Evaluation of the Patient-Reported Outcomes Measurement Information System in a Large Cohort of Patients With Inflammatory Bowel Diseases

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BACKGROUND & AIMS: Patient-reported outcomes (PROs) convey important aspects of health status, complementing physician-reported measures. The PRO Measurement Information System (PROMIS) provides valid, widely available measures applicable to patients with chronic illness and the general population. We sought to evaluate these measures in a large cohort of patients with inflammatory bowel disease (IBD).

METHODS: By using data from the Crohn's and Colitis Foundation Association Partners internet cohort, we performed cross-sectional and longitudinal analyses to evaluate associations between PROMIS measures and validated disease activity indices (Short Crohn's Disease Activity Index and Simple Clinical Colitis Activity Index) and the Short IBD Questionnaire quality-of-life instrument.

RESULTS: A total of 10,634 individuals (6689 with Crohn's disease and 3945 with ulcerative colitis or indeterminate colitis) completed PRO testing. Compared with the general population (mean PROMIS score, 50), IBD patients in this cohort reported more depression (mean, 54), anxiety (mean, 52), fatigue (mean, 56), sleep disturbance (mean, 52), and pain interference (mean, 53); and they had less social satisfaction (mean, 48). In each PROMIS domain, there was worse functioning with increasing levels of disease activity and worsening Short IBD Questionnaire scores ($P < .001$ for all). Longitudinal analyses showed improved PROMIS scores with improved disease activity and worsening PROMIS scores with worsening disease ($P < .001$ for all comparisons).

CONCLUSIONS: In a cross-sectional and longitudinal study, we observed differences between patients with IBD and the general population in several important aspects of health. The improvement in diverse health outcome measures with improved disease control provides strong support for the construct validity of PROMIS measures in the IBD population. Their use should advance patient-centered outcomes research in IBD.

Crohn's disease (CD) and ulcerative colitis (UC), collectively known as inflammatory bowel disease (IBD), affect nearly 1.2 million Americans.[1] To date, much of the evidence used to formulate treatment recommendations stems from placebo-controlled trials. However, real-world, population-based clinical effectiveness and comparative effectiveness research is required to better understand the risks and benefits of IBD therapies, particularly in populations often excluded from clinical trials. Consequently, the Institute of Medicine recently declared IBD as one of the top national priorities for comparative effectiveness research.[2]

Study outcomes of comparative effectiveness research often differ from end points of randomized trials. Practically speaking, in population-based research it is often not

possible to complete assessments required to calculate disease activity scores and/or assess for endoscopic remission. In addition, the generally accepted clinical trial end points do not necessarily reflect the well-being of patients with chronic illnesses, such as IBD. In contrast, patient-reported outcomes (PROs) are direct responses from patients about how they feel or function in relation to a health condition and its therapy without interpretation by health care professionals or anyone else. PROs can evaluate symptoms, signs, functional status, perceptions, or other aspects such as convenience and tolerability. As such, PROs represent what is most important to patients about a condition or its treatment[3] and are important end points for clinical trials and comparative effectiveness studies.[4]

The Patient-Reported Outcomes Measurement Information System (PROMIS) initiative of the National Institutes of Health was developed to advance the science and application of PROs among patients with chronic diseases for use in research and clinical practice.[5] PROMIS instruments are general (not disease specific) measures that are valid and responsive, allow comparisons within and between conditions, and are grouped into item banks based on symptoms, function, well-being, and general health.[6] PROMIS measures have not been evaluated comprehensively in patients with IBD. We sought to evaluate the performance of PROMIS measures in this patient population.

Methods

Overall Study Design

Within a large internet cohort of adult patients with IBD, we performed a series of cross-sectional and longitudinal analyses to evaluate associations between PROMIS measures and disease activity indices, a disease-specific health-related quality-of-life (HRQOL) instrument, prednisone use, and ileal pouch-anal anastomosis (IPAA) status.

Study Population

The Crohn's and Colitis Foundation of America (CCFA) Partners study is a longitudinal internet-based cohort of patients with IBD. The development of the cohort has been described in detail previously.[7] In brief, we recruited participants with a self-reported diagnosis of UC, CD, or indeterminate colitis (IC) who were older than 18 years of age through CCFA e-mail rosters, the CCFA website, various social media outlets, and at educational and fundraising events. All participants completed a baseline survey including demographic information and questions about their IBD history, symptoms, and medication use. A random subset of patients completed an optional module regarding HRQOL and various PROs. Follow-up questionnaires every 6 months ascertained changes in disease treatment, symptoms, and PROs.

The study population for the cross-sectional portion of this analysis included all participants in the CCFA Partners cohort enrolled between June 2011 and October 2012 who completed PRO measures on at least one occasion. The study population for the longitudinal section of this analysis included study participants who completed PRO measures on at least 2 occasions.

Patient-Reported Outcome Measures

Participants completed 4 items from each of 6 PROMIS item banks measuring individual dimensional constructs of HRQOL. Measured domains, selected based on prior literature, patient feedback, and input from gastroenterologists (M.D.K. and M.D.L.) and PROMIS methodologists (D.A.D.), included anxiety, depression, fatigue, sleep disturbance, satisfaction with social role, and pain interference. Pain interference items were included at a later date than the other items, and hence data are available for only a portion of the overall study population. Participants also completed a single question about general health. A complete list of all PROMIS items included in this study is shown in Supplementary Appendix 1. All PROMIS items have undergone rigorous development and validation based on qualitative research and item response theory in both general and chronically ill populations.[8] Items are calibrated using a T-score metric with the mean of the US general population equal to 50 and SD in the general population equal to 10. Minimal important differences (MIDs) refer to the score that is large enough to have implications for a patient's treatment or care. Because the PROMIS system is relatively new, MIDs are not well defined; however, research in cancer patients suggests that MIDs for many PROMIS domains are in the range of 2 to 6.[9] Higher scores indicate more of the domain being measured. Hence, high scores for anxiety, depression, fatigue, sleep disturbance, and pain interference indicate poorer health, whereas high scores for satisfaction with social role indicate better health.

Other Variables

The Short IBD Questionnaire (SIBDQ) was administered as a disease-specific measure of HRQOL.[10] Disease activity was assessed using validated measures—the Short Crohn's Disease Activity Index (SCDAI) for CD[11] and the Simple Clinical Colitis Activity Index (SCCAI) for UC and IC.[12] An SCDAI less than 150 or an SCCAI of 4 or less indicated clinical remission for CD and UC, respectively, with values greater than this threshold indicating active disease.[11,12] Patient demographics, IBD medication use including oral mesalamine or sulfasalazine, prednisone, immunomodulators, and biologic therapies (infliximab, adalimumab, certolizumab pegol, and natalizumab), and pouch and ostomy status were all measured by self-report.

Statistical Analysis

We first performed cross-sectional analyses using descriptive statistics and bivariate comparisons to assess

Table 1. Baseline Characteristics of the Study Population

	Characteristic	CD (n = 6689)	UC or IC (n = 3945)	Overall IBD (n = 10,634)
Demographics	Age, y	44.0 (14.8)	44.1 (14.7)	44.0 (14.8)
	Female sex	72.1%	69.6%	71.2%
	Race/ethnicity			
	White	93.4%	90.8%	92.4%
	African American	2.3%	2.1%	2.2%
	Asian	0.6%	1.9%	1.1%
	Other	3.7%	5.2%	4.2%
	Hispanic	2.3%	4.6%	3.2%
	Education completed			
	<12th grade	1.0%	0.8%	0.9%
	12th grade	8.3%	6.8%	7.7%
	Some college	23.5%	20.1%	22.3%
	College graduate	40.9%	41.8%	41.2%
	Graduate school	26.3%	30.5%	27.9%
	Current smoker	13.8%	6.3%	11.1%
Disease characteristics	Years since IBD diagnosis	16.3 (12.9)	12.5 (11.1)	14.9 (12.4)
	≥1 hospitalization in the past year	16.4%	10.4%	14.1%
	≥1 bowel surgery	31.4%	11.3%	24.0%
	Current ileal or Koch pouch	3.0%	9.5%	5.4%
	Current ostomy	9.1%	4.6%	7.4%
	SCDAI or SCCAI	149 (99)	3.6 (2.9)	N/A
	SIBDQ	4.8 (1.2)	4.9 (1.2)	4.8 (1.2)
Current medication use	Mesalamine or sulfasalazine	35.5%	63.1%	45.7%
	Prednisone	10.4%	12.1%	11.0%
	Immunomodulators (6-mercaptopurine, azathioprine, or methotrexate)	29.5%	21.3%	26.4%
	Biologic therapy (infliximab, adalimumab, certolizumab pegol, and natalizumab)	39.8%	17.3%	31.4%
PROMIS[a] measures	Anxiety	52 (10)	52 (9)	52 (10)
	Depression	54 (10)	54 (10)	54 (10)
	Fatigue	56 (11)	54 (11)	56 (11)
	Sleep disturbance	53 (9)	52 (8)	52 (9)
	Satisfaction with social role	48 (10)	49 (10)	48 (10)
	Pain interference	53 (10)	51 (10)	53 (10)

NOTE. Values in table are shown as mean (SD) or a percentage.

N/A, not applicable

[a]PROMIS items are calibrated so that the mean of the US general population is 50 and the standard deviation is 10. Higher scores indicate more of the domain being measured.

the relationships between PROMIS T-scores and patient demographics, disease activity indices, the SIBDQ, current corticosteroid use, and other health measures. Because disease activity indices and SIBDQ scores were not normally distributed, these values were categorized into quartiles. Mean PROMIS scores were compared across quartiles of disease activity and SIBDQ scores using a nonparametric test of trend for the ranks across ordered groups. We also used multinomial logistic regression to evaluate associations between PROMIS measures and disease activity, controlling for the effects of current corticosteroid use. As a secondary analysis, mean PROMIS scores were compared between patients in remission and with active disease.

We next performed longitudinal analyses by grouping participants into categories of stable disease, worsening disease, or improving disease based on a threshold change between baseline and follow-up surveys of 100 points or more on the SCDAI (CD patients) or 2 points or more on the SCCAI (UC and IC patients). The mean

change (and SD) in each PROMIS domain was calculated for each of these 2 groups.

All analyses were calculated for the entire cohort and then stratified by patient sex and disease type (CD or UC/IC). For subjects who indicated a change in disease type between the baseline and follow-up survey, their disease type was categorized as that reported during the most recent survey. All statistical analyses were performed using SAS version 9.3 (Cary, NC). The study protocol was reviewed and approved by the Institutional Review Board of the University of North Carolina.

Results

Study Population

A total of 10,634 individuals with self-reported IBD joined CCFA Partners through October 22, 2012, and completed PRO testing. Of these, 6689 reported having CD,

and 3945 reported UC or IC. Seventy-one percent of the study participants were women. The mean age of the study population was 44 years, and the mean time from diagnosis to PRO testing was 14.9 years. Additional demographic details are provided in Table 1.

Patient-Reported Outcomes Measurement Information System Testing

The mean PROMIS scores for depression, anxiety, fatigue, sleep disturbance, satisfaction with social role, and pain interference are shown in Table 1. For each of these domains, patients in this IBD population reported worse health compared with the general population (T-score in the general population, 50), and patients with CD reported marginally worse health than those with UC. The relationships between PROMIS scores and sex, age, race/ethnicity, educational status, and time from diagnosis are shown in Table 2. Across all measured domains, patients living with IBD for less than 1 year reported worse health outcomes than

patients who had IBD for longer periods of time. However, these differences were independent of disease activity only for anxiety and depression in CD patients, and for anxiety and fatigue in UC patients. For most measures, older patients (age, ≥60 y) reported better outcomes than younger patients (age, 18–30 y), men reported better outcomes than women, and outcomes were better with increasing levels of education. Hispanics reported worse health than non-Hispanics. Other racial/ethnic differences in PROMIS measures were inconsistent.

Associations With Disease Severity and the Short Inflammatory Bowel Disease Questionnaire

As expected, the mean PROMIS scores for depression, anxiety, fatigue, sleep disturbance, and pain interference all increased with increasing quartiles of disease activity, whereas mean scores for social satisfaction decreased (Table 3). These data indicate that,

Table 2. Relationships Between Patient Demographics and PROMIS Scores

	Anxiety (n = 10,630)	Depression (n = 10,633)	Fatigue (n = 10,632)	Sleep disturbance (n = 10,627)	Social role satisfaction (n = 10,633)	Pain interference (n = 7354)
Age, y						
18–30	56 (10)	53 (10)	57 (11)	52 (9)	48 (10)	53 (10)
31–40	54 (10)	52 (10)	56 (11)	53 (9)	48 (10)	52 (10)
41–50	54 (10)	52 (10)	57 (11)	53 (8)	47 (10)	54 (10)
51–60	53 (9)	52 (9)	55 (11)	52 (8)	48 (10)	53 (10)
>60	51 (9)	50 (9)	52 (11)	51 (8)	50 (10)	51 (10)
Sex						
Male	52 (9)	51 (9)	53 (11)	51 (8)	49 (10)	51 (10)
Female	54 (10)	52 (10)	57 (11)	53 (9)	48 (10)	53 (10)
Race/ethnicity						
White	53 (10)	52 (10)	56 (11)	52 (9)	48 (10)	52 (10)
African American	54 (11)	52 (10)	56 (12)	54 (10)	48 (11)	55 (12)
Asian	53 (9)	51 (9)	51 (10)	51 (8)	49 (10)	52 (10)
Other	57 (10)	55 (11)	58 (11)	54 (9)	46 (10)	55 (11)
Hispanic						
Yes	56 (10)	54 (11)	57 (11)	54 (9)	47 (10)	55 (11)
No	54 (10)	52 (10)	56 (11)	52 (9)	48 (10)	53 (10)
Education completed						
<12th grade	62 (10)	61 (12)	63 (11)	58 (10)	40 (10)	59 (12)
12th grade	55 (10)	54 (10)	58 (11)	54 (10)	46 (10)	55 (10)
Some college	55 (10)	54 (10)	58 (11)	54 (9)	46 (10)	55 (10)
College graduate	53 (10)	51 (9)	55 (11)	52 (8)	49 (10)	52 (10)
Graduate school	52 (9)	50 (9)	54 (11)	51 (8)	80 (9)	51 (9)
Time since IBD diagnosis, y						
<1	58 (10)	55 (10)	59 (11)	54 (9)	45 (10)	57 (10)
1–5	55 (10)	53 (10)	56 (11)	52 (9)	48 (10)	53 (10)
6–10	54 (10)	52 (10)	56 (11)	52 (9)	48 (10)	52 (10)
>10	53 (10)	51 (9)	55 (11)	52 (8)	48 (10)	52 (10)

NOTE. PROMIS items are calibrated so that the mean of the US general population is 50 and the standard deviation is 10. Higher scores indicate more of the domain being measured. Values in table are shown as mean (SD).

Table 3. Relationships Between Quartiles of Disease Activity Indices in CD (n = 5960) and UC/IC (n = 3394) and PROMIS Scores

	PROMIS[a] domain	Quartile 1, SCDAI[b] ≤79, SCCAI[c] ≤1	Quartile 2, SCDAI[b] 80–128, SCCAI[c] 1–3	Quartile 3, SCDAI[b] 129–198, SCCAI[c] 4–5	Quartile 4, SCDAI[b] ≥199, SCCAI[c] ≥6	P value[d]
CD	Anxiety	49 (8)	52 (9)	55 (9)	59 (10)	<.0001
	Depression	47 (8)	50 (9)	53 (9)	58 (10)	<.0001
	Fatigue	49 (10)	54 (10)	59 (9)	65 (9)	<.0001
	Sleep disturbance	48 (8)	51 (8)	54 (8)	58 (8)	<.0001
	Social role satisfaction	54 (9)	50 (9)	46 (8)	41 (8)	<.0001
	Pain interference	46 (7)	51 (8)	56 (8)	62 (8)	<.0001
UC/IC	Anxiety	48 (8)	52 (9)	56 (9)	60 (9)	<.0001
	Depression	46 (7)	51 (8)	53 (9)	58 (9)	<.0001
	Fatigue	47 (9)	53 (9)	57 (10)	62 (9)	<.0001
	Sleep disturbance	47 (8)	51 (8)	53 (8)	56 (8)	<.0001
	Social role satisfaction	55 (8)	50 (9)	47 (8)	41 (9)	<.0001
	Pain interference	45 (6)	50 (9)	54 (8)	59 (9)	<.0001
Total IBD	Anxiety	49 (8)	52 (9)	55 (9)	59 (9)	<.0001
	Depression	47 (7)	50 (8)	53 (9)	58 (10)	<.0001
	Fatigue	48 (9)	54 (9)	58 (10)	64 (9)	<.0001
	Sleep disturbance	48 (8)	51 (8)	54 (8)	57 (8)	<.0001
	Social role satisfaction	54 (9)	50 (9)	46 (8)	41 (8)	<.0001
	Pain interference	45 (7)	50 (9)	55 (8)	61 (9)	<.0001

NOTE. Values in table are shown as mean (SD).
[a]PROMIS items are calibrated so that the mean of the US general population is 50 and the standard deviation is 10. Higher scores indicate more of the domain being measured.
[b]Scores are interpreted as follows: inactive disease (≤150), mild disease (151–199), and moderate to severe disease (≥200).
[c]A score of ≤2 is associated with remission and a score of ≥5 defines a relapse of UC.
[d]P values are from a nonparametric test of trend for the ranks across ordered groups.

for each of the PROMIS domains, higher levels of IBD disease activity are associated with worsening health. Sex-stratified analyses indicated that the magnitude and strength of each of these associations was independent of patient sex. These relationships remained, after adjusting for current corticosteroid use ($P < .001$ for all comparisons), indicating that PROMIS measures are associated with disease activity independent of corticosteroid use.

PROMIS scores also differed between patients in remission and those with active disease ($P < .001$ for all comparisons, Supplementary Table 1). Notably, among patients in remission, PROMIS scores were in the same range as members of the general US population (T-score in the general population, 50).

Associations between PROMIS measures and SIBDQ scores showed a similar relationship (Table 4). As expected, the direction of the effect was opposite that of the disease activity indices because higher scores on SIBDQ indicated improved health. We observed similar relationships within each of the 4 SIBDQ subdomains: bowel, emotional, systemic, and social (data not shown).

Additional Associations

All 6 PROMIS domains tested showed the expected correlation with the PROMIS measure of general health ($P < .001$ for all comparisons). Prednisone use was

associated with worsening patient-reported functioning for all domains (Supplementary Table 2; $P < .001$ for all comparisons). Notably, among UC patients, having a pouch was associated with higher functioning on all PROMIS domains, as compared with those in the highest quartile of disease activity ($P < .001$ for all domains, Supplementary Table 3). Conversely, having a pouch was associated with slightly worse functioning than patients in remission ($P ≤ .001$ for all domains).

Longitudinal Evaluation of Patient-Reported Outcomes Measurement Information System Measures

Data from 2079 participants were available for longitudinal analyses. Of these, 229 had worsening disease activity, 1633 had stable disease activity, and 217 had improved disease activity as measured by the SCDAI and SCCAI. The mean change in PROMIS measures for each of these groups is shown in Table 5 and Figure 1. As expected, patients with worsening disease activity had worse health outcomes for each of the PROMIS domains, and those with improving disease had improved PROMIS outcome scores.

Discussion

PROs are an essential component of patient-centered research, including clinical trials and comparative

Table 4. Relationships Between Quartiles of the SIBDQ in CD (n = 6689) and UC/IC (n = 3945) and PROMIS Scores

	PROMIS[a] domain	Quartile 1, SIBDQ[b] ≤4	Quartile 2, SIBDQ[b] 4.1–5.0	Quartile 3, SIBDQ[b] 5.1–5.8	Quartile 4, SIBDQ[b] ≥5.9	P value[c]
CD	Anxiety	61 (8)	55 (8)	51 (8)	45 (7)	<.0001
	Depression	60 (9)	53 (8)	48 (7)	44 (5)	<.0001
	Fatigue	67 (7)	59 (8)	53 (8)	45 (8)	<.0001
	Sleep disturbance	58 (8)	54 (7)	51 (7)	46 (7)	<.0001
	Social role satisfaction	39 (7)	46 (7)	51 (7)	57 (8)	<.0001
	Pain interference	63 (7)	55 (8)	49 (8)	44 (6)	<.0001
UC/IC	Anxiety	62 (8)	56 (8)	51 (8)	46 (7)	<.0001
	Depression	60 (9)	54 (8)	49 (7)	44 (5)	<.0001
	Fatigue	65 (8)	58 (8)	52 (8)	44 (8)	<.0001
	Sleep disturbance	57 (8)	53 (7)	50 (7)	46 (7)	<.0001
	Social role satisfaction	40 (7)	46 (7)	51 (8)	57 (8)	<.0001
	Pain interference	62 (8)	53 (8)	48 (8)	44 (6)	<.0001
Total IBD	Anxiety	62 (8)	55 (8)	51 (8)	45 (7)	<.0001
	Depression	60 (9)	53 (8)	49 (7)	44 (5)	<.0001
	Fatigue	66 (8)	58 (8)	52 (8)	44 (8)	<.0001
	Sleep disturbance	58 (8)	53 (7)	51 (7)	46 (7)	<.0001
	Social role satisfaction	40 (7)	46 (7)	51 (7)	57 (8)	<.0001
	Pain interference	62 (7)	54 (8)	49 (8)	44 (6)	<.0001

NOTE. Values in table are shown as mean (SD).
[a]PROMIS items are calibrated so that the mean of the US general population is 50 and the standard deviation is 10. Higher scores indicate more of the domain being measured.
[b]SIBDQ scores range from 10 to 70, with 10 associated with lower HRQOL.
[c]P values are from a nonparametric test of trend for the ranks across ordered groups.

effectiveness research. The PROMIS provides measures that are efficient (minimizes item number without compromising reliability), flexible (enables optional use of interchangeable items), and precise (has minimal errors in estimate).[5,6] PROMIS measures have been evaluated extensively in the general population and in individuals with chronic illness.[8] Here, we report a wide-scale, cross-sectional, and longitudinal evaluation of PROMIS measures in the IBD population. Health status and functioning measured by PROMIS are associated with self-reported validated disease activity indices and an IBD-specific HRQOL instrument, and changes in disease activity were associated with changes in PROMIS measures. These data show the construct validity of PROMIS PROs in the IBD population.

We found that IBD patients in this cohort had worse PROs as compared with the general population for each of the PROMIS domains tested and similar findings to those reported for other chronic diseases. For example, mean domain scores for depression, anxiety, fatigue, and social satisfaction were 52, 52, 54, and 48, respectively, in an arthritis population, and 53, 53, 55, and 48, respectively, in a chronic obstructive pulmonary disease population.[8] Among patients in remission, PROs were comparable with the general population.

Consistent with population-based data suggesting that health care use is highest in the year after IBD diagnosis,[13] we found that patients within 1 year of diagnosis reported worse health status in all measured domains. Generally speaking, these PRO trends were related to changes in disease activity. This also may be explained by

the phenomenon of response shift—a change in the meaning of one's self-evaluation as a result of a recalibration, a change in the importance of the outcome, or a re-definition of the outcome, which has been described previously among IBD patients.[14] Notably, fatigue was the PRO most affected among our IBD cohort and was associated strongly with quartiles of disease activity, consistent with recently published findings from a population-based study in Manitoba, Canada.[15]

The magnitude of difference in most PROMIS measures between IBD patients in this cohort and the general population were in the range of 2 to 6. Similarly, the magnitude of difference in PROMIS scores across quartiles of disease activity was also in this range. Hence, data from this cohort were consistent with emerging data suggesting that MIDs for PROMIS measures are in the range of 2 to 6.[9]

Another noteworthy finding was that UC patients who have undergone prior colectomy and IPAA reported better health outcomes compared with UC patients in the highest quartile of disease activity, consistent with prior reports suggesting improvement in quality of life in UC patients after colectomy.[16] In fact, after IPAA, patients reported only slightly worse outcomes than patients in remission. These data can be used to reassure UC patients contemplating surgery, and underscore another distinct advantage of non–disease-specific measures such as PROMIS—the ability to compare disease populations with the general population. In this case, patients with UC after colectomy and IPAA reported health outcomes within half of a standard deviation from the

Table 5. Relationships Between Changes in Disease Activity and Changes in PROMIS Scores

	PROMIS[a] domain	Worsening disease activity[b] (n = 229)	Stable disease activity[b] (n = 1633)	Improving disease activity[b] (n = 217)	P value[c]
CD	Anxiety	3 (9)	−1 (7)	−5 (7)	<.0001
(n = 1303)	Depression	3 (7)	−0 (7)	−5 (7)	<.0001
	Fatigue	6 (9)	−0 (7)	−7 (9)	<.0001
	Sleep disturbance	2 (9)	−0 (7)	−2 (7)	<.0001
	Social role satisfaction	−4 (8)	0 (8)	4 (8)	<.0001
	Pain interference	5 (9)	−0 (8)	−7 (10)	<.0001
UC/IC	Anxiety	2 (8)	−1 (8)	−4 (10)	<.0001
(n = 776)	Depression	3 (7)	−1 (7)	−4 (8)	<.0001
	Fatigue	5 (9)	−0 (8)	−4 (10)	<.0001
	Sleep disturbance	3 (8)	−0 (7)	−3 (8)	<.0001
	Social role satisfaction	−4 (9)	1 (8)	4 (10)	<.0001
	Pain interference	5 (10)	0 (7)	−3 (10)	<.0001
Total IBD	Anxiety	3 (8)	−1 (7)	−4 (9)	<.0001
(n = 2079)	Depression	3 (7)	−1 (7)	−4 (8)	<.0001
	Fatigue	5 (9)	−0 (8)	−5 (10)	<.0001
	Sleep disturbance	2 (8)	−0 (7)	−3 (8)	<.0001
	Social role satisfaction	−4 (8)	0 (8)	4 (9)	<.0001
	Pain interference	5 (10)	−0 (7)	−4 (10)	<.0001

NOTE. Values in table are shown as mean change (SD).
[a]PROMIS items are calibrated so that the mean of the US general population is 50 and the standard deviation is 10. Higher scores indicate more of the domain being measured.
[b]The thresholds used to indicate changes in disease activity were ≥100 points for the SCDAI and ≥2 points for the Simple Clinical Colitis Index.
[c]P values are from a nonparametric test of trend for the ranks across ordered groups.

population norm. These findings are consistent with the results of a conjoint analysis showing that UC patients are equally willing to accept colectomy and IPAA vs a partial response to medical therapy.[17]

There are several additional implications of these findings. First, PROMIS item banks appear to be very attractive as outcome measures for clinical and epidemiologic research in IBD. They have excellent construct validity, are flexible and efficient, are easy to administer and interpret, and are publicly available. Additional PROMIS item banks not included in this study (ie, physical function, pain intensity, and so forth) also are available. Because the PROMIS instruments are designed to be applicable to a range of chronic illnesses, they offer some advantages over disease-targeted instruments, such as the SIBDQ, by allowing for comparisons across a variety of chronic health conditions and studies. Given the recent policy support for comparative effectiveness research in IBD, including the American Recovery and Reinvestment Act, and, more recently, the establishment of the Patient Centered Outcomes Research Institute, there will be abundant opportunities to use PROMIS measures in the near future. Second, the high burden of emotional distress (depression, anxiety) observed in this large cohort of IBD patients reinforces prior observations regarding the high level of psychological comorbidity in this patient population,[18] highlighting the need to include proper mental health screening and treatment in clinical practice, particularly for patients with incompletely controlled disease. Finally, there also may be a

role for PRO assessment in the context of clinical care, perhaps facilitated through computerized adaptive testing (CAT) and automated scoring. However, further research is needed to determine whether PRO assessment will influence treatment decisions and the impact of such decisions on clinical outcomes.

In this study, we used 4-item short forms for each PROMIS domain. This demonstrates remarkably low respondent burden with apparent little loss of precision in statistical comparisons in a large study. PROMIS provides short forms of varying length and CAT. Researchers can select the length of the short form or CAT that matches their research need. Specifically, longer forms and CAT provide more measurement precision. Studies with a smaller sample size may choose longer forms to improve statistical power for group comparisons.

There were several strengths to this study, including the large and geographically diverse patient population, and the prospective nature of the cohort study, which allowed both cross-sectional and longitudinal analyses of PROMIS instruments. Most of the prior evaluations of PROMIS instruments were based only on cross-sectional data.[8] We acknowledge several limitations. First, CCFA Partners is a volunteer sample of patients. IBD patients enrolled in CCFA Partners differ from population-based IBD cohorts (ie, higher percentage of women), limiting the ability to make broad generalizations about patient-reported outcomes among the broader IBD population. Nevertheless, the associations described here still have a high degree of internal validity. Indeed, after stratifying
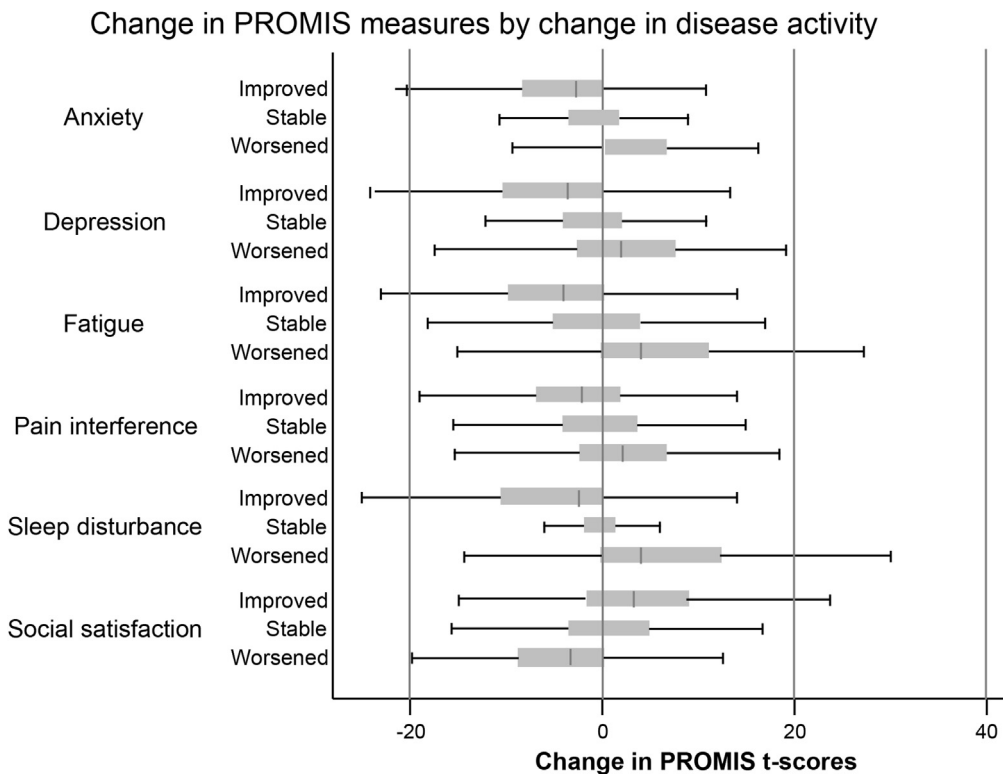
Figure 1. Mean change in PROMIS scores by change in disease activity. PROMIS T-scores are calibrated so that the mean of the US general population is 50 and the standard deviation is 10. Higher scores indicate more of the domain being measured. The thresholds used to indicate changes in disease activity were ≥100 points for the SCDAI and ≥2 points for the Simple Clinical Colitis Index.

by sex, the direction, magnitude, and strength of most associations remained unaffected. Another limitation was that IBD status and disease type in this study were identified by self-report, rather than medical records. However, preliminary results from a validation study found that physicians confirmed IBD status in 96% and IBD subtype (CD or UC/IC) in 94% of cohort participants.[19] Similarly, the use of symptom-based disease activity scores also is subject to limitations including influence by superimposed irritable bowel syndrome.

In conclusion, this cross sectional and longitudinal evaluation provides strong support for the construct validity of the PROMIS instruments in the IBD population. We anticipate that the use of these PROs will advance patient-centered outcomes research in IBD.

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.2013.10.019.

References

1. Kappelman MD, Moore KR, Allen JK, et al. Recent trends in the prevalence of Crohn's disease and ulcerative colitis in a commercially insured US population. Dig Dis Sci 2013;58:519–525.

2. Eden J, Wolman D, Greenfield S, et al. Initial national priorities for comparative effectiveness research: Institute of Medicine. Washington, DC: National Academies Press, 2009.

3. Patrick D, Guyatt G, Acquadro C. Patient-reported outcomes. In: Higgins JPT, Green S, eds. Cochrane handbook for systematic reviews of interventions. Chapter 17. Version 5.0.1. The Cochrane Collaboration, 2008 Available at: http://handbook.cochrane.org/.

4. US Department of Health and Human Services Food and Drug Administration. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims. December 2009 Available at: http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf. Accessed December 18, 2013.

5. Adler D. Developing the Patient-Reported Outcomes Measurement Information System (PROMIS). Med Care 2007;45(Suppl 1): S1–S2.

6. Cella D, Yount S, Rothrock N, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS): progress of an NIH roadmap cooperative group during its first two years. Med Care 2007;45:S3–S11.

7. Long MD, Kappelman MD, Martin CF, et al. Development of an internet-based cohort of patients with inflammatory bowel diseases (CCFA partners): methodology and initial results. Inflamm Bowel Dis 2012;18:2099–2106.

8. Rothrock NE, Hays RD, Spritzer K, et al. Relative to the general US population, chronic diseases are associated with poorer health-related quality of life as measured by the Patient-Reported Outcomes Measurement Information System (PROMIS). J Clin Epidemiol 2010;63:1195–1204.

9. Yost KJ, Eton DT, Garcia SF, et al. Minimally important differences were estimated for six Patient-Reported Outcomes Measurement Information System-cancer scales in advanced-stage cancer patients. J Clin Epidemiol 2011;64:507–516.

10. Irvine EJ, Zhou Q, Thompson AK. The Short Inflammatory Bowel Disease Questionnaire: a quality of life instrument for community physicians managing inflammatory bowel disease. CCRPT

Investigators. Canadian Crohn's Relapse Prevention Trial. Am J Gastroenterol 1996;91:1571–1578.

11. Thia K, Faubion WA Jr, Loftus EV Jr, et al. Short CDAI: development and validation of a shortened and simplified Crohn's disease activity index. Inflamm Bowel Dis 2011; 17:105–111.

12. Jowett SL, Seal CJ, Phillips E, et al. Defining relapse of ulcerative colitis using a symptom-based activity index. Scand J Gastroenterol 2003;38:164–171.

13. Longobardi T, Bernstein CN. Utilization of health-care resources by patients with IBD in Manitoba: a profile of time since diagnosis. Am J Gastroenterol 2007;102:1683–1691.

14. Lix LM, Sajobi TT, Sawatzky R, et al. Relative importance measures for reprioritization response shift. Qual Life Res 2013; 22:695–703.

15. Graff LA, Vincent N, Walker JR, et al. A population-based study of fatigue and sleep difficulties in inflammatory bowel disease. Inflamm Bowel Dis 2011;17:1882–1889.

16. Heikens JT, de Vries J, van Laarhoven CJ. Quality of life, health-related quality of life and health status in patients having restorative proctocolectomy with ileal pouch-anal anastomosis for ulcerative colitis: a systematic review. Colorectal Dis 2012; 14:536–544.

17. Bewtra M, Kilambi V, Siegel CA, et al. Patient preferences for surgical and pharmaceutical treatment of ulcerative colitis: when is surgery better than drugs? Gastroenterology 2012; 142:S68–S69.

18. Graff LA, Walker JR, Bernstein CN. Depression and anxiety in inflammatory bowel disease: a review of comorbidity and management. Inflamm Bowel Dis 2009;15:1105–1118.

19. Randell RL, Cook S, Wrennall CE, et al. 982 Validation of an internet-based cohort of patients with inflammatory bowel diseases (CCFA partners). Gastroenterology 2013;144:S180.

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Supplementary Table 1. PROMIS Scores According to Remission Status in Patients With CD (n = 5960) and UC/IC (n = 3394)

	PROMIS[a] domain	Remission	Active disease[b]	P value[c]
CD	Anxiety	51 (9)	58 (10)	<.0001
	Depression	49 (8)	56 (10)	<.0001
	Fatigue	52 (10)	63 (9)	<.0001
	Sleep disturbance	50 (8)	56 (8)	<.0001
	Social role satisfaction	51 (9)	42 (8)	<.0001
	Pain interference	49 (8)	60 (8)	<.0001
UC/IC	Anxiety	51 (9)	58 (9)	<.0001
	Depression	49 (8)	56 (10)	<.0001
	Fatigue	51 (10)	60 (10)	<.0001
	Sleep disturbance	50 (8)	55 (8)	<.0001
	Social role satisfaction	52 (9)	43 (9)	<.0001
	Pain interference	48 (8)	58 (9)	<.0001
Total IBD	Anxiety	51 (9)	58 (10)	<.0001
	Depression	49 (8)	56 (10)	<.0001
	Fatigue	52 (10)	62 (10)	<.0001
	Sleep disturbance	50 (8)	56 (8)	<.0001
	Social role satisfaction	51 (9)	43 (9)	<.0001
	Pain interference	49 (8)	59 (9)	<.0001

NOTE. Values in table are shown as mean change (SD).
[a]PROMIS items are calibrated so that the mean of the US general population is 50 and the standard deviation is 10. Higher scores indicate more of the domain being measured.
[b]Active disease corresponds to a SCDAI of ≥150 points or an increase in SCCAI of ≥5 points.
[c]P values generated by t tests.

Supplementary Table 2. Relationships Between Prednisone and PROMIS Scores

PROMIS[a] domain	Prednisone (n = 1165)	No prednisone (n = 9423)	P value[b]
Anxiety	57 (10)	53 (10)	<.0001
Depression	55 (10)	51 (9)	<.0001
Fatigue	60 (11)	55 (11)	<.0001
Sleep disturbance	55 (8)	52 (8)	<.0001
Social role satisfaction	44 (9)	49 (10)	<.0001
Pain interference	57 (10)	52 (10)	<.0001

NOTE. Values in table are shown as mean change (SD).
[a]All items were calibrated using a T-score metric with the mean of the US general population equal to 50 and the SD fixed at 10. Higher scores indicate more of the domain being measured.
[b]P values generated by t tests.

Supplementary Table 3. Relationships Between IPAA Status and PROMIS Scores

PROMIS[a] domain	IPAA (N = 372)	Highest quartile of disease activity SCCAI ≥6 (n = 730)	Remission (n = 2325)
Anxiety	53 (10)	60 (9)	51 (9)
Depression	52 (10)	58 (9)	49 (8)
Fatigue	55 (11)	62 (9)	51 (10)
Sleep disturbance	53 (8)	56 (8)	50 (8)
Social role satisfaction	48 (10)	41 (9)	52 (9)
Pain interference	52 (10)	59 (9)	48 (8)

NOTE. Values in table are shown as mean change (SD).
[a]PROMIS items are calibrated so that the mean of the US general population is 50 and the standard deviation is 10. Higher scores indicate more of the domain being measured.

Supplementary Appendix 1. PROMIS Items Used in the CCFA Partners Cohort Study

In the past 7 days…

PROMIS domain		Never	Rarely	Sometimes	Often	Always
Anxiety	I felt fearful	❍	❍	❍	❍	❍
	I found it hard to focus on anything other than my anxiety	❍	❍	❍	❍	❍
	My worries overwhelmed me	❍	❍	❍	❍	❍
	I felt uneasy	❍	❍	❍	❍	❍
Depression	I felt worthless	❍	❍	❍	❍	❍
	I felt helpless	❍	❍	❍	❍	❍
	I felt depressed	❍	❍	❍	❍	❍
	I felt hopeless	❍	❍	❍	❍	❍
		Not at all	A little bit	Somewhat	Quite a bit	Very much
Fatigue	I feel fatigued	❍	❍	❍	❍	❍
	I have trouble starting things because I am tired	❍	❍	❍	❍	❍
	How run-down did you feel on average	❍	❍	❍	❍	❍
	How fatigued were you on average	❍	❍	❍	❍	❍
		Very poor	Poor	Fair	Good	Very good
Sleep disturbance	My sleep quality was	❍	❍	❍	❍	❍
		Not at all	A little bit	Somewhat	Quite a bit	Very much
	My sleep was refreshing	❍	❍	❍	❍	❍
	I had a problem with my sleep	❍	❍	❍	❍	❍
	I had difficulty falling asleep	❍	❍	❍	❍	❍
Satisfaction with social role	I am satisfied with my ability to do things for fun with others	❍	❍	❍	❍	❍
	I am satisfied with my ability to do things for my family	❍	❍	❍	❍	❍
	I am satisfied with my ability to meet the needs of my friends	❍	❍	❍	❍	❍
	I am satisfied with my ability to do the work that is really important to me (include work at home)	❍	❍	❍	❍	❍
Pain interference	How much did pain interfere with your day-to-day activities?	❍	❍	❍	❍	❍
	How much did pain interfere with work around the home?	❍	❍	❍	❍	❍
	How much did pain interfere with your ability to participate in social activities?	❍	❍	❍	❍	❍
	How much did pain interfere with your household chores?	❍	❍	❍	❍	❍

General Health Question: In general, my health is…
❍ Excellent
❍ Very good
❍ Good
❍ Fair
❍ Poor