

Looking beyond symptoms and disease activity to define disease severity in inflammatory bowel disease: results of an IOIBD specialist panel

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Abstract

Background and Aim: The aims of this study were to select the attributes determining disease severity, to rank the importance of and to score these individual attributes for both Crohn's disease (CD) and ulcerative colitis (UC).

Methods: Using a modified Delphi panel, 14 members of the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) selected the most important attributes. 18 IOIBD members independently completed a conjoint analysis exercise. Following group discussion, these specialists then repeated the conjoint analysis exercise, first as a group and then independently to yield a final relative ranking of these attributes. Adjusted utilities were developed by creating proportions for each level within an attribute.

Results: For CD 15.8% of disease severity was attributed to the presence of mucosal lesions, 10.9% to history of a fistula, 9.7% to history of abscess and 7.4% to history of intestinal resection. For UC 18.1% of disease severity was attributed to mucosal lesions, followed by 14.0% for impact on daily activities, 11.2% C-reactive protein and 10.1% for prior experience with biologics. Disease severity scores were created on a 100-point scale by applying each attribute's average importance to the adjusted utilities.

Conclusion: Based on specialist opinion, mucosal lesions were the most important attribute associated with disease severity for both diseases. CD severity was associated more with intestinal damage, in contrast to UC disease severity, which was more dependent on symptoms and impact on daily life. Disease severity indices may provide a useful tool for consistent assessment of patients with IBD.

Introduction

Inflammatory bowel disease (IBD) includes Crohn's disease (CD) and ulcerative colitis (UC), which are chronic disabling conditions.[1-3] There is accumulating evidence indicating that we need to treat beyond symptoms due to the well-known disconnect between clinical symptoms and disease activity, especially in CD. IBD are destructive diseases which may result in irreversible bowel damage and the need for surgery. Avoidance of hospitalization surgery and progression to bowel damage are increasingly considered as a therapeutic goals in disease-modification trials.[4-9] The premise is to treat inflammatory disease before intestinal damage becomes irreversible and disability ensues.

Disease activity and disease severity may refer to two distinct yet overlapping concepts. Disease activity reflects a cross sectional assessment of biological severity whereas disease severity may include longitudinal and historical factors which gives a more complete picture of the overall burden of disease. To be included in the registration clinical trials for biologics, IBD patients had to have moderate to severely *active* disease (often abbreviated to the simplistic 'severe disease') according to the Crohn's Disease Activity Index (CDAI) for CD or Mayo Score for UC, both of which were developed to measure disease activity at a point in time.[10-12] However, basing disease severity on symptoms alone misses the many other patient and disease characteristics that drive our decisions towards appropriate medical therapy, including bowel damage and impact on daily activities (disability). Since the labels for biologic drugs are based on the registration trials, these disease-modifying medications are limited to patients with moderate to severe disease activity. Therefore, patients need to have substantial enough symptoms at the time of prescribing for doctors to recommend and payers to

agree to initiate treatment, even if the past pattern or burden of disease would be likely to benefit from treatment in those with disease that is currently less active or inactive.

A patient's historical disease course and risk of future complications are important features of IBD that should also guide management. In an effort to shift the paradigm from stratifying patients based on current disease activity towards global course of disease severity, researchers conducted a systematic review identifying three main domains relevant to the evaluation of disease severity in IBD: inflammatory burden, disease course and impact of the disease on the patient's daily activities,. [10] There are multiple attributes within these domains, some of which have more influence over long term disease course than others.

The aims of this study were to: 1. Define the attributes within these three domains that are most important to determining disease severity; 2. Rank the importance of and score these individual attributes for both CD and UC; and 3. With these rankings and an understanding of how much each attribute contributes to overall disease severity, to generate a disease severity index to place an individual's disease in context.

Methods:

PHASE 1: Identification of Key Attributes

Determining the main patient attributes influencing determination of IBD severity began with a systematic review process to identify all potential elements of disease activity and severity of IBD. Using a set of predefined MeSH terms, researchers conducted a comprehensive literature search in PubMed from inception until April 2014. During the systematic review, researchers identified three domains instrumental in determining IBD severity: impact on the patient, inflammatory burden, and course of complication. [10]

After a list of attributes was identified, 16 IBD experts met in Frankfurt, Germany on December 10-11th, 2014 to discuss the results using a modified RAND panel. With the intention of reviewing and short-listing the list of attributes identified through the systematic review, an open discussion ensued. There was an automated response process and participants voted on the attributes on the list by assigning values 1-9 (with 9 being the most preferred) to each of the attributes on the list. Variables that received a score ranging from 7-9 by at least 75% of participants were included in the final attribute set. For those attributes not initially receiving a score between 7-9, following a group discussion, a secondary vote was initiated. At this point, if an attribute received fewer than 75% of votes with scores from 7-9, it was dropped from the final item set. Output included two defined sets of attributes considered to be markers of severe disease, one for CD and one for UC (**Supplemental Tables 1 and 2**).

PHASE 2: Conjoint analysis

Conjoint Analysis in Healthcare

Conjoint Analysis (CA) has been used as a method to elicit how people make complex decisions with many driving factors by determining the willingness to “trade-off” certain attributes in favor of others. The CA process is a choice-experiment wherein we assume stakeholder choices are influenced by multiple driving forces that may be underlying. CA uses multinomial logit regression to model the choice process through applying multiple approximations of the utility of an attribute.

A particular form of CA, called Adaptive Choice-Based Conjoint (ACBC), takes respondents through a process of evaluating competing profiles of a product (or patient) that are comprised of various attributes, or characteristics. Increasingly, CA is being

applied to healthcare decision-making processes. Examples of their applications include: conducting cost-effectiveness analysis with a consideration for process of care, assessment of willingness to pay, assessing health status, quality-adjusted life-years (QALY), health-related quality of life (HRQoL), and valuing patient-reported outcome measures to assess perceived risk and preference for various treatment options.[13-17] When making healthcare decisions, the profiles contain a list of patient clinical factors that influence a decision-making process, (e.g. frequency of loose stools, disease extent, and CRP level), each with a set of levels. This technique has been used previously to study patient and providers preferences in IBD.[18-21]

During a CA exercise, each response provided influences subsequent questions until there is ample consistency among respondent clinical factor choices to inform a series of complete hypothetical patient profiles containing varying levels of clinical attributes. In this project, participants were asked to focus on how different clinical factors of IBD influenced their impression of overall disease severity. Respondents indicate which patient profiles meet their evaluation criteria until finally, respondents are shown two side-by-side profiles and asked to select which is *more* severe. A series of profile comparison continues until the responses achieve internal consistency and a rank order of the respondent's prioritization of clinical factors can be determined.

Survey Design

The CA survey was created using the Sawtooth Software (Orem, UT) ACBC module. To conduct a CA exercise, it is essential that attributes are evaluated individually and partitioned into levels with varying degrees of severity. In March 2015, attributes and their corresponding levels were adapted for CA from the Frankfurt-based RAND panel (**Table 1**).

The first section of the CA displayed a series of patient vignettes and respondents were asked to select either “Yes, this patient has severe disease” or “No, this patient does not have severe disease” (**Figure 1**). Each question in the CA was generated according to the respondent’s previous selection. The length of the survey varied depending on the internal consistency of the responses. The next set of questions asked respondents to select from a list of attributes whether they believed any specific attributes to always be markers of severe disease, or were never markers of severe disease. Based off of respondents’ selections, a series of side-by-side patients profiles was generated. Respondents then selected, amongst the two patients, which they believed had more severe disease. Some of the attributes remained constant between the two patient profiles. Respondents continued to select between pairs of patients until they established internal consistency and their preferences for certain attributes emerged. **Figure 2** displays an example of the side-by-side comparison of two hypothetical Crohn’s disease patients.

Conjoint Analysis Administration

In the context of this study, the CA methodology was applied to an in-person panel of experts to replace a traditional RAND decision panel. The underlying statistics behind CA are similar to that of regression modeling with the main output being a part-worth utility, or a number ranging from zero to one, with one being the most preferred and zero the least preferred clinical factor. The average importance of all clinical factors in the CA profiles add up to 1.0 (100 percent). It is through these outputs that we are able to see not only a rank ordering of attributes, but also the relative importance of one attribute compared to another, as well as the levels *within* each attribute.

During the month of April 2015, we asked a selection of IBD specialists to complete the CA exercise at three different time points to determine the importance of each of the attributes as identified through the systematic review and then to determine if discussion of the attributes had an effect on their importance rankings. Initially, specialists completed the survey independently without any discussion or influence from others. All CA results were presented and reviewed anonymously at an in-person panel in Montreal, QC at the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) Conference on April 23, 2015. After a period of discussion, experts then repeated the CA exercise in a group setting using an automated response system, (where the majority for question selection was set at 51%). Finally, specialists completed the CA for a third time, independently, after commencement of the group discussion. This last round of ratings was used as the final results.

PHASE 3: Disease Severity Score

Following the compilation of third round of CA results, we worked to translate average importances into a baseline set of IBD severity scores that could be applied to the patient setting and in the future be adapted for use by clinicians in practice. To create the score, we utilized the average utility scores to determine minimum and maximum relative scores of each attribute level. Scores were converted to a 100-point scale, where the scores for the absence of a symptom within each attribute (the lowest average utility) were set to zero. Scores for levels within each attribute were calculated by applying the magnitude of their average utility to the attribute's overall importance, or weight. By applying the average utilities to the scoring schema, the score within a given attribute became relative to the level of importance that attribute had in determining severity across all of the clinical factors included in the CA. Scores within each attribute were rounded to the nearest integer.

Results

Sample Characteristics

Eighteen IBD specialists completed the final CA exercise. Their ages were equally distributed from 35-65+, but only one was female. All participants had practiced medicine with a major interest in IBD for more than 10 years and were geographically diverse, representing 12 different countries.

PHASE 1: Attribute Selection Process

Following the initial panel (**Supplemental Tables 1 and 2**), specialists defined CD and UC severity using a set of 13 and 12 key attributes, respectively. To meet the parameters of CA methodology, some of these attributes were disassociated with one another; a process that would ensure each attribute would not be influenced by the presence of another. The final CA was comprised of 16 attributes for the CD module and 13 attributes for UC module (**Table 1**).

PHASE 2: Pre-Meeting Versus Post-Meeting Conjoint Analysis Results

There was a marked shift from the level of importance recorded from before and after the in-person discussion. Not only did the ranking of attribute importances shift within each disease state, but also, the rank orders differed between CD and UC. The presence of mucosal lesions was significantly more important than all other attributes under consideration in both modules. **Figures 3 and 4** highlight the relative importance of each of the attributes for the CD and UC conjoint analysis modules from most to least influential when determining patient disease severity according to the post-meeting results.

Crohn's Disease Module

Disease severity in CD was dominated by those attributes measuring intestinal damage caused by disease, with mucosal lesions being the most influential clinical factor accounting for 18.1% of the determination of CD severity. Presence of a fistula (11%), perianal abscess (9.7%), and history of intestinal resection (7.4%) were the next most prominent factors influencing the classification of severe disease (**Table 2**).

Comparatively, the presence of daily symptoms (loose stools, experience with biologics, impacts daily activity), were less important factors influencing disease severity.

There was a significant increase in importance for clinical factors associated with intestinal damage following the in-person meeting in Montreal, suggesting that the distinction between CD and UC was influenced by the meeting's group discussions.

Ulcerative Colitis Module

In contrast to CD, UC severity was influenced by the presence of inflammation and the impact of disease on daily activity. While the most important clinical factor for determining UC severity was mucosal lesions (18.1%), the next was the impact of symptoms on daily activity (14.0%). Use and effectiveness of biologics (10.1%) and recent hospitalization (7.7%) were also influential when determining disease severity. The clinical factors measuring intestinal damage were ranked much lower (disease extent, 4.8%, anorectal symptoms, 4.0%) (**Table 2**).

Comparing results from before and after the in-person meeting, those attributes exhibiting significant shifts in importance ranking included: impacts of daily activity, CRP level, experience with biologics, recent hospitalization, and recent steroid use.

PHASE 3: Overall disease severity index

After examining the clinical attribute results for Crohn's disease and UC separately, we adapted the relative importance of each attribute to two unique 100-point scales. The severity scores calculated within attributes for Crohn's disease ranged from 16 (large or deep mucosal lesions as confirmed by MRI or endoscopy) to 2 (confirmed steroid use in the past year).

Disease severity scores calculated for the clinical attributes of UC ranged from 18 (active ulcers confirmed by endoscopy) down to 4 (presence of rectal bleeding, anorectal symptoms, or nocturnal bowel movements) (**Tables 3a, 3b**).

Discussion

Disease severity has historically been synonymous with disease activity, but this ignores the many different aspects of IBD that impact patients' lives and factors that lead to long-term complications. Disease activity can reflect long term or short term activity but is most often measured by a score that reflects only short term activity. These measures do not account for the accumulation of hospitalizations, surgeries, complications, associated diseases and impact on lifestyle over time. Intestinal damage begins soon after diagnosis, often in the absence of significant symptoms.[22] Although more prominent in CD, this phenomenon also occurs in UC.[5] If effective therapy is reserved until moderate-severely active disease is obvious, then the window of opportunity to successfully treat patients to achieve remission is lost for many. To look beyond symptoms and better recognize patients at most risk due to their IBD, we have identified the key attributes that contribute to overall IBD severity. Furthermore, we have created two Overall Disease Severity Indices that can be tested to risk stratify patients with Crohn's disease and ulcerative colitis.

Based on specialist opinion, mucosal lesions are the most important attribute associated with disease severity for both diseases. When comparing CD and UC, CD severity is associated more with accumulating intestinal damage, in contrast to UC disease severity, which is more dependent on symptoms and impact on daily life. This is consistent with how patients are approached in practice. For example, when patients with CD are seen in clinic, although current symptoms are taken into account, prior surgeries, perianal disease and extent of bowel at risk are typically weighted higher than day-to-day symptoms when considering a long-term treatment plan. Conversely, since active inflammation is more overt symptomatically with UC and bowel damage less obvious, it is not surprising that this expert panel treated UC differently than CD.

The work of this panel helps redefine overall disease severity for IBD. Currently, disease-scoring indices are used for clinical trials or to track symptoms prospectively.[23] These indices are valuable to stratify patients into mild, moderate or severe disease activity at a moment in time,[24] but do not take into account overall disease severity in context of bowel damage and impact on daily life. Other groups have identified risk factors for rapid evolution of disease,[25] disabling CD,[26] and have defined features of severe, aggressive, or complicated CD,[27-29] but have not specified and weighted how disease attributes independently contribute to overall disease severity. The disease characteristics identified by the panel, and the overall disease severity score will enable the differentiation between disease activity and disease severity and offer both further research opportunities and a practical tool by which to classify disease severity of patients and offer appropriate treatment without relying on present symptoms alone. In the early 1990s rheumatologists went through a similar process to identify better outcomes to measure for patients with rheumatoid arthritis and

created OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials).[30] Since, this has become a foundation of their field and has led to hundreds of publications. We hope to learn from OMERACT, and use this current work to push the field of IBD towards a more meaningful understanding of overall disease severity.

As with any expert panel, there are limitations of this work based on the participants and validity outside of this group. Although the group was composed primarily of members from the IOIBD, this is a globally diverse cohort of specialists possessing varied opinions across a range of years of clinical experience. There was quite a bit of disagreement among the group in the pre-meeting independent questionnaires, but this gap decreased in the post-meeting voting – demonstrating that the RAND process is a successful method whereby people share opinions, listen to the views of others, and incorporate new points of view into an evolved perspective.

Conjoint analysis has been applied in healthcare fields ranging from mental health[31] to chronic leukemia,[32] and has been used specifically within the field of IBD.[19-21] The methodology of using conjoint tradeoff analysis embedded within a RAND panel is to the best of our knowledge, a novel approach. Integration of these two methodologies brings along with it the benefit of applying expert knowledge to a systematic process for assigning utilities scores to patient disease severity attributes, and then calculating specific values to explain what proportion of overall disease severity is influenced by each attribute.[33] This process could not be completed using a standard RAND format.

Future studies using these results should focus on two important aspects: prospective validation of the disease severity score in different patient populations, and conducting a similar in-person conjoint analysis with patients to see how their valuation of attributes

compares to providers. After testing the application clinically, and refining based on patient input, it is likely that this overall IBD disease severity score could be adjusted and later implemented during clinical practice.

For patients with IBD, it is important to distinguish disease activity at a point in time from disease severity over a period of time. When selecting therapy for patients, providers need to focus on the short-term goal of controlling disease activity and use the overall disease severity to guide long-term management plans. Short-term symptom control is often the easiest part of IBD management, while preventing the consequences of irreversible bowel damage requires preparation and an understanding of the stratification of risk for an individual patient. We expect this work to help identify those at the higher end of the risk spectrum, so that appropriate intensive treatment can be initiated and optimized in an efficient, precise and cost-effective manner.

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Table 1. Clinical Factors (and levels) tested in conjoint analysis exercises.

Clinical Factor (Crohn's Disease)	Levels (Crohn's Disease)	Clinical Factor (Ulcerative Colitis)	Levels (Ulcerative Colitis)
Mucosal lesions	<ul style="list-style-type: none"> • No mucosal lesions • Small mucosal lesions as confirmed by MRI or endoscopy • Large or deep mucosal lesions as confirmed by MRI or endoscopy 	Mucosal lesions	<ul style="list-style-type: none"> • No active erosions or ulcers • Active erosions confirmed by endoscopy • Active ulcers confirmed by endoscopy
Presence of a fistula	<ul style="list-style-type: none"> • No fistula at time of clinic visit • Has fistula at time of clinic visit 	Impacts daily activity	<ul style="list-style-type: none"> • Disease does not significantly impact daily activities • Disease significantly impacts daily activities
Presence of a perianal abscess	<ul style="list-style-type: none"> • No perianal abscess at time of clinic visit • Has perianal abscess at time of clinic visit 	CRP level	<ul style="list-style-type: none"> • Normal CRP levels (1-3 mg/L) • Slightly elevated CRP levels (3-5 mg/L) • Elevated CRP levels (above 5 mg/L)
History of intestinal resection	<ul style="list-style-type: none"> • No intestinal resections • At least one intestinal resection less than 40cm • At least one intestinal resection greater than or equal to 40cm 	Experience with biologics	<ul style="list-style-type: none"> • Has never used biologics/immunomodulators • Has experienced some symptom improvement with use of biologics/immunomodulators • Has not experienced symptom improvement with use of biologics/immunomodulators
Presence of a stoma	<ul style="list-style-type: none"> • No stoma at time of clinic visit • Has stoma at time of clinic visit 	Recent hospitalizations	<ul style="list-style-type: none"> • No disease-related hospitalization within last 12 months • Has disease-related hospitalization within last 12 months
Extent of Disease	<ul style="list-style-type: none"> • Limited disease (less than 40cm ileal involvement, OR absence of pancolitis) 	Recent steroid use	<ul style="list-style-type: none"> • No steroid use within the past year • Has steroid use within the past

	<ul style="list-style-type: none"> • Extensive disease (ileal involvement of at least 40cm OR presence of pancolitis) 		year
Frequency of Loose stools	<ul style="list-style-type: none"> • Less than 10 loose stools per week • At least 10 loose stools per week 	Anemic	<ul style="list-style-type: none"> • Not anemic (according to WHO criteria) • Yes, anemic (according to WHO criteria)
Presence of a stricture	<ul style="list-style-type: none"> • No stricture at time of visit • Has stricture at time of visit 	Loose stools	<ul style="list-style-type: none"> • No change in frequency of loose stools compared to baseline • Increase in frequency of loose stools by one per day compared to baseline • Increase in frequency of loose stools of at least two per day compared to baseline
CRP level	<ul style="list-style-type: none"> • Normal CRP levels (1-3 mg/L) • Slightly elevated CRP levels (3-5 mg/L) • Elevated CRP levels (above 5 mg/L) 	Albumin level	<ul style="list-style-type: none"> • Normal albumin level (more than 3.5-5.0 g/dL) • Low albumin level (less than 3.5 g/dL)
Experience with biologics	<ul style="list-style-type: none"> • Has never used biologics/immunomodulators • Has experienced some symptom improvement with use of biologics/immunomodulators • Has not experienced symptom improvement with use of biologics/immunomodulators 	Disease extent	<ul style="list-style-type: none"> • Distal colitis (inflammation potentially treatable using enemas) • Extensive colitis (inflammation extending beyond the reach of enemas)
Impacts daily activity	<ul style="list-style-type: none"> • Disease does not significantly impact daily activities • Disease significantly impacts daily activities 	Nocturnal bowel movements	<ul style="list-style-type: none"> • Does not have nocturnal bowel movements • Has nocturnal bowel movements
Albumin level	<ul style="list-style-type: none"> • Normal albumin level (more than 3.5 g/dL) • Low albumin level (less than 3.5 g/dL) 	Anorectal symptoms	<ul style="list-style-type: none"> • None of the following: anorectal pain, bowel urgency, incontinence, discharge, tenesmus • At least one of the following: anorectal pain, bowel urgency, incontinence, discharge, tenesmus
Anorectal symptoms	<ul style="list-style-type: none"> • None of the following: anorectal pain, bowel urgency, incontinence, discharge, tenesmus • At least one of the following: anorectal pain, bowel urgency, incontinence, discharge, tenesmus 	Rectal bleeding	<ul style="list-style-type: none"> • No rectal bleeding • Has rectal bleeding
Anemia	<ul style="list-style-type: none"> • Not anemic (according to WHO criteria) • Yes, anemic (according to WHO 		

	criteria)		
Abdominal pain	<ul style="list-style-type: none"> • Infrequent abdominal pain (less than daily) • Daily abdominal pain 		
Recent steroid use	<ul style="list-style-type: none"> • No steroid use within past year • Has used steroids within past year 		

Table 2. Disease attribute contributions to overall disease severity

Attribute of Crohn's	Proportion	Attribute of UC	Proportion
Mucosal lesions	15.8%	Mucosal lesions	18.1%
Fistula	10.9%	Impact on daily activities	14.0%
Perianal abscess	9.7%	C-reactive protein	11.2%
Prior bowel resection	7.4%	Prior biologic use	10.1%
Stoma	7.1%	Recent hospitalization	7.7%
Disease extent	5.8%	Recent steroid use	7.6%
Frequency of loose stools	5.6%	Anemia	5.1%
Stricture	5.4%	Frequency of loose stools	4.8%
C-reactive protein	5.3%	Albumin	4.8%
Prior biologic use	5.3%	Disease extent	4.8%
Impact on daily activities	4.8%	Nocturnal bowel movements	4.3%
Albumin	4.2%	Anorectal symptoms	4.0%
Anorectal symptoms	3.9%	Rectal bleeding	3.5%
Anemia	3.6%		
Abdominal pain	3.1%		
Recent steroid use	2.3%		

Table 3a Ulcerative Colitis Overall Disease Severity Index

Attribute	Level	Score
Mucosal lesions	No active erosions or ulcers	0
	Active erosions confirmed by endoscopy	14
	Active ulcers confirmed by endoscopy	18
Daily activity impact	Disease does not significantly impact daily activities	0
	Disease significantly impacts daily activities	14
CRP level	Normal CRP levels (1-3 mg/L)	0
	Slightly elevated CRP levels (3-5 mg/L)	4
	Elevated CRP levels (above 5 mg/L)	11

Biologics use	Has never used biologics/immunomodulators	0
	Has experienced some symptom improvement with use of biologics/immunomodulators	4
	Has not experienced symptom improvement with use of biologics/immunomodulators	10
Recent hospitalization	No disease-related hospitalization within last 12 months	0
	Has disease-related hospitalization within last 12 months	8
Steroid use	No steroid use within the past year	0
	Has steroid use within the past year	8
Anemia	Not anemic (according to WHO criteria)	0
	Yes, anemic (according to WHO criteria)	5
Frequency of loose stools	No change in frequency of loose stools compared to baseline	0
	Increase in frequency of loose stools by one per day compared to baseline	5
	Increase in frequency of loose stools of at least two per day compared to baseline	4
Albumin level	Normal albumin level (more than 3.5-5.0 g/dL)	0
	Low albumin level (less than 3.5 g/dL)	5
Disease extent	Distal colitis (inflammation potentially treatable using enemas)	0
	Extensive colitis (inflammation extending beyond the reach of enemas)	5
Nocturnal bowel movements	Does not have nocturnal bowel movements	0
	Has nocturnal bowel movements	4
Anorectal symptoms	None of the following: anorectal pain, bowel urgency, incontinence, discharge, tenesmus	0
	At least one of the following: anorectal pain, bowel urgency, incontinence, discharge, tenesmus	4
Rectal Bleeding	No rectal bleeding	0
	Has rectal bleeding	3

Table 3b. Crohn's Disease Overall Severity Index

Attribute	Level	Score
Mucosal lesions	No mucosal lesions	0
	Small mucosal lesions as confirmed by MRI or endoscopy	6
	Large or deep mucosal lesions as confirmed by MRI or endoscopy	16

Fistula	No fistula at time of clinic visit	0
	Has fistula at time of clinic visit	11
Perianal abscess	No perianal abscess at time of clinic visit	0
	Has perianal abscess at time of clinic visit	10
Intestinal resections	No intestinal resections	0
	At least one intestinal resection less than 40cm	2
	At least one intestinal resection greater than or equal to 40cm	7
Stoma	No stoma at time of clinic visit	0
	Has stoma at time of clinic visit	7
Disease extent	Limited disease (less than 40cm ileal involvement, OR absence of pancolitis)	0
	Extensive disease (ileal involvement of at least 40cm OR presence of pancolitis)	6
Frequency loose stools	Less than 10 loose stools per week	6
	At least 10 loose stools per week	0
Stricture	No stricture at time of visit	0
	Has stricture at time of visit	5
CRP level	Normal CRP levels (1-3 mg/L)	0
	Slightly elevated CRP levels (3-5 mg/L)	2
	Elevated CRP levels (above 5 mg/L)	5
Biologics use	Has never used biologics/immunomodulators	0
	Has experienced some symptom improvement with use of biologics/immunomodulators	2
	Has not experienced symptom improvement with use of biologics/immunomodulators	5
Daily activity impact	Disease does not significantly impact daily activities	0
	Disease significantly impacts daily activities	5
Albumin level	Normal albumin level (more than 3.5 g/dL)	0
	Low albumin level (less than 3.5 g/dL)	4
Anorectal symptoms	None of the following: anorectal pain, bowel urgency, incontinence, discharge, tenesmus	4
	At least one of the following: anorectal pain, bowel urgency, incontinence, discharge, tenesmus	0
Anemia	Not anemic (according to WHO criteria)	0
	Yes, anemic (according to WHO criteria)	4
Abdominal pain	Infrequent abdominal pain (less than daily)	0
	Daily abdominal pain	3
Steroid use	No steroid use within the past year	0
	Has steroid use within the past year	2

Supplemental Table 1. Crohn's Disease Statements Following Phase 1

ITEMS	CRITERIA
IMPACT OF DISEASE	
Clinical symptoms	Frequency of loose stool (>10/week) and/or daily abdominal pain (pain scale >1)
	Anorectal symptoms (pain, urgency, incontinence, discharge, tenesmus, active fistula)
Impact on daily activities	Disease having significant impact on daily activities
INFLAMMATORY BURDEN	
Serum biomarkers	Anaemia (WHO criteria; abnormal) and/or elevated CRP (cut off 5) and/or low albumin
Mucosal lesions (MRI, endoscopy)	Active; If yes: large and/or deep ulcers
DISEASE COURSE	
Complicated disease	Fistula at time of clinic visit and/or abscess at time of clinic visit and/or stricture at time of clinic visit and/or stoma at time of clinic visit and/or >1 intestinal resection or 1 intestinal resection >40 cm
Response to medication	Steroid use within past year and/or failure of biologics and/or immunomodulators
Disease extent	Extensive disease (>40 cm ileal involvement and/or pancolitis)

Supplemental Table 2. UC Statements Following Phase 2

ITEMS	CRITERIA
IMPACT OF DISEASE	
Clinical symptoms	Frequency of loose stool (>1 above baseline) and/or rectal bleeding (present or absent) and/or nocturnal bowel movements

	Anorectal symptoms (pain, urgency, incontinence, discharge, tenesmus)
Impact on daily activities	Disease having significant impact on daily activities
INFLAMMATORY BURDEN	
Serum biomarkers	Anemia (WHO criteria; abnormal) and/or elevated CRP (cut off 5) and/or low albumin
Mucosal lesions (endoscopy)	Active; If yes: Erosions, ulcers and/or friability
DISEASE COURSE	
Response to medication	Steroid use within past year and/or failure of biologics and/or immunomodulators
Disease extent	Extensive colitis
Need for hospitalisation	Need for hospitalisation within last 12 months

Figure Legend

Figure 1. Sample patient vignette.

Figure 2. Side-by side profiles of two hypothetical Crohn's disease patients generated by the conjoint analysis exercise.

Figure 3. Pre-Meeting and Post-Meeting Average Crohn's Disease Attribute Importances. Patient characteristics of CD ordered by relative importance based on conjoint analysis part-worth utilities before and after the in-person meeting in Montreal, Quebec. Bars are displayed with standard errors to highlight significant differences in the rankings between the two time periods. Mucosal lesions accounted for 17.6% and 15.8% of IBD severity followed by presence of a fistula (5.7% and 10.9%) in pre and post-meeting results, respectively. Having a fistula, perianal abscess, or stoma, all became more important in determining disease severity after the meeting, while having a stricture, use of biologics, impacts on daily activity, albumin level, and being anemic, all became less important.

Figure 4. Pre-Meeting and Post-Meeting Average Ulcerative Colitis Importances. Patient characteristics of UC, ordered by relative importance based on conjoint analysis part-worth utilities before and after the in-person meeting in Montreal, Quebec. Bars are displayed with standard errors to highlight significant differences in the rankings between the two time periods. Mucosal lesions accounted for 18.4% and 18.1% of IBD severity followed by impacts on daily activity (9.3% and 14.0%) in pre and post-meeting results, respectively. The relative rankings of impacts on daily activity, CRP level, experience with biologics and recent steroid use all increased after the in-person meeting.

Figure 1

Patient Vignette	
Take a look at this patient with Crohn's disease and tell us whether you think the patient's disease is "severe" or not.	
Abdominal pain?	Daily abdominal pain
Anorectal symptoms?	None of the following: anorectal pain, bowel urgency, incontinence, discharge, tenesmus
Loose stools?	Less than 10 loose stools per week
Impacts daily activity?	Disease does not significantly impact daily activities
Mucosal lesions?	No mucosal lesions
Anemic?	Yes, anemic (according to WHO criteria)
CRP level	Elevated CRP levels (above 5 mg/L)
Albumin level	Low albumin level (less than 3.5 g/dL)
Has a fistula?	Has fistula at time of clinic visit
Has a perianal abscess?	No perianal abscess at time of clinic visit
Has a stricture?	Has stricture at time of visit
Has a stoma?	No stoma at time of clinic visit
History of intestinal resection?	No intestinal resections
Recent steroid use?	No steroid use within the past year
Experience with biologics?	Has never used biologics/immunomodulators
Disease extent	Extensive disease (ileal involvement of at least 40cm OR presence of pancolitis)
	<input type="radio"/> Yes, this patient has severe disease <input type="radio"/> No, this patient does not have severe disease

Figure 2

Side-by-Side Comparison

This next section will present pairs of patients. For each pair, select which of the two you think has more severe disease.

We've grayed out any clinical factors that are the same, so you can just focus on the differences.

We understand that the differences might be minimal between the two patients, but please do your best to select one patient.

Abdominal pain?	Infrequent abdominal pain (less than daily)	Daily abdominal pain
Anorectal symptoms?	None of the following: anorectal pain, bowel urgency, incontinence, discharge, tenesmus	None of the following: anorectal pain, bowel urgency, incontinence, discharge, tenesmus
Loose stools?	At least 10 loose stools per week	Less than 10 loose stools per week
Impacts daily activity?	Disease significantly impacts daily activities	Disease significantly impacts daily activities
Mucosal lesions?	Large or deep mucosal lesions as confirmed by MRI or endoscopy	Small mucosal lesions as confirmed by MRI or endoscopy
Anemic?	Not anemic (according to WHO criteria)	Not anemic (according to WHO criteria)
CRP level	Slightly elevated CRP levels (3-5 mg/L)	Slightly elevated CRP levels (3-5 mg/L)
Albumin level	Normal albumin level (more than 3.5 g/dL)	Low albumin level (less than 3.5 g/dL)
Has a fistula?	No fistula at time of clinic visit	No fistula at time of clinic visit
Has a perianal abscess?	No perianal abscess at time of clinic visit	Has perianal abscess at time of clinic visit
Has a stricture?	Has stricture at time of visit	Has stricture at time of visit
Has a stoma?	No stoma at time of clinic visit	Has stoma at time of clinic visit
History of intestinal resection?	At least one intestinal resection less than 40cm	At least one intestinal resection greater than or equal to 40cm
Recent steroid use?	Has steroid use within the past year	Has steroid use within the past year
Experience with biologics?	Has not experienced symptom improvement with use of biologics/immunomodulators	Has never used biologics/immunomodulators
Disease extent	Extensive disease (ileal involvement of at least 40cm OR presence of pancolitis)	Extensive disease (ileal involvement of at least 40cm OR presence of pancolitis)
	<input type="radio"/>	<input type="radio"/>

Figure 3.

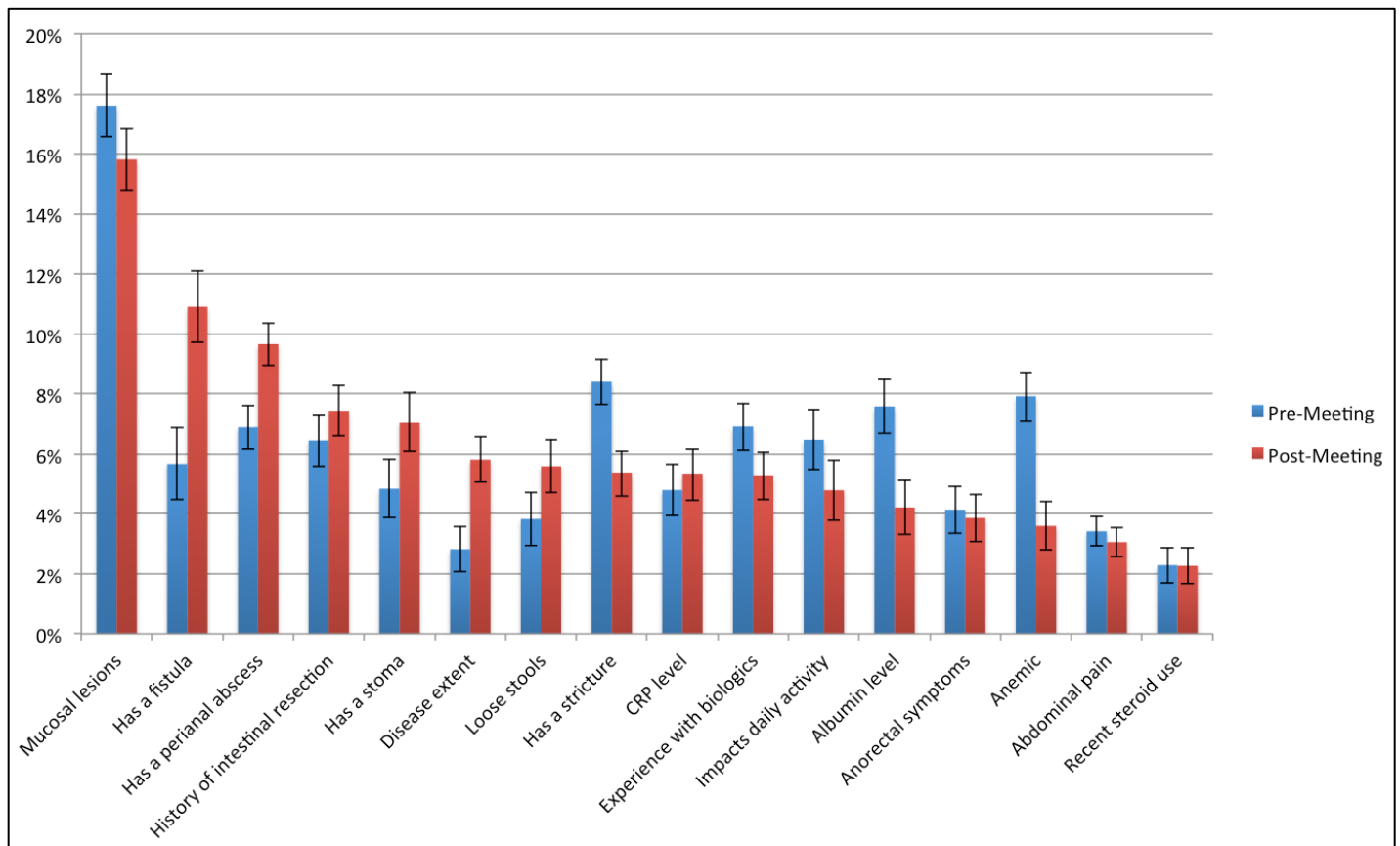


Figure 4

