Development and Validation of an Inflammatory Bowel Diseases Monitoring Index for Use With Mobile Health Technologies

Welmoed K. Van Deen,[*,‡] Andrea E. van der Meulen-de Jong,[‡] Nimisha K. Parekh,[§] Ellen Kane,[*] Aria Zand,[*] Courtney A. DiNicola,[*] Laurin Hall,[*] Elizabeth K. Inserra,[*] Jennifer M. Choi,[*] Christina Y. Ha,[*] Eric Esrailian,[*] Martijn G. H. van Oijen,[*,||] and Daniel W. Hommes[*]

[*]UCLA Center for Inflammatory Bowel Diseases, Melvin and Bren Simon Digestive Diseases Center, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California; [‡]Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, the Netherlands; [§]Division of Gastroenterology and Hepatology, University of California, Irvine, Irvine, California; and [||]Department of Medical Oncology, Academic Medical Center, Amsterdam, the Netherlands

BACKGROUND & AIMS: **Mobile health technologies are advancing rapidly as smartphone use increases. Patients with inflammatory bowel disease (IBD) might be managed remotely through smartphone applications, but no tools are yet available. We tested the ability of an IBD monitoring tool, which can be used with mobile technologies, to assess disease activity in patients with Crohn's disease (CD) or ulcerative colitis (UC).**

METHODS: **We performed a prospective observational study to develop and validate a mobile health index for CD and UC, which monitors IBD disease activity using patient-reported outcomes. We collected data from disease-specific questionnaires completed by 110 patients with CD and 109 with UC who visited the University of California, Los Angeles, Center for IBD from May 2013 through January 2014. Patient-reported outcomes were compared with clinical disease activity index scores to identify factors associated with disease activity. Index scores were validated in 301 patients with CD and 265 with UC who visited 3 tertiary IBD referral centers (in California or Europe) from April 2014 through March 2015.**

RESULTS: **We assessed activity of CD based on liquid stool frequency, abdominal pain, patient well-being, and patient-assessed disease control, and activity of UC based on stool frequency, abdominal pain, rectal bleeding, and patient-assessed disease control. The indices identified clinical disease activity with area under the receiver operating characteristic curve values of 0.90 in patients with CD and 0.91 in patients with UC. They identified endoscopic activity with area under the receiver operating characteristic values of 0.63 in patients with CD and 0.82 in patients with UC. Both scoring systems responded to changes in disease activity ($P < .003$). The intraclass correlation coefficient for test-retest reliability was 0.94 for CD and for UC.**

CONCLUSIONS: **We developed and validated a scoring system to monitor disease activity in patients with CD and UC that can be used with mobile technologies. The indices identified clinical disease activity with area under the receiver operating characteristic curve values of 0.9 or higher in patients with CD or UC, and endoscopic activity in patients with UC but not CD.**

Keywords: Patient-Reported Outcomes; Telemedicine; Severity; Management.

Abbreviations used in this paper: **AUC, area under the curve; CD, Crohn's disease; CDAI, Crohn's disease activity index; DA-VAS, disease activity visual analogue scale; HBI, Harvey Bradshaw index; Hgb, hemoglobin; IBD, inflammatory bowel disease; LUMC, Leiden University Medical Center; mHealth, mobile health; mHI, mobile health index; NPV, negative predictive value; pMayo, partial Mayo score; PPV, positive predictive value; PROs, patient-reported outcomes; ROC, receiver operating characteristics; SCCAI, simple clinical colitis activity index; SES-CD, simple endoscopic index for Crohn's disease; UC, ulcerative colitis; UCI, University of California, Irvine; UCLA, University of California, Los Angeles; VAS, visual analogue scale.**

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See editorial on page 1751; see similar article on page 1697.

The shift from symptom-oriented to prevention-oriented care delivery has accelerated the development of mobile health (mHealth) technologies and is thought to radically transform health care delivery.[1] Smartphone adoption is increasing rapidly, with 64% of Americans using smartphones in 2014 of which 62% used their telephones to look up health information.[2] Many health apps are available, most of which provide health information or support data collection.[3] For patients with inflammatory bowel diseases (IBD), apps are available that assist in tracking symptoms, logging meals, and managing medications.[4,5] These apps can create reports for providers but do not allow for real-time interactions between patient and provider.

Self-monitoring and self-management for chronic diseases is widely practiced in diabetes care[6] and anticoagulation therapy.[7] Additionally, e-technologies for symptom reporting between patients and providers are increasingly used in chronic diseases.[8] Several systems for online symptom reporting and disease management have been developed for IBD. In the Danish Constant-Care web system, patients with ulcerative colitis (UC) filled out a clinical symptom score and logged fecal calprotectin levels weekly; based on these scores the system made real-time recommendations for adjusting mesalamine dosing. This approach was shown to empower patients and decrease relapse duration.[9,10] Similarly, individualization of infliximab dosing in patients with Crohn's disease (CD) was reported to be practical and feasible.[11] A study evaluating another home tele-management system in UC (UC-HAT) did not show significant differences in disease activity and quality of life between users and control subjects, and more than one-third of the patients discontinued participation.[12] An ongoing multicenter randomized controlled trial is testing the use of a mobile tele-management system using text messaging in IBD. This system sends personalized alerts and educational texts, and assesses symptoms and side effects, based on which treatment can be modified.[13]

Patient-reported outcomes (PROs) are increasingly used to evaluate health status, and the importance of PROs in outcome measurement, symptom management, and quality improvement efforts is increasingly recognized.[14] Furthermore, the use of PROs as primary outcome measures for evaluating effectiveness of IBD interventions is progressively supported by the Food and Drug Administration.[15] Therefore, PROs are promising for use in mHealth apps. An example is the HealthPROMISE app, which tracks patient-reported quality of life scores in patients with IBD and provides decision support to physicians.[16] However, accurate e-monitoring tools for disease activity in IBD are yet to be developed. Previous efforts have aimed to develop PRO questionnaires by adjusting existing scores.[17–19] We aimed to identify the most optimal PRO score to use on an IBD disease-monitoring app. The best PROs were selected from an exhaustive list of PROs in a prospective cohort of patients with IBD. Subsequently, the developed scores were tested prospectively in an independent cohort at 3 independent IBD centers.

Methods

Design

We performed a prospective, observational study that aimed to develop and validate an mHealth index (mHI) for CD and UC that accurately monitors IBD disease activity using PROs. The study consisted of 2 phases: a development phase and a validation phase. During the development phase the mHIs were developed using collected PROs and clinical disease activity indices. During the validation phase the developed mHIs were validated in an independent cohort.

Population

Development phase. Patients with IBD were identified during clinic visits between May 2013 and January 2014 at the University of California, Los Angeles (UCLA) Center for IBD. Patients with esophageal or anal CD involvement alone, patients with a pouch or stoma, and pregnant women were excluded. Eligible patients filled out disease-specific questionnaires assessing PROs of most common clinical disease activity indices: partial Mayo (pMayo), simple clinical colitis activity index (SCCAI), and modified Truelove and Witts index for UC; Harvey Bradshaw index (HBI) and CD activity index (CDAI) including a 7-day diary before the visit (Supplementary Figure 1) for CD. Additionally, patients were asked to assess their symptoms and perceived disease activity using visual analogue scales (VAS). The PROs were categorized into 10 domains: stool frequency, abdominal pain, general well-being, urgency, stool consistency, rectal bleeding, fever, anorexia, nausea/vomiting, and perceived disease activity (Table 1).

During clinic visits, vital signs were measured and physicians collected the physician-reported outcomes required for the clinical disease activity indices (Table 1). Hemoglobin (Hgb), hematocrit, white blood cell count, platelets, albumin, C-reactive protein, and erythrocyte sedimentation rate were requested. Furthermore, stool testing for calprotectin was requested either at the patient's preferred laboratory or using a free stool kit (Genova Diagnostics, Asheville, NC) picked up at the patient's home. A dedicated study nurse (E.K.) followed up with patients via telephone or e-mail to ensure laboratory and stool tests were performed.

Validation phase. Eligible patients with IBD were identified during clinic and endoscopy visits between

Table 1. Collected PROs and Clinical Markers in CD and Patients With UC

Domain	Question	CD	UC
1. Stool frequency	Number of liquid/very soft stools for each of the last 7 days	X	
	How many stools did you have yesterday during the day?	X	X
	How many stools did you have yesterday during the night?	X	X
	How many stools do you have normally during the day?	X	X
	How many stools do you have normally during the night?	X	X
2. Abdominal pain	Abdominal pain for each of the last 7 days (no/mild/moderate/severe)	X	
	Abdominal pain (no/mild/moderate/severe)		X
	Abdominal pain (no abdominal pain/with bowel actions/continuous)	X	X
	Rate your abdominal pain on a scale from 0 to 10 (VAS)	X	X
3. General well-being	General well-being for each of the last 7 days (very well/slightly below par/poor/very poor/terrible)		X
	General well-being (very well/slightly below par/poor/very poor/terrible)	X	
	General well-being (perfect/very good/good/average/poor/terrible)		X
	Well-being (no impairment/impaired, but able to continue activities/activities reduced/unable to work)	X	X
	Rate your well-being on a scale from 0 to 10 (VAS)	X	X
4. Urgency	Urgency of defecation (no urgency/hurry/immediate/incontinence)	X	X
5. Stool consistency	Stool consistency (normal or variably normal/semiformed/liquid)	X	X
	Do you take opiates or lomotil/imodium for diarrhea?	X	X
	How often do you take antidiarrheals? (0–10 VAS)	X	X
6. Rectal bleeding	What % of bowel movements contains visible blood? (none/less than 50%/50% or more/blood alone)	X	X
	Amount of blood in stool (none/trace/occasionally frank [bright red]/usually frank)	X	X
	How often do you experience rectal bleeding? (0–10 VAS)	X	X
7. Fever	Fever on each of the last 7 days	X	
8. Anorexia	Loss of appetite (yes/no)	X	X
9. Nausea/vomiting	Nausea and/or vomiting (yes/no)	X	X
10. Disease activity	How well do you feel your disease is under control? (0–10 VAS)	X	X
11. Clinical markers	Temperature	X	X
	Weight and height	X	
	Pulse		X
	Abdominal tenderness		X
	Abdominal mass	X	
	Extraintestinal manifestations	X	X
	Physician global assessment of disease activity	X	X
	Hgb, hematocrit, white blood cell, platelets, albumin, C-reactive protein, erythrocyte sedimentation rate (blood) and calprotectin (stool)	X	X

April 2014 and March 2015 in 3 tertiary IBD referral centers (UCLA; University of California, Irvine [UCI]; and Leiden University Medical Center [LUMC], the Netherlands). Patients who participated in the development phase of the study were excluded. For patients with CD, the developed mHI-CD and HBI were completed during clinic visits; during endoscopic visits, the simple endoscopic score for CD (SES-CD) was additionally completed. For patients with UC, the mHI-UC and pMayo were collected during clinic visits, and the Mayo endoscopic subscore was additionally obtained during endoscopic visits. Patients at LUMC completed a Dutch version of the mHI-CD and mHI-UC. After translation to Dutch, the questionnaires were translated back to English by an independent translator; the Dutch questionnaire was then revised and retested. To assess sensitivity of the mHI to detect changes in clinical disease activity, a subset of patients was included a second time during scheduled follow-up visits. To assess test-test reliability, a subset of UCLA patients was asked to complete a second questionnaire at home after their clinic visit.

Definitions

For CD, clinical disease activity was defined as an HBI >4 or a CDAI >150. A change of ≥ 3 in HBI was considered a clinically relevant change.[20] Endoscopic disease activity was defined as an SES-CD >3. For UC, clinical disease activity was defined as a pMayo >2, a MTWI >3, or an SCCAI >2. A change of ≥ 3 in the pMayo was considered a clinically relevant change.[18] Endoscopic disease activity was defined as a Mayo endoscopic subscore >1.

Ethical Considerations

All patients consented to participate in this study. This study was approved by the institutional review

boards of participating centers under the following protocol numbers: UCLA, IRB#13-000402; UCI, HS# 2014-1231; and LUMC, P14.158.

Statistical Analysis

Descriptive statistics were used for clinical characteristics and demographic information. Numeric values are presented as mean and standard deviation or median and range. SAS version 9.2 (SAS Institute, Cary, NC) was used for statistical analyses.

Development phase. Univariate logistic regression was performed using disease activity (HBI >4 for CD or pMayo >2 for UC) as the dependent variable and the PROs as independent variables. For each of the PROs, different cutoffs were used, which roughly created linear associations between the groups and the chance of active disease. Because different PROs represented the same domain (Table 1), the variables with the highest Wald chi-square value for predicting clinical disease activity were selected within each domain for inclusion in the multivariate logistic regression models. If 2 variables within the same domain had a similar predictive value (difference between Wald chi-square values <0.5), both were tried in separate models unless the question type was less preferable. Because of usability on a mobile application VAS, yes/no, or numeric questions were preferred over categorical questions; within those, questions with less response options were preferred. Variables with a P value >.1 in the univariate analysis were omitted from subsequent analyses. Stepwise forward multivariate logistic regression was performed with clinical disease activity as the dependent variable and the selected PROs as independent variables. A significance level of $P < .1$ was required for entry in the model and a significance level of $P < .1$ to stay in the model. Several models were performed using different clinical disease activity indices to define clinical disease activity as the dependent variable.

Composite scores were created using the regression coefficients of independent predictors in the multivariate model. Spearman correlation coefficients were estimated between the newly developed mHIs and clinical disease activity indices. Receiver operating characteristic (ROC) curves were used to assess the capability of the mHI to discriminate active versus nonactive disease using different clinical disease activity indices, and the areas under the curves (AUC) were calculated. The composite score with overall highest AUC using different gold standards was selected.

Because the main aim of the developed score was to identify patients at risk for active disease, we defined the optimal cutoff for disease activity as a negative predictive value (NPV) of ≥95% and a sensitivity of ≥85% while maintaining maximum specificity. The overall prevalence of active disease was estimated at 22% based on cross-sectional cohort data from UCLA.

Validation phase. To validate the mHI against clinical and endoscopic disease activity indices, the mHI-UC was compared with the pMayo and the endoscopic subscore of the Mayo; the mHI-CD was compared with the HBI and SES-CD. Spearman correlation coefficients between the scores were calculated and ROC curves to assess the ability to predict clinical and endoscopic disease activity were generated. To assess sensitivity to change, we compared patients who clinically improved, remained stable, and deteriorated. A Kruskal-Wallis test was used to compare groups. Test-retest reliability was assessed by the intraclass correlation coefficient. The performance of the VAS for patient-reported disease activity (DA-VAS) as single predictor for clinical and endoscopic disease activity also was assessed.

Results

Development Phase

In total, 219 patients (110 CD and 109 UC) were included in the development phase of the study (Figure 1*A*, Table 2). In 108 out of 110 patients with CD the HBI was calculated, whereas the CDAI could only be calculated in 93 out of 110. The pMayo, SCCAI, and modified Truelove and Witts index were calculated in all patients with UC. Complete laboratory and stool tests were obtained from only 48% of patients. Despite intensive follow-up by a dedicated research nurse (E.K.), 39% of patients did not perform stool testing and 13% did not have laboratory values drawn. Additionally, 14% of patients had blood drawn, but laboratory sets were incomplete because of protocol deviations.

Univariate logistic regression was performed for PROs and blood and stool tests (Supplementary Tables 1 and 2). Stool frequency, abdominal pain, general well-being, urgency, and patient-reported disease activity were all strong predictors for clinical disease activity in both CD and UC ($P < .0001$). Incontinence was only present in 3% of patients and did not predict disease activity in either CD ($P = .54$) or UC ($P = .99$). In CD the use of antidiarrheals was predictive for disease activity ($P = .019$) but not in UC ($P = .96$), whereas the VAS assessing frequency of antidiarrheal use was a predictor for neither CD ($P = 1.00$) nor UC ($P = .26$). Rectal bleeding was a predictor for disease activity in both UC ($P < .0001$) and CD ($P = .019$). Anorexia was predictive in both CD ($P = .019$) and UC ($P = .0025$), whereas nausea and vomiting predicted only CD disease activity ($P = .035$) and not UC disease activity ($P = .14$). High C-reactive protein ($P = .0009$), high erythrocyte sedimentation rate ($P = .0022$), low Hgb ($P = .022$), and low albumin (0.034) were predictors for clinical disease activity in CD. High calprotectin was not a significant predictor for CD disease activity ($P = .054$), although calprotectin as continuous variable had predictive value

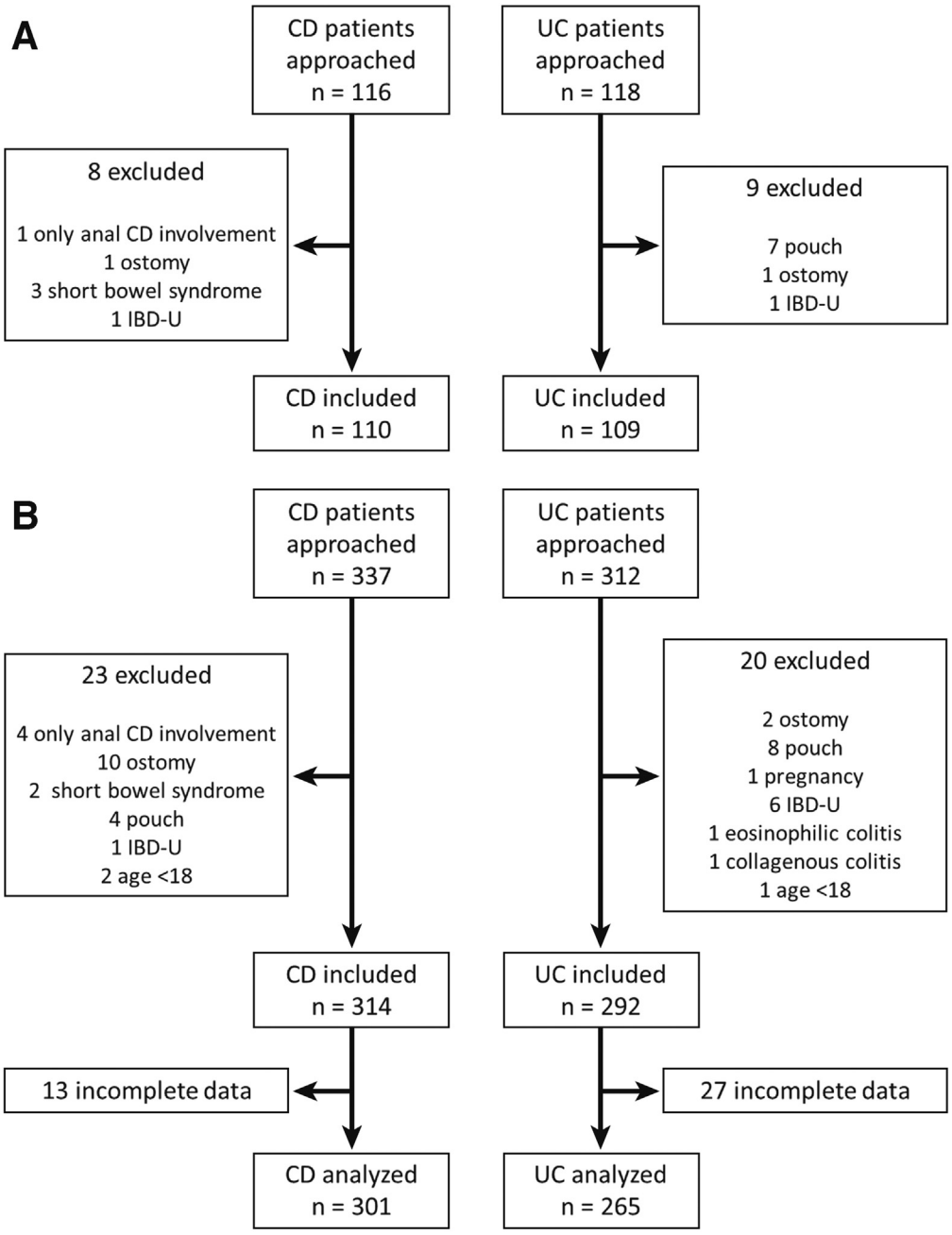

Figure 1. Inclusion flowcharts for development phase (*A*) and validation phase (*B*).

($P = .011$). Low platelets ($P = .98$), low hematocrit ($P = .28$), and high white blood cell ($P = .11$) were not predictive in CD (Supplementary Table 1). In UC high C-reactive protein ($P = .0067$), high calprotectin ($P = .022$), high white blood cell (0.013), high erythrocyte sedimentation rate ($P = .028$), and low hematocrit ($P = .0047$) were all predictive for clinical disease activity. Low albumin ($P = .98$) was not predictive for clinical activity in UC, although albumin as continuous variable was ($P = .02$). Low platelets ($P = .99$) and low Hgb ($P = .13$) were not predictive for disease activity in UC, whereas Hgb as continuous variable ($P = .032$) was (Supplementary Table 2).

The most representative PROs were selected for inclusion in the multivariate regression model (Supplementary Tables 1 and 2). Because of low completion rates of laboratory testing despite intensive follow-up, laboratory tests were initially excluded from the multivariate analysis and score development. In CD, 4 composite scores were developed (Supplementary Table 3); in UC, 11 composite scores were evaluated (Supplementary Table 4). Addition of laboratory variables to the selected models decreased the sample size and therefore the power of the regression models; addition of the laboratory variables to the model did not result in inclusion of these variables in the models,

Table 2. Demographics of Included Patients in Development and Validation Phase of the Study

	Development phase		Validation phase	
	CD	UC	CD	UC
N	110	109	301	265
Median age, median (range)	33 (19–79)	35 (18–81)	33 (18–75)	42 (18–86)
Male, n (%)	56 (51)	57 (52)	144 (48)	132 (50)[a]
Smoking, n (%)	9 (8)	7 (6)[a]	19 (6)[b]	12 (5)[c]
Age at diagnosis, median (range)	24 (8–68)	28 (10–81)	25 (8–66)	29 (2–76)
Disease duration, median (range)	8 (0–46)	6 (0–52)	8 (0–52)	7 (0–59)
Surgical history, n (%)	48 (44)	1 (1)	132 (44)[d]	13 (5)[d]
CD fistulizing disease, n (%)	5 (5)[a]	—	59 (20)[a]	—
Active disease (HBI >4 /pMayo >2), n (%)	32 (30)[a]	37 (34)	82 (27)	82 (31)

[a]n = 1 unknown.
[b]n = 8 unknown.
[c]n = 9 unknown.
[d]n = 2 unknown.

because they did not reach the required significance level of $P < .1$ for entry in the model.

For CD the selected composite score (Table 3) had an AUC of >0.95 for predicting clinical disease activity, using both CDAI and HBI as gold standards (0.951 and 0.963, respectively). The Spearman correlation coefficients were 0.837 and 0.830, respectively (Supplementary Table 3). The optimal cutoff for the mHI-CD to predict clinical disease activity was set at ≥5.5, resulting in an NPV of 96%, positive predictive value (PPV) of 63%, sensitivity of 88%, and specificity of 85%. For UC the selected composite score (Table 3) had an AUC of >0.91 to predict disease activity using pMayo, SCCAI, and modified Truelove and Witts index as gold standards (0.960, 0.915, and 0.913, respectively). The Spearman correlation coefficients were 0.820, 0.832, and 0.790, respectively (Supplementary Table 4). The optimal cutoff for the mHI-UC to predict clinical disease activity was set at ≥4.99, resulting in an NPV of 97%, PPV of 72%, sensitivity of 89%, and specificity of 90%.

Validation Phase

A total of 301 patients with CD (UCLA, n = 127; UCI, n = 82; LUMC, n = 92) and 265 patients with UC (UCLA, n = 119; UCI, n = 67; LUMC, n = 79) were analyzed in the validation phase (Figure 1B, Table 2). For CD the Spearman correlation coefficient was 0.75 ($P < .0001$) between HBI and mHI-CD, the AUC of the ROC for predicting clinical disease activity was 0.90, and a sensitivity of 94% and specificity of 67% were achieved using a cutoff of ≥5.5 (Figures 2A and 2B). To achieve the optimal NPV of 95% and sensitivity of 85%, the cutoff in this cohort would be ≥6.38, which would result in 85% sensitivity, 80% specificity, 95% NPV, and 55% PPV. The mHI-CD was poorly correlated with the SES-CD ($\rho = .30$; $P = .0039$), with an AUC of 0.63 (Figures 2A and 2C).

For UC the Spearman correlation coefficient was 0.72 ($P < .0001$) between pMayo and mHI-UC, the AUC of the ROC for predicting clinical disease activity was 0.91, and a sensitivity of 73% and specificity of 90% specificity were achieved using a cutoff of ≥4.99 (Figures 2D and

Table 3. Calculation of the mHI-CD and mHI-UC

mHI-CD questions	Answer	Score	mHI-UC questions	Answer	Score
Number of liquid/very soft stools/day	0	0.0000	How many stools did you	≤2	0.0000
	1–2	1.6983	have yesterday?	3–4	1.4428
	≥3	3.3966		>4	2.8856
Abdominal pain	No	0.0000	Rate your abdominal pain on a	0–2	0.0000
	Yes	2.3868	scale from 0 to 10 (0 = none, 10 = worst)	3–6	1.0392
				7–10	2.0784
Rate your well-being on a scale from	8–10	0.0000	How often do you experience rectal bleeding?	0–3	0.0000
0 to 10 (0 = worst, 10 = best)	4–7	2.1336	(0 = none, 10 = always)	4–10	2.2019
	0–3	4.2672			
How well do you feel your disease is	0–2	0.0000	How well do you feel your disease is under control	0–2	0.0000
under control (0 = no disease activity,	3–6	2.1175	(0 = no disease activity, 10 = worst disease activity)	3–5	1.7557
10 = worst disease activity)	7–10	4.2350		6–10	3.5114
Total score (SUM)			Total score (SUM)		

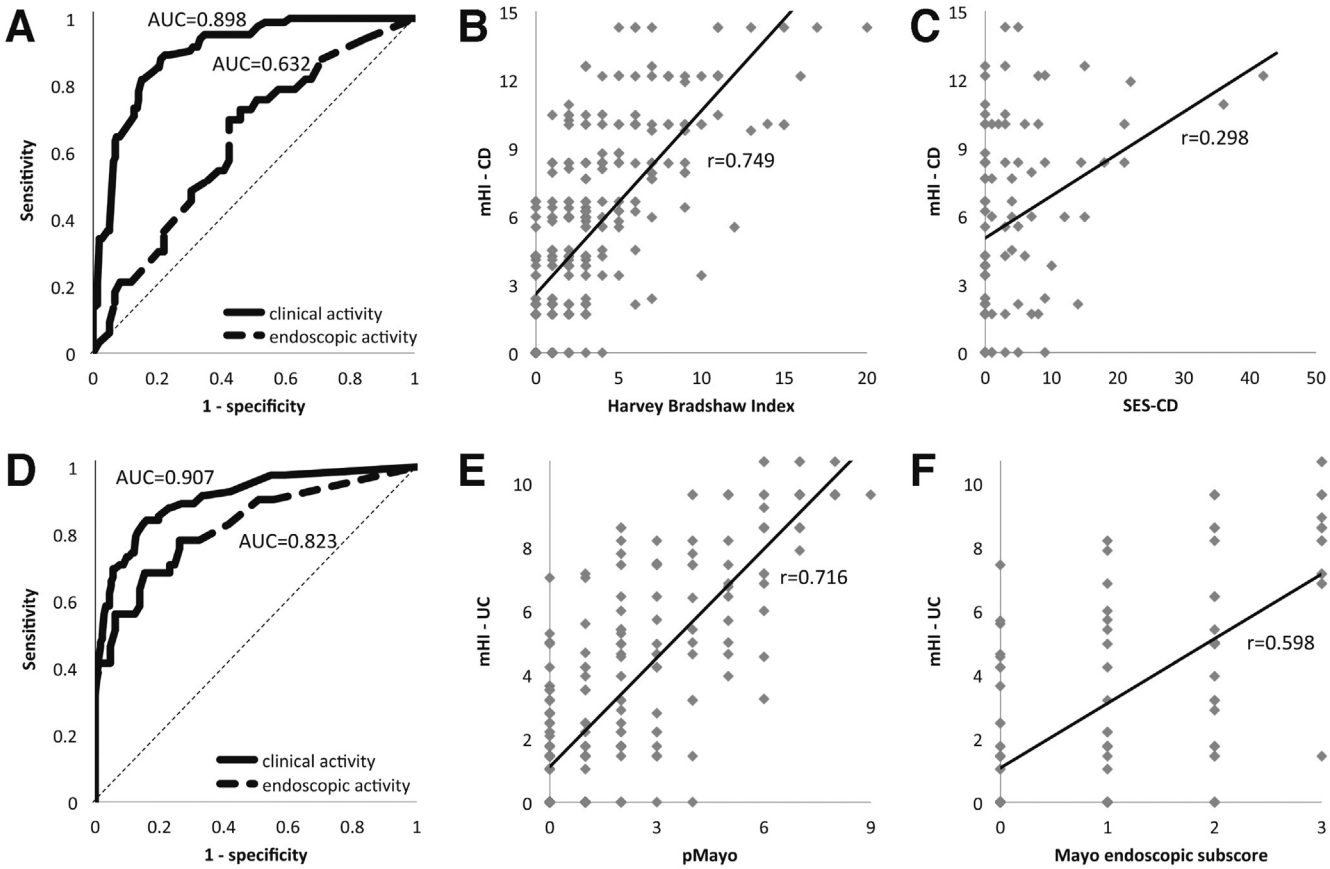

Figure 2. Performance of the developed mHI scores to detect disease activity in CD (*A–C*) and UC (*D–F*). ROC curves of the mHI to predict clinical and endoscopic disease activity (*A* and *D*), scatter plot of the mHI versus clinical disease activity scores (*B* and *E*), and endoscopic disease activity scores (*C* and *F*).

2E). The optimal cutoff in this cohort would be ≥3.2, which would result in 85% sensitivity, 80% specificity, 95% NPV, and 55% PPV. The mHI-UC was strongly correlated with the Mayo endoscopic subscore ($\rho = .60$; $P < .0001$), with an AUC of 0.82 (Figures 2D and 2F).

Sensitivity to change was assessed in a subset of 50 patients with CD and 44 patients with UC. Median time between questionnaires was 46 days (range, 2–352) for CD and 57.5 days (range, 3–275) for UC. Four (8%) patients with CD deteriorated, 31 (62%) had stable disease activity, and 15 (30%) improved. Of the patients with UC, 5 (11%) deteriorated, 27 (61%) remained stable, and 12 (27%) improved. There was a significant difference in mHI between patients who clinically improved, remained stable, or worsened, with either CD ($P = .0030$) or UC ($P = .0025$) (Figures 3A and 3C). Test-retest reliability was assessed in a subset of 40 patients with CD and 37 patients with UC. The median time to second questionnaire completion was 21 hours (range, 7–36) for the mHI-CD and 23 hours (range, 11–144) for the mHI-UC. The intraclass correlation coefficient was 0.94 (confidence limits, 0.89–0.97) for the mHI-CD and 0.94 (confidence limits, 0.89–0.97) for the mHI-UC (Figures 3B and 3D).

One question in both the mHI-CD and the mHI-UC assessed patient-reported disease activity using a VAS (DA-VAS). In patients with CD (n = 301) the DA-VAS had a Spearman correlation of 0.63 ($P < .0001$) with the HBI, and the AUC for predicting clinical disease activity was 0.83 (compared with $\rho = .75$ and AUC = 0.90 for the full mHI-CD). The CD DA-VAS was weakly correlated with the SES-CD ($\rho = .21$; $P = .040$), and had an AUC to predict endoscopic disease activity of 0.59 (compared with $\rho = 0.30$ and AUC = 0.63 for the full mHI-CD). The DA-VAS was not significantly different among patients who deteriorated, remained stable, or improved ($P = .12$). In patients with UC (n = 265) the DA-VAS had a Spearman correlation of 0.67 ($P < .0001$) with the pMayo, and the AUC for predicting clinical disease activity was 0.86 (compared with $\rho = .72$ and AUC = 0.91 for the full mHI-UC). The UC DA-VAS was also correlated with the endoscopic component of the Mayo score ($\rho = .55$; $P < .0001$), and had an AUC to predict endoscopic disease activity of 0.79 (compared with $\rho = .60$ and AUC = 0.82 for the full mHI-UC). A significant difference between the DA-VAS of patients with UC that deteriorated, remained stable, or improved was observed ($P = .0052$).

Discussion

We developed 2 questionnaires of 4 items consisting solely of PROs for remote monitoring of patients with

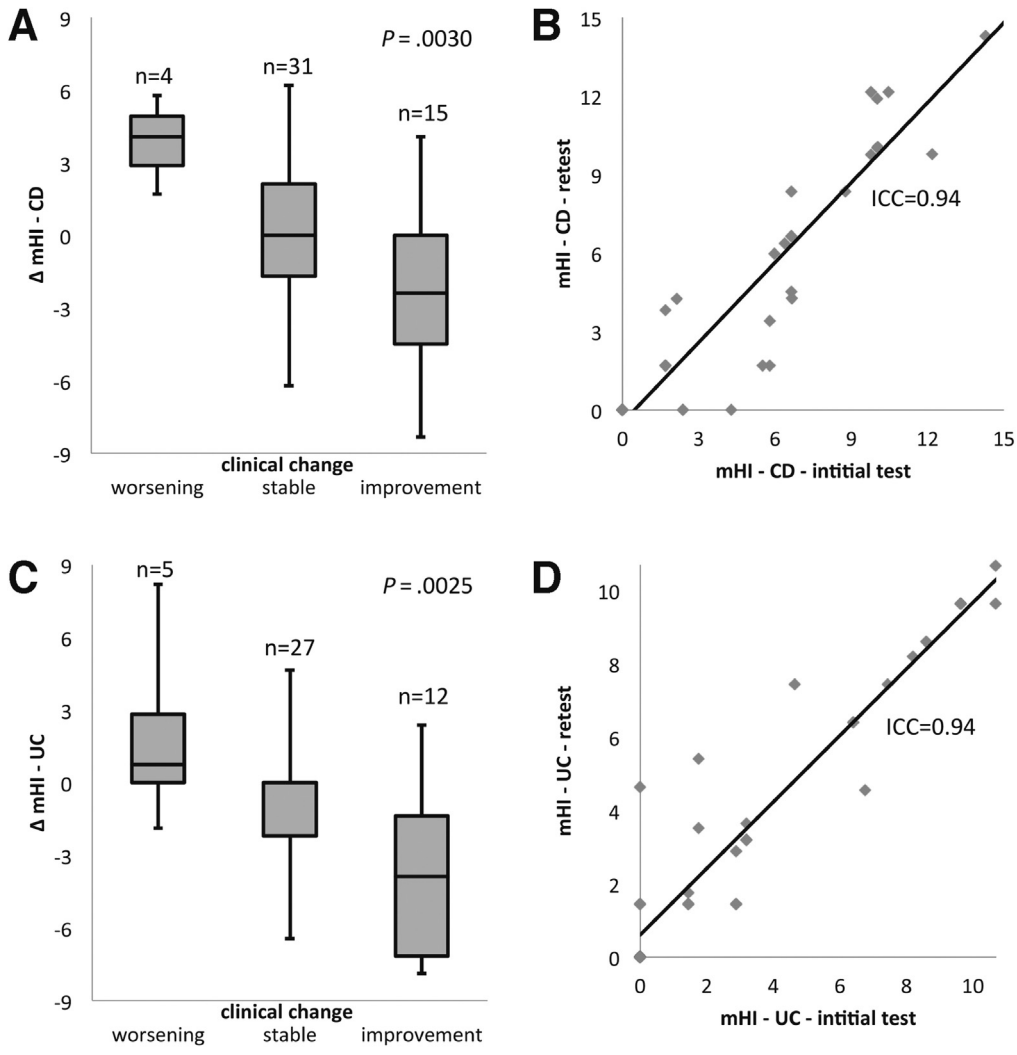

Figure 3. Sensitivity to change (*A* and *C*) and test-retest reliability (*C* and *D*) of the mHI-CD (*A* and *B*) and mHI-UC (*C* and *D*).

IBD, which can be used on mobile technology. The questionnaires were validated in a multicenter validation study and showed excellent characteristics to monitor clinical disease activity and symptom changes. As previously shown, UC clinical disease activity highly correlates with endoscopic disease activity, whereas correlation between CD symptoms and endoscopic findings is poor.[21]

Although previous studies have aimed to identify PROs for disease monitoring either by adjusting existing questionnaires,[16] or by using subcomponents of existing questionnaires,[18,19] we were able to prospectively identify PROs relevant for clinical disease monitoring and validate those in an independent cohort. Interestingly, patient-reported disease activity was shown to be an independent predictor for clinical disease activity in patients with UC and patients with CD, even after inclusion of common IBD symptoms, such as stool frequency and abdominal pain. Patient-reported disease activity alone had a comparable performance with the complete mHI in both CD and UC for detecting clinical and endoscopic activity, although responsiveness to changes in disease activity was reduced in particular in patients with CD.

A limitation of this study is the potential for recall bias in CDAI calculation. Although 7-day diary forms were sent out in advance, we did not log whether diaries were filled out daily or by recall. Additionally, in the validation cohort, optimal cutoffs of the mHI for detection of disease activity were higher than expected for CD and lower than expected for UC. This might be caused by the reduction of questionnaire items from >20 PROs to just 4, or by differences in the patient population. The validation phase of the study most accurately represents the real-life situation. Therefore, we implemented the cutoff for optimal sensitivity and specificity as observed in the validation cohort in clinical practice.

This study was not primarily designed to evaluate correlations between PROs and endoscopic healing. In at-risk patients, clinical assessments remain warranted, which may lead to further endoscopic evaluation. This tool offers an optimal screening method to monitor and evaluate disease activity in and outside of clinical practice with a high NPV. The mHIs are currently implemented in the UCLA eIBD patient app (Supplementary Figure 2) and automated messages are sent to a nurse coordinator when the mHI indicates disease activity. The

app is currently available to patients treated at the UCLA Center for IBD and can be downloaded in iOS or Android by searching for "UCLA eIBD."

The calculation of the mHI is complex. However, simplifying the score would most likely result in loss of accuracy. Because the index is meant to be automated and implemented on digital platforms, we believe that using the more complex calculations is justified.

Cloud-based health technologies are predicted to revolutionize care delivery and patient engagement. Patients can participate in their care by signaling meaningful health outcomes during year-round monitoring. Barriers for more widespread implementation of mHealth in IBD care include policies affecting reimbursement and regulatory requirements,[22] and privacy and security concerns.[1]

In summary, we developed the mHI-CD and mHI-UC for remote monitoring of patients with CD and patients with UC. The scores are specifically designed for implementation on a mobile application and are currently available to patients with IBD treated at the UCLA Center for IBD. Prospective randomized studies need to assess the effect of remote monitoring on disease control, quality of life, patient satisfaction, and health care costs.

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.2015.10.035.

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Reprint requests
Address requests for reprints to: Welmoed K. Van Deen, MD, Center for Inflammatory Bowel Diseases, Melvin and Bren Simon Digestive Diseases Center, David Geffen School of Medicine, University of California at Los Angeles, 10945 Le Conte Avenue, #2114, Los Angeles, California 90095. e-mail: wvandeen@mednet.ucla.edu; fax: (310) 206-9906.

Conflicts of interest
The authors disclose no conflicts.

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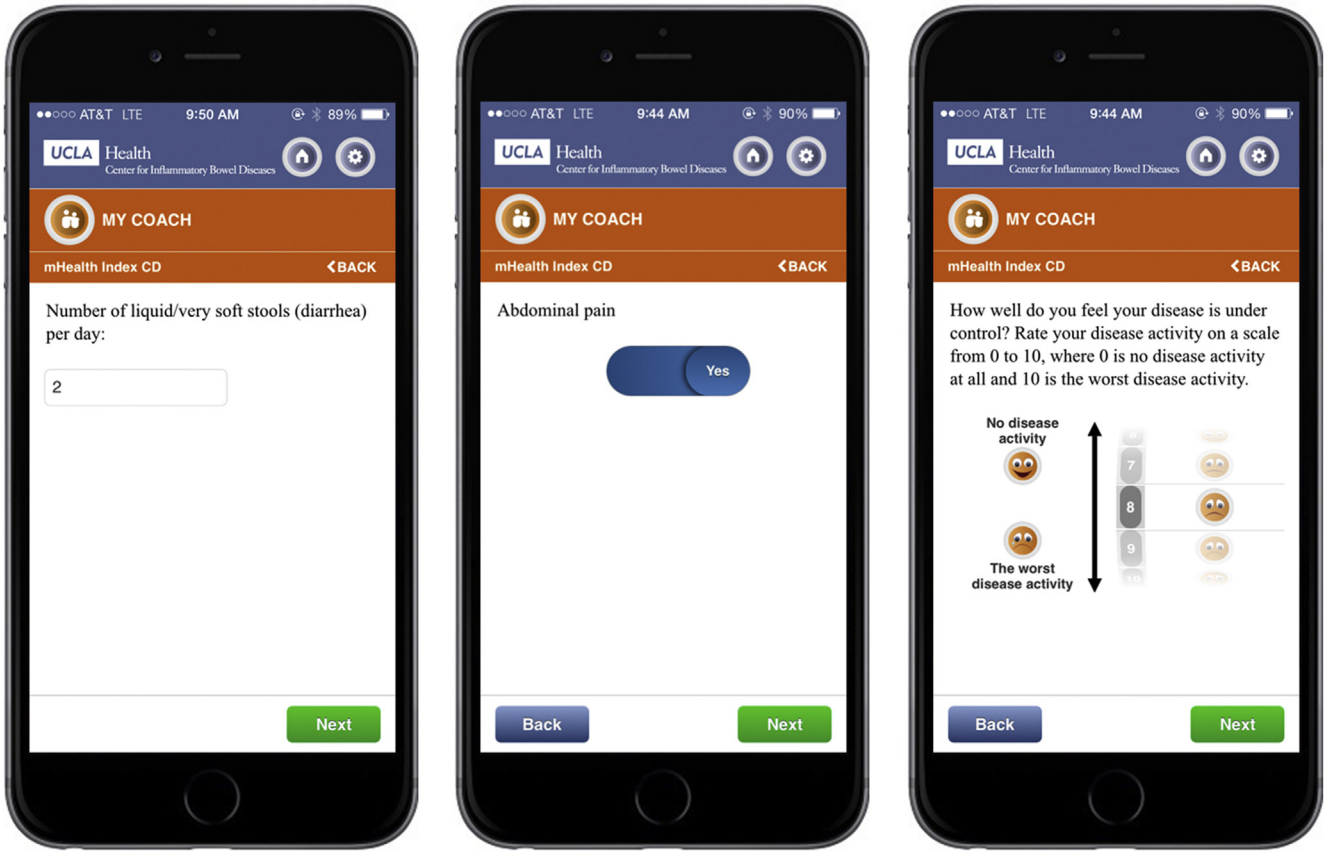
UCLA Health System
Center for Inflammatory Bowel Diseases

7 Day Diary

Day/date	Number of liquid/very soft stools (diarrhea)	Abdominal pain	General well being	Fever 100°F (>37.8°C)
Day 1 __/__/__ mm dd yy	____	☐ No ☐ Mild ☐ Moderate ☐ Severe	☐ Very well ☐ Slightly below par ☐ Poor ☐ Very poor ☐ Terrible	Yes / No
Day 2 __/__/__ mm dd yy	____	☐ No ☐ Mild ☐ Moderate ☐ Severe	☐ Very well ☐ Slightly below par ☐ Poor ☐ Very poor ☐ Terrible	Yes / No
Day 3 __/__/__ mm dd yy	____	☐ No ☐ Mild ☐ Moderate ☐ Severe	☐ Very well ☐ Slightly below par ☐ Poor ☐ Very poor ☐ Terrible	Yes / No
Day 4 __/__/__ mm dd yy	____	☐ No ☐ Mild ☐ Moderate ☐ Severe	☐ Very well ☐ Slightly below par ☐ Poor ☐ Very poor ☐ Terrible	Yes / No
Day 5 __/__/__ mm dd yy	____	☐ No ☐ Mild ☐ Moderate ☐ Severe	☐ Very well ☐ Slightly below par ☐ Poor ☐ Very poor ☐ Terrible	Yes / No
Day 6 __/__/__ mm dd yy	____	☐ No ☐ Mild ☐ Moderate ☐ Severe	☐ Very well ☐ Slightly below par ☐ Poor ☐ Very poor ☐ Terrible	Yes / No
Day 7 __/__/__ mm dd yy	____	☐ No ☐ Mild ☐ Moderate ☐ Severe	☐ Very well ☐ Slightly below par ☐ Poor ☐ Very poor ☐ Terrible	Yes / No

Supplementary Figure 1. Seven-day diary form, which was sent to patients to log symptoms during the 7 days before the clinic visit for calculation of the CDAI.



Supplementary Figure 2. Screenshots of the mHI as implemented in the UCLA eIBD patient app available to patients treated at the UCLA IBD Center.

Supplementary Table 1. CD Variables, Univariate Logistic Regression Outcomes for Prediction of Active Disease (HBI>4)

Domain	Variable	n	Cutoffs	MLE	SE	Chi-square	*P* value	Model[a]	Var#
Stool frequency	Number of liquid/very soft stools per day	108	Continuous	1.63	0.35	22.34	<.0001	—	
			0/1–3/>3	3.49	0.73	23.11	<.0001	—	
			0/1–2/>2	3.55	0.66	28.58	<.0001	1	V1.1
			0/>0	3.36	0.77	19.10	<.0001	—	
	How many stools did you have yesterday during the day?	108	Continuous	0.85	0.19	20.09	<.0001	—	
			0–1/>1	2.00	0.65	9.53	.0020	—	
	Number of stools more than normal per day	108	Continuous	0.87	0.36	5.88	.015	—	
			0/>0	0.84	0.51	2.69	.10	—	
	Total number of stools per day	108	Continuous	0.97	0.20	22.75	<.0001	—	
			≤1/>1	1.75	0.77	5.08	.024	—	
			0–2/>2	2.58	0.55	22.19	<.0001	—	
			0–1/2–4/>4	2.64	0.58	20.79	<.0001	—	
			0–2/3–4/>4	2.16	0.40	28.49	<.0001	2	V1.2
Stools at night	How many stools did you have last night?	108	Continuous	0.88	0.26	11.59	.0007	—	
			0/>0	1.15	0.44	6.90	.0086	—	
			0/1/>1	0.99	0.30	11.01	.0009	—	
			0/1–2/>2	1.28	0.36	12.29	.0005	1, 2	V2
Abdominal pain	Abdominal pain (no–severe)	108	No/mild/moderate/severe	2.68	0.50	28.11	<.0001	—	
			No/yes	3.72	0.62	35.35	<.0001	1, 2	V3
	Abdominal pain (no pain–continuous)	108	No abdominal pain/with bowel actions/continuous	1.52	0.31	23.97	<.0001	—	
	Abdominal pain VAS	108	Continuous	0.51	0.10	24.99	<.0001	—	
			0–3/>3, <8/8–10	2.02	0.41	24.17	<.0001	—	
			<3/3–6/>6	1.94	0.39	25.03	<.0001	—	
General well-being	General well-being (very well– terrible)	108	Very well slightly below par/poor/very poor/terrible	1.31	0.30	18.93	<.0001	—	
	Well-being VAS	108	Continuous	0.47	0.11	18.44	<.0001	—	
			<4/≥4, <7/≥7	1.42	0.35	16.76	<.0001	—	
			≤2/>2, <7/≥7	1.80	0.40	20.09	<.0001	1, 2	V4
	Well-being (no impairment–unable to work)	108	No impairment/impaired but able to continue activities/activities reduced/unable to work	1.21	0.83	17.90	<.0001	—	
Urgency	Urgency of defecation (no urgency–incontinence)	108	No urgency/hurry/immediately/incontinence	1.30	0.32	16.99	<.0001	1, 2	V5
			No incontinence/incontinence	0.88	1.43	0.38	.54	—	
Stool consistency	Stool consistency	108	Normal or variably normal/semiformed/liquid	2.09	0.48	19.06	<.0001	1, 2	V6
	Do you take opiates or lomotil/imodium for diarrhea?	108	No/yes	1.22	0.52	5.47	.019	—	
	Antidiarrheals VAS	108	Continuous	0.00	0.09	0.00	1.00	—	
Rectal bleeding	Rectal bleeding VAS	108	Continuous	0.16	0.09	3.06	.080	—	
			≤3/>3	1.22	0.52	5.47	.019	1, 2	V7
	What % of bowel movements contains visible blood?	108	None/<50%/≥50%/blood alone	0.36	0.34	1.08	.30	—	
	Amount of blood in stool	108	None/trace/occasionally frank/usually frank	0.61	0.28	4.72	.030	—	
Fever	Did you have fever yesterday?	108	No/yes	14.53	913.40	0.00	.99	—	
Anorexia	Loss of appetite	108	No/yes	1.04	0.45	5.51	.019	1, 2	V8
Nausea/vomiting	Nausea and/or vomiting	108	No/yes	1.03	0.49	4.44	.035	1, 2	V9

Supplementary Table 1. Continued

Domain	Variable	n	Cutoffs	MLE	SE	Chi-square	*P* value	Model[a]	Var#
Disease activity	Disease control VAS	108	Continuous	0.42	0.09	21.88	<.0001	—	
			≤3, >3, <7/≥7	1.60	0.32	24.41	<.0001	—	
			≤2, >2, <7/≥7	1.80	0.36	24.58	<.0001	1, 2	V10
Laboratory studies	C-reactive protein (mg/dL)	93	Continuous	0.27	0.14	3.80	.051	—	
			≤0.8/>0.8	1.77	0.53	11.11	.0009	—	
	Calprotectin (μg/g)	63	Continuous	0.00	0.00	6.45	.011	—	
			<163/≥163	1.22	0.63	3.71	.054	—	
			<50/≥50	0.28	0.66	0.18	.67	—	
	White blood cell count (*10^3 cells/μL)	96	Continuous	0.15	0.08	3.20	.074	—	
			≤9.95/>9.95	1.06	0.66	2.60	.11	—	
	Albumin (g/dL)	94	Continuous	-1.55	0.61	6.47	.011	—	
			≥3.7/<3.7	1.92	0.90	4.51	.034	—	
	Platelets (*10^3 cells/μL)	96	Continuous	0.00	0.00	1.43	.23	—	
			≥143/<143	15.17	770.20	0.00	.98	—	
	Erythrocyte sedimentation rate (mm/hr)	85	Continuous	0.05	0.02	7.28	.0070	—	
			≤22 (F) or ≤10 (M)/>22 (F) or >10 (M)	1.62	0.53	9.38	.0022	—	
	Hemoglobin (g/dL)	95	Continuous	-0.10	0.14	0.59	.44	—	
			>11.6 (F) or >13.5 (M)/≤11.6 (F) or ≤13.5 (M)	1.15	0.50	5.24	.022	—	
	Hematocrit	96	Continuous	-3.34	5.39	0.38	.54	—	
			>0.349 (F) or >0.385 (M)/≤0.349 (F) or ≤0.385 (M)	0.61	0.57	1.15	.28	—	

F, female; M, male; MLE, maximum likelihood estimate, SE, standard error.
[a]Variables selected for multivariate regression models (Supplementary Table 4).

Supplementary Table 2. UC Variables, Univariate Logistic Regression Outcomes for Prediction of Active Disease (pMayo >2)

Domain	Variable	n	Cutoffs	MLE	SE	Chi-square	*P* value	Model[a]	Var#
Stool frequency	How many stools did you have yesterday during the day?	109	Continuous	0.87	0.79	20.57	<.0001	—	
			<3/3–4/5–6/7–9/>9	1.61	0.33	23.11	<.0001	—	
			<4/4–6/>6	2.24	0.50	19.69	<.0001	—	
			<4/4–6/>6	2.32	0.49	22.35	<.0001	—	
	Stools more than normal	109	Continuous	0.99	0.33	9.23	.0024	—	
			0/1–2/3–4/>4	1.65	0.41	16.17	<.0001	—	
			0/1–2/>2	1.78	0.41	19.18	<.0001	—	
	Total number of stools/day	109	Continuous	0.78	0.16	23.03	<.0001	—	
			<3/3–6/>6	2.24	0.42	28.86	<.0001	—	
			0–4/>4	3.57	0.62	32.79	<.0001	1, 2	V1.1
			0–2/3–4/>4	1.95	0.34	32.46	<.0001	3, 4	V1.2
Stools at night	How many stools did you have last night?	109	Continuous	0.95	0.26	12.77	.0004	—	
			0/>0	1.48	0.43	11.79	.0006	—	
			0/1–3/>3	1.49	0.38	15.01	.0001	1, 2, 3, 4	V2
Abdominal pain	Abdominal pain (no– severe)	109	No/mild/moderate/severe	0.78	0.25	9.60	.0019	—	
			No/yes	1.47	0.45	10.62	.0011	—	
	Abdominal pain (no– continuous)		No abdominal pain	1.02	0.30	11.44	.0001	—	
	Abdominal pain VAS	109	Continuous	0.40	0.09	19.21	<.0001	—	
			<3/≥3, ≤6/>6	1.75	0.37	21.84	<.0001	1, 2, 3, 4	V3
			0/>0, ≤4/>4	1.40	0.33	18.20	<.0001	—	
General well-being	General well-being? (very well–terrible)	109	Very well/slightly below par/poor/very poor/terrible	1.27	0.34	14.12	.0002	—	
	General well-being (perfect–terrible)	109	Perfect/very good/good/average/poor/terrible	0.91	0.23	16.08	<.0001	1, 3	V4.1
	Well-being VAS	109	Continuous	0.43	0.11	15.30	<.0001	—	
			≤3/>3	1.62	0.45	13.31	.0003	—	
			≤3/>3, ≤6/>6	1.42	0.36	15.73	<.0001	2, 4	V4.2
	Well-being (no impairment–unable to work)	109	No impairment/impaired but able to continue activities/activities reduced/unable to work	1.14	0.36	15.93	<.0001	—	
Urgency	Urgency of defecation	109	No urgency/hurry/immediate/incontinence	2.01	0.40	24.82	<.0001	—	
			No urgency/hurry/immediate	2.03	0.40	25.13	<.0001	1, 2, 3, 4	V5
			No incontinence/incontinence	14.13	826.90	0.00	.99	—	
Stool consistency	Stool consistency	109	Normal or variably normal/semiformed/liquid	2.13	0.46	21.68	<.0001	1, 2, 3, 4	V6
	Do you take opiates or lomotil/imodium for diarrhea?	109	No/yes	-0.03	0.59	0.00	.96	—	
	Antidiarrheals VAS	109	Continuous	0.05	0.09	0.26	.26	—	
Rectal bleeding	Rectal bleeding VAS	109	Continuous	0.59	0.11	27.82	<.0001	—	
			≤3/>3	2.71	0.49	29.97	<.0001	—	
			<2/≥2, <5/≥5, <8/≥8	1.66	0.31	28.15	<.0001	1, 2, 3, 4	V7
	What % of bowel movements contains visible blood?	109	None/<50%/≥50%/blood alone	2.84	0.59	22.89	<.0001	—	
			None/<50%/≥50%	2.95	0.60	24.26	<.0001	—	
			None/>0%	3.86	1.04	13.76	.0002	—	
	Amount of blood in stool	109	None/trace/occasionally frank/usually frank	1.83	0.35	27.22	<.0001	—	
			None/trace/more than a trace	1.95	0.37	27.53	<.0001	—	
Anorexia	Loss of appetite	109	No/yes	1.44	0.48	9.10	.0025	1, 2, 3, 4	V8
Nausea/vomiting	Nausea and/or vomiting	109	No/yes	0.72	0.49	2.12	.14	—	

Supplementary Table 2. Continued

Domain	Variable	n	Cutoffs	MLE	SE	Chi-square	*P* value	Model[a]	Var#
Disease activity	Disease control VAS	109	Continuous	0.46	0.10	21.67	<.0001	—	
			≤3/>3, <7, ≥7	1.44	0.31	21.37	<.0001	—	
			≤2/>2, ≤5/>5	1.82	0.36	25.86	<.0001	1, 2, 3, 4	V10
			≤2/>2, <7/≥7	1.68	0.36	21.76	<.0001	—	
Labs	C-reactive protein (mg/dL)	91	Continuous	1.03	0.42	5.87	.015	—	
			≤0.8/>0.8	1.50	0.55	7.35	.0067	—	
	Calprotectin (μg/g)	70	Continuous	0.00	0.00	4.31	.038	—	
			<163/≥163	1.29	0.56	5.22	.022	—	
			<50/≥50	1.96	0.80	6.06	.014	—	
	White blood cell count (*10^3 cells/μL)	93	Continuous	0.20	0.08	5.91	.015	—	
			≤9.95/>9.95	1.39	0.56	6.19	.013	—	
	Albumin (g/dL)	88	Continuous	-1.52	0.66	5.39	.02	—	
			≥3.7/<3.7	14.36	610.50	0.00	.98	—	
	Platelets (*10^3 cells/μL)	93	Continuous	0.00	0.00	2.54	.11	—	
			≥143/<143	-12.66	805.50	0.00	.99	—	
	Erythrocyte sedimentation rate (mm/hr)	85	Continuous	0.04	0.01	8.38	.0038	—	
			≤22 (F) or ≤10 (M)/>22 (F) or >10 (M)	1.04	0.47	4.81	.028	—	
	Hemoglobin (g/dL)	93	Continuous	-0.31	0.15	4.59	.032	—	
			>11.6 (F) or >13.5 (M)/≤11.6 (F) or ≤13.5 (M)	0.75	0.50	2.25	.13	—	
	Hematocrit	93	Continuous	-9.46	5.91	2.66	.10	—	
			>0.349 (F) or >0.385 (M)/≤0.349 (F) or ≤0.385 (M)	1.84	0.65	7.99	.0047	—	

F, female; M, male; MLE, maximum likelihood estimate, SE, standard error.
[a]Variables selected for multivariate regression models (Supplementary Table 4).

Supplementary Table 3. Development and Evaluation of Composite Scores for CD

Composite score development			AUC ROC curves		*P* value	
Dependent variable	Model	Variables in composite scores[a]	HBI	CDAI	HBI	CDAI
HBI	1	V1.1; V3	0.981	0.912	0.903	0.739
	2	V1.2; V3; V10	0.956	0.898	0.750	0.702
CDAI	1	V1.1; V3; V4; V10	0.951	0.963	0.837	0.830
	2	V3; V4; V10	0.900	0.942	0.731	0.771

V1.1, number of liquid/very soft stools per day; V1.2, total number of stools per day; V3, abdominal pain; V4, well-being VAS; V10, disease control VAS.
[a]See Supplementary Table 1 for full details on each variable.

Supplementary Table 4. Development and Evaluation of Composite Scores for UC

Composite score development			AUC ROC curves			*P* value		
Dependent variable	Model	Variables in composite scores[a]	pMayo	SCCAI	MTWI	pMayo	SCCAI	MTWI
pMayo	1, 2	V1.1; V3; V7; V8; V10	0.960	0.865	0.849	0.769	0.769	0.703
	1, 2[b]	V1.1; V3; V7; V10	0.957	0.879	0.883	0.797	0.803	0.762
	3	V1.2; V3; V7; V8; V10	0.964	0.908	0.890	0.808	0.812	0.748
	3[b]	V1.2; V3; V7; V10	0.960	0.915	0.913	0.820	0.832	0.790
	4	V1.2; V 4.2; V7; V10	0.956	0.920	0.909	0.809	0.838	0.787
SCCAI	1	V2; V4.1; V5; V7	0.872	0.974	0.896	0.711	0.907	0.836
	2, 4	V2; V3; V4.2; V5; V7; V10	0.904	0.971	0.883	0.765	0.911	0.810
	3	V1.2; V2; V4.1; V5; V7	0.885	0.981	0.923	0.721	0.914	0.869
MTWI	1	Unbalanced model	NA	NA	NA	NA	NA	NA
	2	V1.1; V2; V6; V7; V8	0.928	0.879	0.937	0.801	0.806	0.855
	3	V1.2; V2; V4.1	0.880	0.907	0.984	0.712	0.797	0.933
	4	V1.2; V2; V4.2; V7; V8	0.906	0.894	0.950	0.777	0.810	0.866

MTWI, modified Truelove and Witts index; NA, not applicable; V1.1 and V1.2, number of stools per day; V2, number of stools at night; V3, abdominal pain VAS; V4.1, general well-being; V4.2, well-being VAS; V5, urgency of defecation; V6, stool consistency; V7, rectal bleeding VAS; V8, anorexia; V10, disease control VAS.
[a]See Supplementary Table 2 for full details on each variable.
[b]In these models loss of appetite was excluded as independent variable because of a clinically irrelevant negative value in the model.