, Immundiagnostik, Mitsubishi Tanabe Pharma Corporation, MSD, Otsuka, PDL, Pharmacosmos, PLS Education, Schering-Plough, Shire, Takeda, Therakos, Vifor, and Yakult; served as a consultant for Abbott Laboratories, AbbVie, Aesca, Algenon, Amgen, AM Pharma, AMT, AOP Orphan, Arena Pharmaceuticals, Astellas, Astra Zeneca, Avaxia, Roland Berger GmbH, Bioclinica, Biogen IDEC, Boehringer Ingelheim, Bristol-Myers Squibb, Cellerix, Chemocentryx, Celgene, Centocor, Celltrion, Covance, Danone Austria, DSM, Elan, Eli Lilly, Ernest & Young, Falk Pharma GmbH, Ferring, Galapagos, Genentech, Gilead, Grünenthal, ICON, Index Pharma, Inova, Intrinsic Imaging, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, LivaNova, Mallinckrodt, Medahead, MedImmune, Millenium, Mitsubishi Tanabe Pharma Corporation, MSD, Nash Pharmaceuticals, Nestle, Nippon Kayaku, Novartis, Ocera, OMass, Otsuka, Parexel, PDL, Periconsulting, Pharmacosmos, Philip Morris Institute, Pfizer, Procter & Gamble, Prometheus, Protagonist, Provention, Robarts Clinical Trial, Sandoz, Schering-Plough, Second Genome, Seres Therapeutics, Setpointmedical, Sigmoid, Sublimity, Takeda, Therakos, Theravance, Tigenix, UCB, Vifor, Zealand, Zyngenia, and 4SC; and served as an advisory board member for Abbott Laboratories, AbbVie, Aesca, Amgen, AM Pharma, Astellas, Astra Zeneca, Avaxia, Biogen IDEC, Boehringer Ingelheim, Bristol-Myers Squibb, Cellerix, Chemocentryx, Celgene, Centocor, Celltrion, Danone Austria, DSM, Elan, Ferring, Galapagos, Genentech, Grünenthal, Inova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, MedImmune, Millenium, Mitsubishi Tanabe Pharma Corporation, MSD, Nestle, Novartis, Ocera, Otsuka, PDL, Pharmacosmos, Pfizer, Procter & Gamble, Prometheus, Sandoz, Schering-Plough, Second Genome, Setpointmedical, Takeda, Therakos, Tigenix, UCB, Zealand, Zyngenia, and 4SC. Jürgen Schölmerich

declares lecture honoraria from AbbVie and Dr.Falk during the past 5 years. William Sandborn reports research grants from Atlantic Healthcare Limited, Amgen, Genentech, Gilead Sciences, AbbVie, Janssen, Takeda, Lilly, Celgene/Receptos, Pfizer, Prometheus Laboratories (now Prometheus Biosciences); consulting fees from AbbVie, Allergan, Amgen, Arena Pharmaceuticals, Avexigen Therapeutics, BeiGene, Boehringer Ingelheim, Celgene, Celltrion, Conatus, Cosmo, Escalier Biosciences, Ferring, Forbion, Genentech, Gilead Sciences, Gossamer Bio, Incyte, Janssen, Kyowa Kirin Pharmaceutical Research, Landos Biopharma, Lilly, Oppilan Pharma, Otsuka, Pfizer, Progenity, Prometheus Biosciences (merger of Precision IBD and Prometheus Laboratories), Reistone, Ritter Pharmaceuticals, Robarts Clinical Trials (owned by Health Academic Research Trust, HART), Series Therapeutics, Shire, Sienna Biopharmaceuticals, Sigmoid Biotechnologies, Sterna Biologicals, Sublimity Therapeutics, Takeda, Theravance Biopharma, Tigenix, Tillots Pharma, UCB Pharma, Ventyx Biosciences, Vimalan Biosciences, Vivelix Pharmaceuticals; and stock or stock options from BeiGene, Escalier Biosciences, Gossamer Bio, Oppilan Pharma, Prometheus Biosciences (merger of Precision IBD and Prometheus Laboratories), Progenity, Ritter Pharmaceuticals, Ventyx Biosciences, Vimalan Biosciences. Spouse: Iveric Bio - consultant, stock options; Progenity - consultant, stock; Oppilan Pharma - consultant, stock options; Escalier Biosciences - prior employee, stock options; Prometheus Biosciences (merger of Precision IBD and Prometheus Laboratories) - employee, stock options; Ventyx Biosciences - stock options; Vimalan Biosciences - stock options. Willem Bemelman served as speaker for Johnson & Johnson, Braun and Takeda, and obtained research grants from Braun, VIFOR, and Medtronic. Bruce E. Sands discloses consulting fees from 4D Pharma, Abbvie, Allergan, Amgen, Arena Pharmaceuticals, AstraZeneca, BoehringerIngelheim, Boston Pharmaceuticals, Capella Biosciences, Celgene, Celltrion Healthcare, EnGene, Ferring, Genentech, Gilead, Hoffmann-La Roche, Immunic, Ironwood Pharmaceuticals, Janssen, Lilly, Lyndra, MedImmune, Morphic Therapeutic, Oppilan Pharma, OSE Immunotherapeutics, Otsuka, Palatin Technologies, Pfizer, Progenity, Prometheus Laboratories, Redhill Biopharma, Rheos Medicines, Seres Therapeutics, Shire, Synergy Pharmaceuticals, Takeda, Target PharmaSolutions, Theravance Biopharma R&D, TiGenix, and Vivelix Pharmaceuticals; honoraria for speaking in CME programs from Takeda, Janssen, Lilly, Gilead, Pfizer, Genetech; and research funding from Celgene, Pfizer, Takeda, Theravance Biopharma R&D, and Janssen. Anne Griffiths has served as a speaker or consultant or advisory board member for AbbVie, Amgen, Bristol Meyers Squibb, Celgene, Janssen, Lilly, Merck, Nestle, Pfizer, and Roche, and has received a research grant from AbbVie. Jean-Frederic Colombel reports receiving research grants from AbbVie, Janssen Pharmaceuticals and Takeda; receiving payment for lectures from AbbVie, Amgen, Allergan, Inc. Ferring Pharmaceuticals, Shire, and Takeda; receiving consulting fees from AbbVie, Amgen, Arena Pharmaceuticals, Boehringer Ingelheim, Celgene Corporation, Celltrion, Eli Lilly, Enterome, Ferring Pharmaceuticals, Geneva, Genentech, Janssen Pharmaceuticals, Landos, LimmaTech Biologics AG, Ipsen, Imedex, Imtbio, MedImmune, Merck, Novartis, O Mass, Ostuka, Pfizer, SERENE CD, Shire, Takeda, Tigenix, Viela bio; and holds stock options in Intestinal Biotech Development and Genfit. The remaining authors disclose no conflicts.