Clinical Gastroenterology and Hepatology 2016;14:348–354

Defining Disease Severity in Inflammatory Bowel Diseases: Current and Future Directions

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Although most treatment algorithms in inflammatory bowel disease (IBD) begin with classifying patients according to disease severity, no formal validated or consensus definitions of mild, moderate, or severe IBD currently exist. There are 3 main domains relevant to the evaluation of disease severity in IBD: impact of the disease on the patient, disease burden, and disease course. These measures are not mutually exclusive and the correlations and interactions between them are not necessarily proportionate. A comprehensive literature search was performed regarding current definitions of disease severity in both Crohn's disease and ulcerative colitis, and the ability to categorize disease severity in a particular patient. Although numerous assessment tools for symptoms, quality of life, patient-reported outcomes, fatigue, endoscopy, cross-sectional imaging, and histology (in ulcerative colitis) were identified, few have validated thresholds for categorizing disease activity or severity. Moving forward, we propose a preliminary set of criteria that could be used to classify IBD disease severity. These are grouped by the 3 domains of disease severity: impact of the disease on the patient (clinical symptoms, quality of life, fatigue, and disability); measurable inflammatory burden (C-reactive protein, mucosal lesions, upper gastrointestinal involvement, and disease extent), and disease course (including structural damage, history/extension of intestinal resection, perianal disease, number of flares, and extraintestinal manifestations). We further suggest that a disease severity classification should be developed and validated by an international group to develop a pragmatic means of identifying patients with severe disease. This is increasingly important to guide current therapeutic strategies for IBD and to develop treatment algorithms for clinical practice.

Keywords: Disease Severity; Disease Course; Inflammatory Bowel Disease.

Inflammatory bowel diseases (IBDs) are chronic disabling conditions. Biologics are licensed to treat moderate-to-severe Crohn's disease (CD) and ulcerative colitis (UC) using randomized controlled trial definitions: a Crohn's Disease Activity Index (CDAI)[1] score of 220 to 450 points (for CD) and a Mayo Score[2] of 6 to 12 points (including an endoscopic subscore of 2 or more points for UC). These indices were developed to evaluate disease activity at a given time, but evaluating long-term disease severity to guide therapeutic decisions also is important because CD and UC are progressive disorders.

Three main domains are relevant to the evaluation of disease severity in IBD:

(1) impact of disease on the patient: clinical symptoms, patient-reported outcomes (PROs), quality of life (QoL), and disability; (2) inflammatory burden: extent, location, and severity of bowel involvement at a given time; and (3) disease course, including structural damage.

These measures are not mutually exclusive and the correlations and interactions between them are not necessarily proportionate.

Working definitions, but no formal validated or consensus definitions, of mild, moderate, or severe CD or UC currently exist.[3,4]

We review the evidence regarding current definitions of disease severity in CD and UC. We conducted a computerized search of English language publications listed in PubMed from inception to April 2014 using relevant medical subject headings and free text variations of these terms (see Supplementary Information). Reference lists were hand-searched for other relevant studies. Only studies with adult IBD populations were considered.

Abbreviations used in this paper: **CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; ECCO, European Crohn's and Colitis Organisation; EIM, extraintestinal manifestation; ESR, erythrocyte sedimentation rate; HBI, Harvey–Bradshaw Index; IBD, inflammatory bowel disease; PRO, patient-reported outcome; QoL, quality of life; UC, ulcerative colitis.**

Most current article

1542-3565
http://dx.doi.org/10.1016/j.cgh.2015.06.001

Crohn's Disease

International Disease Severity Definitions

Several working definitions of CD severity have been proposed,[3] primarily based on CDAI score[1] (Supplementary Table 1). These classifications predominantly rely on symptomology without consideration for PROs, underlying inflammatory activity, structural damage, or adverse prognostic factors.

Impact of Disease on Patient

Clinical symptoms. The standard instrument for evaluating clinical symptoms in CD is the CDAI.[1] A shortened and simplified version of the CDAI has shown good agreement with the original instrument,[5] as has the PRO-2 scale, which uses 2 CDAI diary card items (abdominal pain and stool frequency) to assess disease activity[6] (Supplementary Table 2).

The Harvey–Bradshaw Index (HBI),[7] another CDAI modification, only requires 1 day of patient diary entries (rather than 7 days, as required by the [short] CDAI), and omits body weight, hematocrit level, and antidiarrheal medication use (Supplementary Table 2). Correlation of HBI and CDAI scores allowed the development of disease activity thresholds (not validated).[8]

The CDAI and HBI correlate poorly with mucosal inflammation.[9,10] Therefore, the van Hees Index combines clinical and laboratory data, with serum albumin levels contributing most to the activity index,[11] whereas the Perianal Disease Activity Index[12] was developed to quantify symptoms specific to perianal fistulizing disease more adequately (Supplementary Table 2). For further information on the burden of fistulizing disease, refer to the review by Peyrin-Biroulet et al.[13]

Quality of life, patient-reported outcomes, and disability. Several generic QoL tools have been shown to be reasonably valid, reliable, and responsive in IBD patients,[14,15] although QoL cut-off levels have not been established.

PROs may become part of the required end points for drug approval.[16] Although no IBD-specific PRO instrument has been formally developed and validated according to regulatory agency guidelines, a number of indices capture the impact of the disease on outcomes reported by the patients, generally without differentiation between CD and UC. These include the Inflammatory Bowel Disease Questionnaire,[17] the Manitoba IBD Index,[18] the numeric rating scale,[19] and the IBD–Control questionnaire.[20] Although these indices do not have validated thresholds to differentiate disease severity, appropriate cut-off points have been proposed (Supplementary Table 3). PROs obtained from CDAI diary items may be appropriate for use in clinical trials for CD.[21]

Thresholds have yet to be established for instruments looking at specific patient concerns in IBD (fatigue, stress, and anxiety/depression). The first IBD-specific disability index is being validated currently.[22] For further information, refer to the article by Peyrin-Biroulet.[23]

Inflammatory Burden

The state of the intestinal mucosa (location, depth, and extent of mucosal lesions) is an important measure of disease severity.

Biomarkers. Some biomarker cut-off values have been described to differentiate active and inactive disease in terms of C-reactive protein (CRP), fecal calprotectin, fecal lactoferrin, and fecal neopterin (Supplementary Table 4). However, it should be noted that low CRP levels (<10 mg/L) have been reported in patients with clinically active disease according to the CDAI,[24] although patients with low CRP and increased CDAI generally have mild mucosal lesions.[25] In addition, CRP levels can be normal in up to one third of CD patients. Determining thresholds for fecal biomarkers to differentiate between different disease severities can be challenging because of variability in values depending on methodology and intrinsic marker concentration in different samples (biomarkers are nonspecific for IBD).

Endoscopy. Endoscopy remains the gold standard for assessing location, depth, and extent of inflammatory mucosal lesions in CD. Several endoscopic scoring systems have been developed (eg, the Crohn's Disease Endoscopic Index of Severity[26] and the Simple Endoscopic Score for Crohn's Disease).[27] A more simple approach is to classify patients according to the presence or absence of ulcers at colonoscopy because there remains a lack of broadly accepted or validated thresholds for active disease and endoscopic remission (Supplementary Table 5).

Cross-sectional imaging. The specificity and sensitivity of ultrasound in differentiating active from inactive disease was calculated to be 85% and 71%, respectively, when assessed against endoscopy or surgery.[28]

The best known instrument for magnetic resonance imaging is the Magnetic Resonance Index of Activity[29] (see the Supplementary Information for other cross-sectional imaging tools).

Disease Course

Available definitions. The European Crohn's and Colitis Organisation (ECCO) consensus on the definitions and diagnosis of CD[3] suggests that some or all of the following factors are used for typically defining a severe evolution: sustained disabling symptoms and impaired QoL, repeated flare-ups, development of irreversible penetrating and/or stricturing lesions, need for repeated courses of steroids, and need for surgery.

A referral center study showed that disabling CD was defined arbitrarily as having 1 of the following: required

more than 2 steroid courses; steroid dependence; hospitalization for disease flare or complication; disabling chronic symptoms for a cumulative time of longer than 12 months; and need for immunosuppressive therapy, intestinal resection, or surgery for perianal disease.[30] In a subsequent study, "severe" disease was defined as the presence of 1 or more of the following criteria: complex perianal disease, any colonic resection, 2 or more small-bowel resections (or a single small-bowel resection measuring >50 cm in length), or the construction of a permanent stoma.[31]

"Aggressive" CD has been defined as penetrating disease, hospitalization for flares or complications of the disease, need for surgery, extraintestinal manifestations (EIMs) involving 2 or more systems, or poor response to currently available treatments.[32] In a review focusing on population-based cohorts, "complicated" disease was defined as the presence of bowel damage, the need for surgery, and/or the presence of EIMs.[33]

A number of studies have examined prognostic factors for surgery or recurrence in CD (see Supplementary Tables 6 and 7 for a summary, and the Supplementary Information for further information).

Structural damage. The specificity and sensitivity of ultrasound in the assessment of disease location and extension were calculated to be 86% and 94%, respectively, when assessed against endoscopy/other imaging techniques or surgery.[28] The sensitivity of magnetic resonance imaging relative to capsule endoscopy for evaluating the extent of CD lesions in the small bowel was 74% in a pooled analysis of 2 studies, with a specificity of 91%.[28]

The CD Digestive Damage Score (Lémann index) measures cumulative structural bowel progression at a specific point in an individual's disease history.[34]

Ulcerative Colitis

International Definitions of Disease Severity

The American College of Gastroenterology, ECCO,[4] and the Japanese Society of Gastroenterology have graded clinical disease activity in UC into mild, moderate, and severe disease (Supplementary Table 1). These classifications predominantly rely on signs and symptoms (frequency of stools, presence of blood, tachycardia, anemia, fever, and increased erythrocyte sedimentation rate [ESR]), without consideration for other aspects of disease severity. UC clinical trials have shown a lack of consistency and clarity for defining disease severity and measures of response, with classifications confounded by disease extent and use of concomitant medications.[35]

Impact of Disease on Patient

Clinical symptoms. Severe UC originally was defined as 6 or more bloody bowel movements per day, fever, tachycardia, anemia, an ESR greater than 30 mm/h, and requirement for hospitalization.[36] Although this definition formed the basis for other indices that can be used to evaluate clinical disease activity (Supplementary Table 2), a rigorous process of item generation, reduction, and weighting was not used to develop these instruments, and their reported threshold disease activity values have not been validated.

The Mayo Score[2] is the best known disease activity instrument for UC. This composite instrument is scored on a scale from 0 to 12 and includes stool frequency, rectal bleeding, a physician's global assessment, and a sigmoidoscopic evaluation. A partial Mayo Score that omits endoscopy and correlates with the full score also has been developed.[37]

Several other disease activity indices that incorporate clinical measures with sigmoidoscopy exist: the UC Disease Activity Index[38] (similar to the Mayo Score); the Rachmilewitz Score[39] (or Clinical Activity Index), which includes 7 objective and subjectively assessed components; and the Powell–Tuck Index[40] (or the St Mark's Index) (Supplementary Table 2). These tools often are used without the endoscopic component. Instruments that rely on clinical assessment alone include the Simple Clinical Colitis Activity Score[41] (or the Walmsley score), which shows very good correlation with composite scores such as the UC Disease Activity Index and the Powell–Tuck Index[42]; the abbreviated Powell–Tuck Index,[43] which includes only self-reported items; the Lichtiger Index[44]; the Seo Index[45]; and the Endoscopic–Clinical Correlation Index[46] (Supplementary Table 2).

Quality of life, patient-reported outcomes, and disability. See the section on CD for more detail.

Inflammatory Burden

Biomarkers. Some cut-off values to differentiate active and inactive disease have been proposed in the literature for CRP, fecal calprotectin, and fecal neopterin (Supplementary Table 4). The same caveats described in relation to CD apply here.

Endoscopy. Grades of disease severity have been proposed (but not validated) only for the Rachmilewitz Endoscopic Index[39] and the Ulcerative Colitis Endoscopic Index of Severity[47] (Supplementary Table 5).

For histology, see the Supplementary Information for more detail.

Disease Course

Available definitions. There is a lack of validated definitions for severe or complicated UC. In a review of predictors of aggressive UC, "severe" or complicated disease was defined as follows:[32] disease that is associated with a high relapse rate (need for 2 or more courses of steroids and/or hospitalization for flares of disease

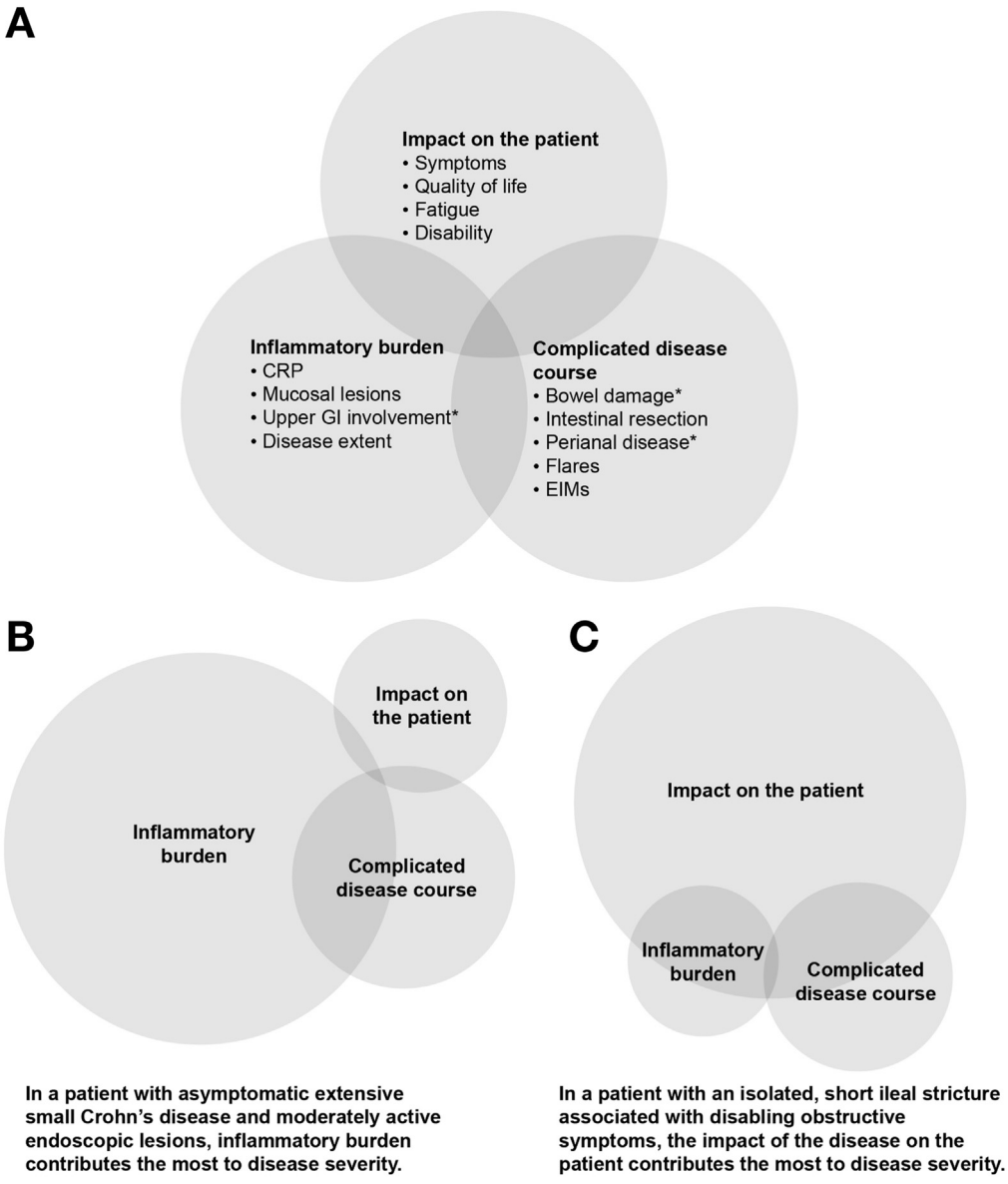

Figure 1. The interplay between the different domains that govern disease severity. (*A*) When discussing disease severity in IBD, it is important to consider the impact of disease on the patient, disease burden, and disease course. However, these measures are not mutually exclusive and the correlations and interactions between them are not necessarily proportionate. (*B*) Example of interplay between domains in a hypothetical patient with asymptomatic extensive small-bowel CD and moderately active endoscopic lesions. (*C*) Example of interplay between domains in a hypothetical patient with an isolated, short ileal stricture associated with disabling obstructive symptoms. GI, gastrointestinal. *Only for Crohn's disease.

after initial diagnosis despite optimal treatment with mesalamine and an immunomodulator), need for surgery, development of colon cancer, and the presence of EIMs.

Another review defined "complicated" disease as the development of colon cancer, the need for colectomy, or the presence of EIMs.[33]

A number of cohort studies have identified prognostic factors for a complicated disease course in patients with UC (Supplementary Table 7, and Supplementary Information).

For structural damage, see the Supplementary Information for more detail.

Future Directions

Although most treatment algorithms in IBD begin with classifying patients according to "disease severity,"[48] these primarily are symptom-based at a point in time (eg, presentation) and there has been no formal consensus or validated definition regarding the course, disease burden, or related disability of mild, moderate, or severe CD or UC. This is problematic when considering therapies with regulatory approval for use according to a patient's disease severity at a particular time when the implication is for use according to disease activity. As discussed, patients may have severe disease warranting aggressive therapies even if their point-in-time disease activity is not severe. Examples include patients who have extensive steroid-dependent UC or CD refractory to immunosuppressives with mild symptoms on high doses of corticosteroids. Conversely, patients may have severe symptoms without evidence of active inflammation. Indeed, approximately 20% of patients entered into the Crohn's disease clinical trial evaluating infliximab in a new long term treatment regimen and study of biologic and immunomodulator naive patients in Crohn's disease studies based on moderate–severe CDAI scores had no evidence of mucosal disease at colonoscopy.

Table 1. Proposed Potential Criteria to Classify Disease Severity in Inflammatory Bowel Disease

Impact of the disease on the patient
Clinical symptoms
Quality of life
Fatigue
Disability
Inflammatory burden
C-reactive protein
Mucosal lesions
Upper gastrointestinal involvement[a]
Disease extent
Disease course
Structural damage
History/extension of intestinal resection
Perianal disease[a]
Number of flares
Extraintestinal manifestations

[a]Crohn's disease only.

Organizations such as ECCO and the American College of Gastroenterology recently have proposed working definitions of CD and UC disease severity for use in clinical practice; however, these predominantly rely on symptoms. When discussing disease severity in either CD or UC, it is important to think beyond clinical symptoms to include other factors important to the patient (PROs, QoL, and disability), as well as disease burden and structural damage. In many patients, relationships between these measures may be evident. For example, patients with mild IBD may have mild symptoms, low levels of disability and fatigue, and mild mucosal lesions. Conversely, patients with severe disease may have severe symptoms, experience high levels of disability and fatigue, and have extensive and/or deep lesions. However, the interplay between these domains is not necessarily proportionate—each needs to be considered separately and as part of the whole patient profile (Figure 1). For example, patients with anorectal CD may experience moderate symptoms but have a low inflammatory burden and no risk factors for a complicated disease course; patients with an ileal stricture may have symptoms but very limited disease extension; steroid-dependent patients may have high disease activity but a minimal disease burden and a moderately complicated course of disease; patients with symptoms such as fecal incontinence may experience a more severe disease course owing to their impact on daily life and activities, as may asymptomatic patients with disease complications such as dysplasia and cancer. Importantly, disease activity should be distinguished from disease severity even though disease activity may contribute to the severity of IBD via clinical symptoms and impact on PROs. Patients may experience a noncomplicated or a complicated disease course not necessarily related to their disease activity at a given time. In addition, patients with IBD may experience irritable bowel syndrome–type symptoms,[49] suggesting that IBD and irritable bowel syndrome are not mutually exclusive and may co-exist in a considerable number of IBD patients.

As we have reviewed, placing a value on disease severity is inherently difficult in IBD and is hampered by a lack of validated instruments with discrete thresholds.

Therefore, we propose developing a disease severity classification for IBD including the 3 main domains that influence severity based on potential criteria such as those listed in Table 1. Future efforts are needed to develop a pragmatic means of classifying patients within the spectrum of disease severity.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2015.06.001.

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Conflicts of interest
The authors disclose the following: Laurent Peyrin-Biroulet has received consulting and/or lecture fees from AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Ferring, Genentech, Hospira, Janssen, Merck, Mitsubishi, Norgine, Pharmacosmos, Pilège, Shire Pharmaceuticals, Takeda, Therakos, Tillotts Pharma, UCB Pharma, and Vifor Pharma; Julián Panés has received speaker fees from, acted as a scientific consultant for, and/or received research grants from AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Ferring, Genentech, Janssen, MSD, NovoNordisk, Nutrition Science Partners, Pfizer, Shire Pharmaceuticals, Takeda, and Tigenics; William Sandborn has received consulting fees, lecture fees, and/or research support from AbbVie, ActoGeniX, AGI Therapeutics, Alba Therapeutics Albireo, Alfa Wasserman, Amgen, AM-Pharma BV, Anaphore, Aptalis, Astellas, Athersys, Atlantic Healthcare, BioBalance, Boehringer-Ingelheim, Bristol-Myers Squibb, Celgene, Celek, Cellerix, Cerimon, ChemoCentryx, CoMentis, Cosmo Technologies, Coronado Biosciences, Cytokine Pharmasciences, Eagle, Eisai Medical Research, Elan, EnGene, Eli Lilly, Enteromedics, Exagen Diagnostics, Ferring, Flexion Therapeutics, Funxional Therapeutics, Genentech, Genzyme, Gilead, Given Imaging, GlaxoSmithKline, Human Genome Sciences, Ironwood, Janssen, KaloBios, Lexicon, Lycera, Meda, Merck & Co, Merck Research Laboratories, MerckSerono, Millennium, Nisshin Kyorin, Novo Nordisk, NPS Pharmaceuticals, Optimer, Orexigen, PDL Biopharma, Pfizer, Procter and Gamble, Prometheus Laboratories, ProtAb, Purgenesis Technologies, Receptos, Relypsa, Salient, Salix, Santarus, Shire Pharmaceuticals, Sigmoid Pharma, Sirtris (a GSK company), S.L.A. Pharma (UK), Targacept, Teva, Therakos, Tillotts, TxCell SA, UCB Pharma, Vascular Biogenics, Viamet, and Warner Chilcott UK; Séverine Vermeire has received consulting fees and/or grant/research support from, and/or been a speaker for AbbVie, Centocor, Ferring, Genentech/Roche, MSD, Novartis, Pfizer, Shire Pharmaceuticals, Takeda, and UCB Pharma; Silvio Danese has served as a speaker, consultant, and/or advisory board member for AbbVie, Actelion, Alphawasserman, Astra Zeneca, Cellerix, Cosmo Pharmaceuticals, Ferring, Genentech, Grunenthal, Johnson&Johnson, Millennium, Merck & Co, NovoNordisk, Nycomed, Pfizer, Pharmacosmos, Schering-Plough, Salix, Takeda, UCB Pharma, and Vifor; Brian Feagan has received consulting fees, lecture fees, and/or research support from AbbVie, ActogeniX, Albireo Pharma, Amgen, Astra Zeneca, Avaxia Biologics, Inc, Avir Pharma, Axcan, Baxter Healthcare Corp, Boehringer Ingelheim, Bristol-Myers Squibb, Calypso Biotech, Celgene, Centocor, Elan/Biogen, EnGene, Ferring Pharmaceuticals, Genentech, GiCare Pharma, Gilead, Given Imaging, GlaxoSmithKline, Ironwood Pharma, Johnson & Johnson/Janssen, Kyowa Kakko, Kirin Co Ltd, Lexicon, Lilly, Merck, Millennium, Nektar, Novartis, Novo Nordisk, Pfizer, Prometheus Therapeutics and Diagnostics, Prometheus Laboratories, Receptos, Salix Pharmaceuticals, Santarus, Sanofi, Serono, Shire Pharmaceuticals, Sigmoid Pharma, Synergy Pharma, Inc, Takeda, Teva, TiGenix, Tillotts Pharma AG, UCB Pharma, Vertex Pharma, VHsquared Ltd, Warner-Chilcott, Wyeth, Zealand Pharma, and Zyngenia, and is a member of the Board of Directors of Roberts Clinical Trials, Inc; Jean-Frédéric Colombel has acted as a consultant, advisory board member, and/or speaker for AbbVie, Bristol-Myers Squibb, Ferring, Genentech, Giuliani SPA, Given Imaging, Merck & Co, Millennium, Pfizer, Prometheus Laboratories, Sanofi, Schering Plough, Takeda, Teva, and UCB Pharma; Stephen Hanauer has acted as a consultant or advisory board member for and/or received grant/research support from AbbVie, Bristol-Myers Squibb, Caremark, Centocor, Elan, McNeal Pharma, Millennium, Novartis, Procter and Gamble, and Salix; and Beth Rycroft is an employee of AbbVie, Inc, and may own AbbVie stock and/or options.

Funding
AbbVie, Inc, funded the literature analysis, provided writing support, and reviewed and approved the publication. Juliette Allport of Leading Edge (part of the Lucid Group) (Burleighfield House, Buckinghamshire, UK) provided medical writing and editorial support to the authors in the development of this manuscript. Financial support to Leading Edge for medical writing and editorial assistance was provided by AbbVie.

Supplementary Information

Search Strategy

Studies evaluating tools to assess disease activity, disease burden, and PROs were identified using the following medical subject heading terms: "inflammatory bowel diseases," "Crohn disease," "colitis, ulcerative," "severity of illness index," "questionnaires," "reproducibility of results," "sensitivity and specificity." Free text variations of these terms also were used. Studies were included if they described a tool with a threshold or cut-off values to differentiate between mild, moderate, and severe disease. Studies evaluating prognostic factors for a complicated disease course were identified using the following medical subject heading terms: "inflammatory bowel diseases/epidemiology OR /complications," "Crohn disease/epidemiology OR /complications," "colitis, ulcerative/epidemiology OR /complications," "risk factors," "disease progression." Free text variations of these terms also were used.

Thresholds for Disease Activity Identified in the Literature

Cross-sectional imaging in Crohn's disease. The Sonographic Lesion Index for CD was developed for small-intestine contrast ultrasonography.[1] This tool evaluates bowel wall thickness, lumen diameter, lesion length, and number of lesion sites. Fistula, mesenteric adipose tissue alteration, abscesses, and lymph nodes also are considered. An algorithm was generated to provide an index value ranging from 0 to 200. This score was subdivided into 5 classes, indicating different levels of disease severity. Ripolles et al[2] compared contrast-enhanced ultrasound with endoscopy for determining disease severity and found that a 46% increase in threshold brightness was able to predict moderate or severe disease (sensitivity, 96%; specificity, 73%; positive predictive value, 92%; and negative predictive value, 85%). In terms of magnetic resonance imaging, Rimola et al[3,4] developed the Magnetic Resonance Index of Activity, an instrument that scores wall thickness, relative contrast enhancement, edema, and ulcers in different segments of the gastrointestinal tract. Mucosal healing is defined as a segmental score less than 7 and ulcer healing is defined as a segmental score less than 11. Another index based on qualitative evaluation of magnetic resonance imaging findings including contrast enhancement, edema, wall thickening, ulcers, presence of a layered pattern, and diffusion hyperintensity found that a segmental magnetic resonance score greater than 2 detected endoscopic inflammation in the colon with a sensitivity and specificity of 58% and 84%, respectively.[5] Gallego et al[6] modified a scoring system developed by Girometti et al[7] to develop a magnetic resonance imaging instrument that measured bowel wall thickness, relative enhancement, motility, percentage of stenosis, bowel wall edema, mucosal abnormalities, lymph nodes, fistulae, and inflammatory masses to provide a cumulative score ranging from 0 to 12. Based on correlation with Simple Endoscopic Scale CD, ileal disease was classified as inactive (0–2), mild (3–6), or moderate–severe ($\geq$7). Finally, a magnetic resonance enterography index was identified, which evaluated recurrent transmural inflammation in the ileum and is based on a scoring system from 0 (no findings) to 3 (severe recurrence with transmural and extramural changes).[8–10]

Cross-sectional imaging in ulcerative colitis. Several grading tools have been developed for cross-sectional imaging in UC, including the Tsuga colorectal ultrasound criteria,[11] and a simplified magnetic resonance colonography index that can detect endoscopic inflammations (score, $\geq$1) or severe lesions (score, $\geq$2).[12] Another index based on qualitative evaluation of magnetic resonance imaging findings including contrast enhancement, edema, wall thickening, ulcers, presence of a layered pattern, and diffusion hyperintensity found that a segmental magnetic resonance score greater than 1 detected endoscopic inflammation in the colon with a sensitivity and specificity of 89% and 86%, respectively.[5]

Histology in ulcerative colitis. A growing body of evidence suggests that histologic healing is associated with better clinical outcomes in UC, including decreasing the risk of colorectal cancer.[13] Several scoring systems exist for the assessment of histologic disease activity in UC, including the Riley scale,[14] the Geboes score,[15] a modified Riley and Geboes scale,[16] the Histologic Activity Index,[17] and the Endocytoscopy System Score.[18] However, none of these scoring systems have been validated and correlation between histologic grade and disease activity or severity has not been shown. No thresholds for differentiating between different levels of disease activity or severity were identified in the literature.

Structural damage in ulcerative colitis. A growing body of evidence indicates that UC is also a progressive disease. A review of the literature found that disease progression involves proximal extension, stricturing, pseudopolyposis, dysmotility, anorectal dysfunction, and impaired permeability, although the true prevalence and relevance of these complications in clinical practice has yet to be established.[19]

Inflammatory lesions in UC are confined to the colon and mainly affect the inner wall layer of the gastrointestinal tract; therefore, cross-sectional imaging is not used as widely for the diagnosis or monitoring in this condition as it is in CD. Nevertheless, there are some UC patients in whom cross-sectional imaging provides important information relating to disease severity, such as those with tight strictures or high risk of perforation that makes endoscopy difficult. Although several grading tools have been developed for cross-sectional imaging in UC (see earlier), validated cut-off values for extent of disease severity are lacking.

Prognostic Factors for a Severe/Complicated Disease Course in Crohn's Disease

Two important cohort studies have evaluated prognostic factors for a disabling disease course in CD[20,21] (Supplementary Table 6) and have used these factors to develop predictive indices for disabling disease. Beaugerie et al[20] created the Beaugerie Index (known as the St Antoine Model), which ranges from a score of 0 (no independent predictors present) to 3 (all 3 independent predictors present). In the Beaugerie et al[20] initial cohort, a score of 2 or 3 provided a positive predictive value of 91% and 93%, respectively, for disabling disease. This was validated in a prospective population of 302 patients, with respective positive predictive values of 84% and 91% for scores of 2 and 3. Loly et al[21] developed a similar index, in which the presence of at least 2 independent risk factors had sensitivity, specificity, positive predictive values, and negative predictive values of 34%, 78%, 68%, and 46%, respectively, for predicting disabling disease at 5 years after diagnosis. When Loly et al[21] extended their analysis into prognostic factors for a severe disease course (Supplementary Table 6), the presence of both identified risk factors at diagnosis had a sensitivity, specificity, positive predictive value, and negative predictive value of 17%, 98%, 78%, and 69%, respectively.

A number of other studies also have looked at prognostic factors for surgery or recurrence in CD (Supplementary Table 7). A prospective Norwegian population-based cohort of new cases of CD with follow-up evaluation at 10 years after diagnosis investigated factors present at diagnosis that predict subsequent surgery.[22] In an adjusted Cox regression analysis, age at diagnosis again was identified as an important prognostic factor: those aged 40 years and older had half the likelihood of needing surgery during the follow-up evaluation than those younger than age 40 years (hazard ratio, 0.5; 95% confidence interval, 0.3–0.9). Isolated colonic or ileocolonic disease was protective against surgery relative to disease in the terminal ileum (hazard ratio, 0.3; 95% CI, 0.2–0.6; hazard ratio, 0.3; 95% confidence interval, 0.2–0.5, respectively), and stricturing or penetrating disease notably increased the risk of surgery (hazard ratio, 2.3; 95% confidence interval, 1.3–4.1; hazard ratio, 5.4; 95% confidence interval, 3.0–9.9, respectively). Smoking and systemic steroid use were not identified as risk factors. Another cohort study based on a population from Olmsted County, Minnesota, also evaluated predictors of surgery in patients with CD.[23] In a regression model that included patients with at least 90 days of follow-up evaluation after diagnosis and who had not had a first major abdominal surgery within 90 days of the diagnosis, the following factors were identified as predictors of time to surgery: male sex (hazard ratio, 1.6; 95% confidence interval, 1.02–2.4), current smoking (hazard ratio, 1.7; 95% confidence interval, 1.1–2.7), penetrating disease behavior (hazard ratio, 2.8; 95% confidence interval, 1.1–6.7), and corticosteroid use within 90 days of the diagnosis (hazard ratio, 1.6; 95% confidence interval, 1.03–2.5). In addition, relative to colonic disease extent, ileocolonic disease (hazard ratio, 3.3; 95% confidence interval, 1.8–5.8), small-bowel disease (hazard ratio, 3.4; 95% confidence interval, 1.9–6.1), and gastroduodenal disease (hazard ratio, 4.0; 95% confidence interval, 1.2–13.8) all were associated with a shorter time to surgery. These findings validate those seen in other cohort studies.[24–26]

Studies also have focused on identifying potential prognostic factors for disease recurrence. In an analysis of patients randomized to placebo in the National Cooperative Crohn's Disease study, multivariate analysis found that use of corticosteroids before study entry, partial resection with disease persistence, perianal disease, and CDAI score of 200 or greater were predictors of short-term relapse.[27] In a prospectively assembled European population-based cohort of 358 CD patients, upper gastrointestinal disease at diagnosis had an excess risk of surgical or medical recurrence, whereas age of at least 40 years at diagnosis was protective against recurrence and colonic disease was protective specifically against resection.[28] Analysis of a Danish population-based registry evaluating the risk of medical or surgical recurrence found that age at diagnosis had a hazard ratio per 10-year period of 0.89 (95% confidence interval, 0.84–0.95), suggesting that the risk of recurrence decreased by 11% per decade of follow-up evaluation.[29] Current smoking was also a negative prognostic factor for disease recurrence or a severe disease course.[29] In a study in New Zealand, Tarrant et al[30] found that perianal disease was a significant predictor of change in CD phenotype. Interestingly, no association between familial disease and subsequent disease course severity has been reported.[31]

Biomarkers also may play a role in predicting a complicated disease course. For example, an increased CRP level at diagnosis predicts future surgery (in patients with ileal disease)[32] and 1-year relapse,[33] and an increased level during a relapse predicts subsequent relapse during the year.[34] The presence of anti–*S cerevisiae* antibodies at diagnosis has been associated with a higher risk of more severe disease behavior during follow-up evaluation or risk of surgery.[26,35–37] In addition, genetic markers may be useful predictors of future disease patterns: several mutations of the *NOD2/CARD15* gene increase the risk of small-bowel stenosis and the need for early surgery.[38–41] A retrospective study including 1528 patients with CD with more than 10 years of follow-up evaluation from 8 European referral hospitals identified the Nucleotide-binding oligomerization domain-containing protein 2 gene as the most important genetic prognostic factor in CD. Nucleotide-binding oligomerization domain-containing

protein 2 was identified as an independent prognostic factor for ileal location, stenosing and penetrating CD behaviors, and need for surgery. Overall, NOD2 is seen as the strongest prognostic factor associated with a complicated disease course.[42]

Prognostic Factors of a Severe/Complicated Disease Course in Ulcerative Colitis

Prognostic factors for a severe/complicated disease course in UC are summarized in Supplementary Table 7. Solberg et al[43] performed an analysis of prognostic factors in a comprehensive follow-up evaluation of a population-based inception cohort of patients with UC from Norway (IBSEN cohort). Of the 423 patients with data at the 10-year follow-up evaluation, 9.8% had undergone colectomy. The following covariates were incorporated into a Cox regression analysis: age at diagnosis, sex, extent of colitis at diagnosis, hemoglobin, ESR, temperature, familial IBD, and smoking status; in a multivariate analysis, only ESR of 30 mm/h or greater (hazard ratio, 2.94; 95% confidence interval, 1.58–5.46) and extensive colitis at diagnosis (hazard ratio, 2.98; 95% confidence interval, 1.25–7.08) were associated with subsequent colectomy. Conversely, neither of these factors was associated with an increased risk of overall relapse during the follow-up evaluation. Rather, a significantly higher proportion of noncolectomized patients with ESR levels less than 30 mm/h were relapse-free during the past 5-year period compared with patients with an increased ESR. The impact of disease extent at diagnosis on colectomy risk also was shown in another cohort study.[44]

In a Cox proportional hazard regression model in a Danish population-based registry of patients with IBD, younger age at diagnosis was predictive of medical or surgical recurrence (hazard ratio per 10 years of follow-up evaluation, 1.08; 95% confidence interval, 1.01–1.16).[29] Interestingly, in this study, extensive colitis had a significant protective effect on recurrence rate relative to left-sided colitis (hazard ratio, 0.78; 95% confidence interval, 0.63–0.96), although the investigators did point out that there may have been a selection bias because patients undergoing colectomy were censored for further analysis of disease recurrence.

In a population-based cohort, multivariate analysis found that smoking was prognostic for relapse.[45] Another study found that smoking was associated with a reduced likelihood of colectomy in UC patients relative to nonsmoking.[46]

Analysis of the impact of serologic markers on disease course found that the presence of perinuclear antineutrophil cytoplasmic antibodies increased the relative risk for first relapse (1.4; 95% confidence interval, 1.1–1.8), and the corresponding relative risk for the total number of relapses was 1.9 (95% confidence interval, 1.7–2.1).[47] The presence of anti–*S cerevisiae* antibodies also increased the risk for the total number of relapses (relative risk, 1.8; 95% confidence interval, 1.5–2.1). Biomarker concentrations also may provide an indication as to the future disease course: Lasson et al[48] found that patients with lower levels of fecal calprotectin in the first 3 months after diagnosis had a significantly likelihood of mild disease in the first, second, and third years (defined as no recurrence in the first year and no more than 1 annual relapse in years 2 and 3) than patients with higher levels. Henriksen et al[32] showed that a CRP level exceeding 23 mg/L at diagnosis in patients with extensive UC increased the risk of colectomy in 5 years (odds ratio, 4.8; 95% confidence interval, 1.5–15.1), and CRP levels greater than 10 mg/L after 1 year predicted an increased risk of surgery during the subsequent 4 years (odds ratio, 3.0; 95% confidence interval, 1.1–7.8).

One component of a severe course of UC is the development of colon cancer. In an early study, Ekbom et al[49] found that extent of disease at diagnosis independently increased the risk of colorectal cancer, as did younger age at diagnosis. These associations have been supported by more recent publications.[50,51] In addition, a diagnosis of primary sclerosing cholangitis markedly increased the risk of colorectal cancer by more than 9-fold in UC patients.[51] Some factors associated with UC also may increase the risk of extraintestinal cancers. A case–control study of UC patients after ileal pouch–anal anastomosis found that older age, left-sided colitis, and chronic pouch inflammation all were associated with an increased risk of extraintestinal cancer.[52]

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Supplementary Table 1. International Definitions of Disease Activity in Crohn's Disease and Ulcerative Colitis

Crohn's disease (international definitions based on CDAI parameters[1])

ACG[2]	**Symptomatic remission** CDAI <150 Asymptomatic/without symptomatic inflammatory sequelae May have responded to medical or surgical therapy and have no residual active disease Does not include patients who require corticosteroids	**Mild–moderate** CDAI 150–220 Ambulatory Able to tolerate oral alimentation without manifestations of dehydration, systemic toxicity (high fevers, rigors, and prostration), abdominal tenderness, painful mass, intestinal obstruction, or >10% weight loss	**Moderate–severe** CDAI 220–450 Failed to respond to treatment for mild–moderate disease *or* Has more prominent symptoms of fever, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (without obstructive findings), or significant anemia	**Severe/fulminant** CDAI >450 Persistent symptoms despite treatment with corticosteroids/biologics as outpatients *or* Has high fevers, persistent vomiting, intestinal obstruction, significant peritoneal signs, cachexia, or abscess
ECCO[3]	**Symptomatic remission** CDAI <150	**Mild** CDAI 150–220 Ambulatory Eating and drinking <10% weight loss No obstruction, fever, dehydration, abdominal mass, or tenderness CRP increased above ULN	**Moderate** CDAI 220–450 Intermittent vomiting or weight loss >10% Treatment for mild disease ineffective or tender mass No overt obstruction CRP increased above ULN	**Severe** CDAI >450 Cachexia or evidence of obstruction/abscess Persistent symptoms despite intensive treatment CRP increased

Ulcerative colitis (international definitions based on Truelove–Witts criteria)[4]

ACG[5]	**Symptomatic remission**	**Mild** <4 stools/d (with or without blood) No systemic signs of toxicity Normal ESR	**Moderate** ≥4 stools/d Minimal signs of toxicity	**Severe** ≥6 bloody stools/d Signs of toxicity (fever, tachycardia, anemia) Increased ESR	**Fulminant** ≥10 stools/d Continuous bleeding Toxicity Abdominal tenderness and distension Blood transfusion requirement Colonic dilation on abdominal plain films
ECCO[6]	**Symptomatic remission** <4 stools/d without bleeding or urgency	**Mild** <4 bloody stools/d Pulse <90 bmp Temperature <37.5°C Hemoglobin >11.5 g/dL ESR <20 mm/h or normal CRP	**Moderate**[a] ≥4 bloody stools/d *if* Pulse ≤90 bmp Temperature ≤37.8°C Hemoglobin ≥10.5 g/dL ESR ≤30 mm/h or CRP ≤30 mg/dL	**Severe**[b] ≥6 bloody stools/d *and* Pulse >90 bmp Temperature >37.8°C Hemoglobin <10.5 g/dL ESR >30 mm/h or CRP >30 mg/dL	

JSG	**Symptomatic remission**	**Mild**	**Moderate**	**Severe**
		≤4 stools/d (with or without blood) Pulse <90 bmp, Temperature <37.5°C Hemoglobin >10.5 g/dL Normal ESR	Not specifically defined; symptoms that fall between mild and severe	≥6 bloody stools/d Pulse ≥90 bmp Temperature ≥37.5°C Hemoglobin ≤10.5 g/dL ESR ≥30 mm/h Patients must meet at least 4 of these conditions, including ≥6 bloody stools/d and either pulse ≥90 bmp, or temperature ≥37.5°C

bmp, beats per minute.
ACG, American College of Gastroenterology; JSG, Japanese Society of Gastroenterology; ULN, upper limit of normal.
[a]Moderate disease was defined as between mild and severe.
[b]ECCO prefers the term "severe colitis" to "fulminant colitis" because the latter is outdated and refers to a single episode progressing to death within 1 year.

Supplementary Table 2. Thresholds for Disease Activity for Symptom-Based Scoring Systems in Crohn's Disease and Ulcerative Colitis

Tool	Parameters assessed	Scoring system	Activity score thresholds			
			Remission	Mild	Moderate	Severe
Crohn's disease						
Short CDAI[7,8]	Soft stool frequency over past week Abdominal pain over past week General well-being over past week	Cumulative score with components given different weightings (+ constant to yield a mean value as close as possible to full CDAI)	<150[a,b]	150–219	220–450	>450
PRO-2[9]	Soft stool frequency over past week Abdominal pain over past week	Cumulative score with components given different weightings	<8	8–13	14–34	>35
HBI[10,11]	General well-being on previous day Abdominal pain on previous day Liquid stool frequency on previous day Abdominal mass EIMs	Cumulative score	<5[c]	5–7	8–16	>16
van Hees index[12]	Albumin ESR Body mass index Abdominal mass Sex Temperature Stool consistency Resection Extraintestinal lesions	Cumulative score with components given different weightings	<100	100–149	150–210	>210
PDAI[13]	Patient report of perianal discharge Pain with restriction of daily activities Restriction of sexual activity Type of perianal disease Degree of induration	Cumulative score with each component score on a scale from 0 (no symptoms) to 4 (severe symptoms)	0[14]	<4[14] (inactive disease not requiring therapy)	≥4[14] (active disease requiring medical or surgical therapy)	
Ulcerative colitis						
Mayo score[15]	Stool frequency Rectal bleeding Physician's global assessment Sigmoidoscopy	Cumulative score	0–2[d]	3–5	6–10	11–12
UCDAI[16,17]	Stool frequency Rectal bleeding Physician's global assessment Sigmoidoscopy	Cumulative score	0–2[e]	3–8		9–12
Rachmilewitz score (CAI)[18,19]	Bowel movement frequency Blood in stools Physician's global assessment Abdominal pain/cramps Temperature EIMs Laboratory findings (ESR, hemoglobin)	Cumulative score	0–4	5–10	11–17	>17
Powell–Tuck index (St Mark's index)[20,21]	Well-being Abdominal pain Bowel movement frequency Stool consistency Bleeding Anorexia Nausea/vomiting Abdominal tenderness Eye, joint, mouth, or skin complications Temperature Sigmoidoscopy	Cumulative score	≤3[f]	4–10	11–14	>14

Supplementary Table 2. Continued

Tool	Parameters assessed	Scoring system	Activity score thresholds			
			Remission	Mild	Moderate	Severe
SCCAI (Walmsley)[22]	Bowel movement frequency (day) Bowel movement frequency (night) Urgency of defecation Blood in stool Well-being Extracolonic features	Cumulative score	≤2[22,23] <2.5[24]	3–20		
Lichtiger index[25,26]	Diarrhea frequency Nocturnal diarrhea Visible blood (% of movements) Fecal incontinence Abdominal pain/cramping Well-being Abdominal tenderness Need for antidiarrheal medications	Cumulative score	≤3	4–8	9–14	>14
Seo index[27,28]	Bowel movement frequency Blood in stool ESR Hemoglobin Albumin	Cumulative score with components given different weightings (+ constant to yield a mean value as close as possible to Truelove–Witts criteria)	<108[29] <120[24]	<150	150–220	>220

CAI, Clinical Activity Index; PDAI, Perianal Disease Activity Index; SCCAI, Simple Clinical Colitis Activity Index; UCDAI, Ulcerative Colitis Disease Activity Score.
[a]One study suggested that a CDAI cut-off value of 55 is more precise for identifying patients in endoscopic remission (sensitivity of 71% and specificity of 64%).[30]
[b]A CDAI score exceeding 150 appears an appropriate cut-off value for defining symptomatic disease in patients with postoperative recurrence; however, sensitivity and specificity were relatively low at 70% and 81%, respectively, with a positive predictive value of 50% and a negative predictive value of 91%.[31]
[c]One study suggested that an HBI cut-off value of 1 is more precise for identifying patients in endoscopic remission.[30]
[d]One study suggested that a full score less than 4 is more precise for identifying patients in patient-defined remission.[32]
[e]One study found that the optimal cut-off value for patient-defined remission with the UCDAI was less than 2.5 points, which had a sensitivity and specificity of 82% and 89%, respectively.[24]
[f]One study suggested that a Powell–Tuck score of 4 is more precise for identifying patients in endoscopic remission,[23] and another study found that a score of less than 3.5 correlates best with patient-defined remission.[24]

Supplementary Table 3. Thresholds for Disease Activity for Patient-Reported Outcome Indices in Inflammatory Bowel Diseases

Tool	Parameters assessed	Scoring system	Thresholds for disease severity
IBDQ[33–35]	32 questions relating to bowel symptoms, systemic symptoms, emotional function, and social function Extended version available with 36 questions	Each question is scored on a Likert scale from 1 (worst) to 7 (best), providing a total score of 32–224 (36–252 in the extended version)	Cut-off value of 168 points is predictive of CDAI-defined remission in CD[36] Cut-off value of 205 points is predictive of patient-defined remission in UC[24] In extended version, a cut-off value of 209 points predicted normal quality of life according to EQ-5D[37]
Manitoba IBD Index[38]	Single-item scale related to self-reported symptom persistence for the previous 6 months	6-level scale ranging from a, my disease has been constantly active, to f, I was well in the past 6 months, what I consider a remission or absence of symptoms	Disease considered active if symptoms experienced for ≥1–2 days/mo (score, a–d)
Numeric rating scale[39]	Single-item scale related to self-reported overall perception of health	11-point scale ranging from 0, as bad as being dead, to 10, perfect health	Patients who believed that they were in remission typically had a numeric rating scale score of ≥6
IBD–Control Questionnaire[40]	13 categoric items relating to disease control, satisfaction with treatment, pain, energy, and social, emotional, and physical function 100-mm VAS in which patients rate their perceived level of disease control	Scores range from 0–16, with higher scores indicating better control VAS ranges from 0 (complete control) to 100 (worst control)	Cut-off value of 13 points on questionnaire and 85 points on VAS identified patients with quiescent disease

EQ-5D, EuroQol-5D; IBDQ, Inflammatory Bowel Disease Questionnaire; VAS, visual analog scale.

Supplementary Table 4. Accuracy of Biomarkers to Predict Disease Activity or Severity in Patients With Crohn's Disease and Ulcerative Colitis

Biomarker	Study	Patients, N	Assessment of disease activity/severity	Biomarker cut-off	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %
Crohn's disease								
CRP	Chamouard et al[41]	150	van Hees Index <150	≤4 mg/L	44	100	100	66
			CDAI <220	≤4 mg/L	49	88	90	46
	Karoui et al[42]	103	CDAI ≤220	<19 mg/L	76	56		
	Sipponen et al[43]	77	CDEIS <3	<5 mg/L	48	91	91	48
	Schoepfer et al[44]	122	SES-CD <4	<5 mg/L	68	58	88	29
	af Bjorkesten et al[30]	64	SES-CD ≤2	≤3 mg/L	50	24		
	Nancey et al[45]	78	SES-CD <2	<5 mg/L	46	86	78	61
Fecal calprotectin	Sipponen et al[43]	77	CDEIS <3	<200 μg/g	70	92	94	61
			CDEIS 3–9	<1000 μg/g	69	93	82	87
	af Bjorkesten et al[30]	64	SES-CD ≤2	≤94 μg/g	84	74		
	Schoepfer et al[44]	122	SES-CD <4	<70 μg/g	89	72	88	76
	D'Haens et al[46]	87	No ulcers	<250 μg/g	52	83	89	38
			No ulcers >5 mm	<250 μg/g	60	80	78	62
			CDEIS <3	<250 μg/g	94	62	49	97
	Nancey et al[45]	78	CDEIS <3	<250 μg/g	71	78	79	71
Fecal lactoferrin	Sipponen et al[43]	77	CDEIS <3	<10 μg/g	66	92	94	59
			CDEIS 3–9	<50 μg/g	65	96	87	83
Fecal neopterin	Nancey et al[45]	78	SES-CD ≤2	<200 pmol/g	74	73	73	74
Ulcerative colitis								
CRP	Nancey et al[45]	55	Rachmilewitz score <2	<5 mg/L	63	100	100	55
	Schoepfer et al[26]	228	Modified Baron Score <2	<6 mg/L	68	72		
Fecal calprotectin	D'Haens et al[46]	39	Mayo Endoscopic subscore 1–3	<250 μg/g	71	100	100	47
			Mayo Endoscopic subscore 2–3	<250 μg/g	86	78	82	82
	Schoepfer et al[26]	228	Modified Baron score <2	<57 μg/g	91	90		
	Nancey et al[45]	55	Rachmilewitz score <2	<250 μg/g	91	87	87	91
Fecal neopterin	Nancey et al[45]	55	Rachmilewitz score <2	<200 pmol/g	74	100	100	73
	Husain et al[47]	52	SCCAI <5	<98.4 ng/g	88	82		

CDEIS, Crohn's Disease Endoscopic Index of Severity; SCCAI, Simple Clinical Colitis Activity Index; SES-CD, Simple Endoscopic Scale–Crohn's Disease.

Supplementary Table 5. Thresholds for Disease Activity for Endoscopic Scoring Systems in Crohn's Disease and Ulcerative Colitis

Tool	Parameters assessed	Scoring system	Activity score thresholds			
			Remission	Mild	Moderate	Severe
Crohn's disease						
CDEIS[43,48,49]	Deep ulceration, superficial ulceration, surface involved by disease, and ulcerated surface scored in up to 5 segments (rectum, sigmoid and left colon, transverse colon, right colon, and ileum) Presence/absence of ulcerated stenosis	Cumulative score adjusted for the number of segments totally or partially explored (maximum score, 44)	0–3	3–9	9–12	≥12
SES-CD[50,51]	Presence and size of ulcers, extent of the ulcerated surface, extent of the affected surface, and the presence and type of narrowings scored in up to 5 segments (rectum, sigmoid and left colon, transverse colon, right colon and ileum)	Cumulative score (maximum score, 56)	0–2	3–6	7–15	≥16
Lewis score[52] (capsule endoscopy)	Villous edema and ulcer scored in the first, second, and third tertiles Stenosis for the whole study	Cumulative score with different weightings given according to number, longitudinal extent, and descriptors	<135	135–790	>790	
Ulcerative colitis						
Rachmilewitz score[18,19]	Granulation, vascular pattern, vulnerability of mucosa, and mucosal damage	Cumulative score with different weightings given according to number, longitudinal extent, and descriptors	<4	4–6	6–9	9–12
UCEIS[53]	Vascular pattern, bleeding, erosions, and ulcers	Cumulative score with each parameter graded on a scale of 1–4	1 on all descriptors			≥3 for vascular pattern and bleeding with ≥2 for erosions and ulcers

CDEIS, Crohn's Disease Endoscopic Index of Severity; SES-CD, Simple Endoscopic Score for Crohn's Disease; UCEIS, Ulcerative Colitis Endoscopic Index of Severity.

Supplementary Table 6. Independent Prognostic Factors for a Disabling or Severe Disease Course in Crohn's Disease: Findings From Two Large Cohort Studies

Factors in Cox regression model	Publication	Independent prognostic factors	Degree of risk
Prognostic factors for disabling disease in the 5-year period after diagnosis			
Sex	Beaugerie et al,[54]	Initial requirement for steroids	OR, 3.1 (95% CI, 2.2–4.4)
Ethnicity[a]		Age at diagnosis < 40 y	OR, 2.1 (95% CI, 1.3–3.6)
Age at onset		Perianal lesions at diagnosis	OR, 1.8 (95% CI, 1.2–2.8)
Location of disease at diagnosis	Loly et al,[55] 2008	Initial requirement for steroids	OR, 1.7 (95% CI, 1.0–2.7)
Previous appendectomy		Perianal lesions at diagnosis	OR, 2.6 (95% CI, 1.4–5.1)
Smoking status		Ileocolonic location of disease	OR, 1.7 (95% CI, 1.1–2.8)
Systemic manifestations at diagnosis			
Perianal lesions at diagnosis			
Initial requirement for steroids			
Prognostic factors for severe disease in the 5-year period after diagnosis			
Earlier-listed factors and	Loly et al,[55] 2008	Stricturing behavior	HR, 2.1 (95% CI, 1.4–3.2)
Family history		Weight loss > 5 kg	HR, 1.7 (95% CI, 1.1–2.4)
Weight loss > 5 kg at diagnosis			
Fever (>38°C) at diagnosis			
Stricturing behaviour at diagnosis			
Intra-abdominal penetrating behavior			
Leukocyte count			
Platelet count			
Hemoglobin			
C-reactive protein			
Albumin			
Ferritin			
CARD-15 genotype for 3 main mutations, ASCA			
pANCA			

ASCA, anti–*S cerevisiae* antibodies; HR, hazard ratio; OR, odds ratio; pANCA, perinuclear antineutrophil cytoplasmic antibodies.
[a]Ethnicity was not a covariate in the study by Loly et al[55] because only 5 patients in the study were not Caucasian.

Supplementary Table 7. Prognostic Factors for a Severe or Complicated Disease Course in Patients With Crohn's Disease and Ulcerative Colitis

Prognostic factor	Outcome
Crohn's disease	
Age <40 y at diagnosis	Disabling disease at 5 years[54]
	Surgery[56,57]
	Disease recurrence[58,59]
Weight loss > 5 kg at diagnosis	Severe disease at 5 years[55]
Small-bowel disease location	Surgery[60–62]
	Disabling disease at 5 years[55]
	Time to complicated disease[63,64]
Ileocolonic disease location	Disabling disease at 5 years[55]
	Surgery[60–62]
Upper gastrointestinal disease location	Surgery[60,62]
	Disease recurrence[59]
Severe endoscopic disease at diagnosis	Penetrating complications[65]
	Surgery[65]
Perianal disease at diagnosis	Surgery[69]
	Disease recurrence[66,67]
	Disabling disease at 5 years[54,55]
	Complicated disease phenotype[63]
Stricturing or penetrating disease at diagnosis	Severe disease at 5 years[55]
	Surgery[56,57,60,61,68]
Initial requirement for steroids	Disease recurrence[66]
	Time to complicated disease[64]
	Disabling disease at 5 years[54,55]
	Surgery[60]
Current smoking	Surgery[60,62,69]
	Disease recurrence[58]
CDAI score >200	Disease recurrence[66]
Increased CRP level	Surgery (in patients with ileal disease)[57]
	Disease recurrence[67,70]
Presence of ASCA	Severe/complicated disease behavior[71,72]
	Surgery[68,73]
NOD2/CARD15 mutations	Risk of small-bowel stenosis and need for early surgery[74–77]
Ulcerative colitis	
Younger age at diagnosis	Relapse[58,78]
	Number of relapses[79,80]
	Colectomy[57]
	Colorectal cancer[81–83]
Extensive disease	Colectomy[84,85]
	Colorectal cancer[81,82]
	Disease recurrence[58]
Disease location	Colectomy[69]
Diagnosis of primary sclerosing cholangitis	Colorectal cancer[83]
Increased ESR	Colectomy[84]
Presence of pANCA	Relapse[86]
Presence of ASCA	Relapse[86]
Increased CRP level	Colectomy (in patients with extensive disease)[57]
Increased fecal calprotectin level	Relapse[78]
Negative smoking status	Colectomy[69]
	Relapse[80]

ASCA, anti–*S cerevisiae* antibodies; pANCA, perinuclear antineutrophil cytoplasmic antibodies.

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