# Can Endoscopy Be Avoided in the Assessment of Ulcerative Colitis in Clinical Trials?

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**Background:** There is no gold standard index in the measurement of ulcerative colitis (UC) disease activity in clinical trials. Mucosal healing has been described as an important clinical endpoint requiring endoscopic assessment, which is unpleasant for the patient and may hamper recruitment to trials. The aim of this study was to determine whether endoscopy is necessary in the assessment of UC disease activity and whether a noninvasive disease activity index (partial Mayo score) could be used to predict the Mayo score.

**Methods:** In all, 149 subjects with moderate to severe UC enrolled in a clinical trial were assessed using total and partial Mayo scores. Histologic assessment of biopsies was performed. A regression model was constructed to predict total Mayo score from the partial Mayo score and histology score from the Mayo score. A Bland–Altman test of agreement was performed.

**Results:** The partial Mayo score correlated closely with the total Mayo score at week 4 (rho = 0.97) and week 8 (rho = 0.98). The model to predict total from partial Mayo score showed excellent correlation (rho = 0.97) and good agreement with the total Mayo score at week 4 and the week 8 validation set (rho = 0.97) and accurately classified disease severity (kappa = 0.82). The model to predict histology score from the Mayo score correlated only moderately with the actual histology score at week 4 (rho = 0.59) and week 8 (rho = 0.36).

**Conclusions:** The Mayo score can be accurately predicted from the partial Mayo score. A noninvasive index can replace the Mayo score in future clinical trials.

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**Key Words:** ulcerative colitis, Mayo score, endoscopy, clinical disease activity

Clinical trials of intervention in ulcerative colitis (UC) require a measure of clinical disease activity. Unfortunately, there is no agreed gold standard and several indices have been developed without careful validation. Fourteen different indices have recently been reviewed in detail.[1] Some of these use symptom scores (for example, stool frequency and general well-being),[2] others combine these with laboratory parameters,[3] or add endoscopic findings.[4,5] With multiple scoring systems and numerous definitions of response and remission, it is challenging to compare interventions used in different trials and standardization is required.

The review of UC activity scoring systems[1] recommends that mucosal healing should be a primary endpoint. Mucosal healing may be used to predict the need for active treatment or colectomy; it is associated with quality of life measures; and may also be used to predict the risk of colorectal cancer. For example, a Norwegian cohort study[6] found that endoscopic remission after 1 year of treatment was predictive of subsequent reduced disease activity and need for active treatment. In the prebiologic era, the presence of severe lesions at endoscopy was significantly associated with risk of colectomy.[7] Clinical and endoscopic indices also correlate with quality of life in patients with UC as measured by the Inflammatory Bowel Disease Questionnaire (IBDQ).[8] A case-controlled study demonstrated that colonoscopic and histologic scores correlated with subsequent colorectal cancer development by univariate analysis[9] and normal endoscopic appearance was associated with lower rates of subsequent colorectal cancer.[10] The impact of mucosal healing in the course of disease and the symptoms suffered by patients is clear.

However, there is currently no consensus definition of mucosal healing. Recent trials have included the persistence of erythema or mucosal edema in their definitions of endoscopic mucosal healing.[11,12] Endoscopy may not even

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be sufficient to assess healing since endoscopic appearance does not always correspond to the histological findings.[13–15] Histology predicts the clinical course of the disease,[16] risk of relapse,[17] and risk of subsequent colorectal cancer.[9,18] Therefore, histological assessment may be the most appropriate measure of mucosal healing. However, histological healing has not been used as a trial endpoint. In the context of clinical trials, histological assessment requires interval flexible proctosigmoidoscopy and biopsy, which is unpleasant for the patient and may adversely impact recruitment into a trial. A noninvasive index that is a surrogate for mucosal healing is required to improve patient acceptability of clinical trials for UC.

The Mayo score[4] has been used in numerous UC clinical trials. Although it has not been formally validated, it correlates with IBDQ and SF-36 measures of quality of life.[19] The Mayo score incorporates the reported stool frequency, presence of rectal bleeding, endoscopic findings, and a physician's global assessment, which acknowledges the other three components of the score together with the patient's symptoms and their subjective assessment of well-being. Calculation of the Mayo score requires proctosigmoidoscopic examination to determine achievement of clinical remission, response, and mucosal healing. A partial Mayo score,[12,20,21] in which the endoscopic component is omitted, has been shown to correlate well with the Mayo score (rho = 0.61)[22] as well as with an independently scored physician's global assessment (rho = 0.65) and had good discriminatory value between subjects in remission and those with active disease.[23] Turner et al[23] reported that the partial Mayo score was only outperformed by the Walmsley and pediatric UC activity (PUCAI) indices in their prospective comparison of nine noninvasive disease activity indices.

The aim of this study was to establish whether sigmoidoscopy was necessary in the clinical assessment of UC by determining whether the noninvasive disease activity index (partial Mayo score), without endoscopy, could be used to predict the total Mayo score. In addition, we compared histological mucosal healing with clinical outcome and invasive and noninvasive indices.

## MATERIALS AND METHODS

Post-hoc analysis of data from a multicenter randomized controlled trial in steroid-refractory moderate to severe UC (NCT00430898),[24] conducted between April 2007 and August 2008 in 46 outpatient centers in North America, Europe, and Asia, was undertaken. Clinical assessment of disease activity was evaluated using the Mayo score[4] (Table 1) at day 0, week 4, and week 8 from the time of first drug administration. Unsedated proctosigmoidoscopy was performed at day 0, week 4, and week 8, during which biopsies were taken for histological analysis. Histological evaluation of biopsies was performed as an optional substudy.

**TABLE 1.** Mayo Scoring System for Assessment of Ulcerative Colitis Activity[4]

| |
|---|
| Stool frequency |
| 0 = "Normal" number of stools for this patient when disease is not active |
| 1 = 1 to 2 stools more than normal |
| 2 = 3 to 4 stools more than normal |
| 3 = 5 or more stools more than normal |
| Rectal bleeding* |
| 0 = No blood seen |
| 1 = Streaks of blood with stool less than half the time |
| 2 = Obvious blood with stool most of the time |
| 3 = Blood alone passes |
| Findings of flexible proctosigmoidoscopy |
| 0 = Normal or inactive disease |
| 1 = Mild disease (erythema, decreased vascular pattern, mild friability) |
| 2 = Moderate disease (marked erythema, lack of vascular pattern, friability, erosions) |
| 3 = Severe disease (spontaneous bleeding, ulceration) |
| Physician's global assessment** |
| 0 = Normal |
| 1 = Mild disease |
| 2 = Moderate disease |
| 3 = Severe disease |

*The daily bleeding score represents the most severe bleeding of the day.
**The physician's global assessment acknowledges the three other criteria, the patient's daily record of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.

The primary endpoint of the trial was clinical remission at week 8 defined as a Mayo score of $\leq 2$ with no individual subscore $>1$. The secondary endpoints were clinical response at week 8 (a decrease in Mayo score by at least 3 points with a reduction in rectal bleeding subscore of at least 1 or an absolute score of 0 or 1) and mucosal healing at week 8 (endoscopic subscore of 0 or 1).

Biopsies were scored by one independent, blinded, experienced gastrointestinal histopathologist using the Riley index[25]; this index assesses both acute features (polymorphonuclear cells in lamina propria and crypt abscesses) and chronic features (mucin depletion, surface epithelial integrity, chronic inflammatory cell infiltrate in lamina propria, and crypt architectural irregularity) of UC.

The week 4 Riley index, total and partial Mayo scores, and the endoscopy subscore were correlated using Spearman's coefficient of correlation. This timepoint was chosen because it gave a full range of histology and Mayo scores. Week 0 scores were not used in this analysis because, as a study inclusion criterion, subjects had to have a Mayo score of $\geq 6$, therefore producing a skewed sample.

To determine whether sigmoidoscopy is necessary in the clinical assessment of UC we assessed whether the Mayo



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score could be predicted from only its noninvasive components (the partial Mayo score). Using week 4 data, a linear regression model was constructed to predict total Mayo score from partial Mayo score, the results of which were tested with week 8 data. Since a simple correlation does not assess agreement between two scores, a Bland–Altman test of agreement[26] was performed between actual and predicted values. In addition, an unweighted kappa statistic was calculated to determine whether the predicted score correctly classified the subject into the correct disease severity group on the Mayo score scale (0–2 remission, 3–5 mild, 6–10 moderate, 11–12 severe). A similar model was constructed to predict week 4 Riley index from the week 4 total Mayo score, which was assessed for agreement with the actual Riley index with week 8 data. As the total Mayo score contains the results from four separate domains, only two of which were thought to be thoroughly independent of the results of the endoscopic examination (stool frequency and rectal bleeding subscores), finally, a model was constructed to predict the partial and the total Mayo score from these symptom scores alone, which we refer to as the 6-point symptom score.

Factor analysis was performed on Week 4 and Week 8 data to determine the contribution of each subscore to the overall variance of the total Mayo score.

## Ethical Considerations

Local ethical approval was obtained from all participating centers and all patients gave written informed consent before participating in the clinical trial.

## RESULTS

In all, 149 subjects were recruited to the clinical trial and 134 had complete assessment by Mayo score as per protocol. A total of 168 biopsies were obtained from 69 subjects in 24 different centers in North America and Europe; 62 at day 0, 51 at week 4, and 55 at week 8.

The partial Mayo score correlated closely with the total Mayo score at both week 4 and week 8 (rho = 0.97 and 0.98, respectively).

### Prediction of Mayo from Partial Mayo Score

A model to predict the total Mayo score was constructed by linear regression using week 4 data (Table 2): A + B + 2C + 0.1 (where A is stool frequency subscore, B rectal bleeding subscore, and C physician's global assessment subscore). This correlated well with actual Mayo score at week 4 (rho = 0.97; Fig. 1) and week 8 (rho = 0.97). The Bland–Altman test of agreement suggests good agreement between actual and predicted Mayo score with limits of ±1.1 points on a 12 point scale (Table 3; Fig. 2). In addition, this model accurately classified cases within the correct disease severity group on the total Mayo scale (kappa = 0.82 at week 4 and 0.92 at week 8).

### Prediction of Mayo from 6-Point Symptom Score

To address the fact that the physician's global assessment may be partially dependent on the endoscopic subscore, we reconstructed the linear regression model using the 6-point symptom score, producing the equation: 1.6A

**TABLE 2.** Linear Regression Models

| Model | Sample Size | $R^2$ | Adjust-ed $R^2$ | Independent Variables: Variable Name | Coefficient | SE | *P*-value |
|---|---|---|---|---|---|---|---|
| Total Mayo from partial Mayo | 134 | 0.94 | 0.94 | Constant | 0.1 | 0.11 | 0.018 |
| (A+B+2C+0.1) | | | | A | 1 | 0.07 | <0.001 |
| | | | | B | 1 | 0.07 | <0.001 |
| | | | | C | 1.8 | 0.09 | <0.001 |
| Total Mayo from 6 point symptom score | 134 | 0.78 | 0.78 | Constant | 1.8 | 0.17 | <0.001 |
| (1.6A+1.3B+1.8) | | | | A | 1.6 | 0.12 | <0.001 |
| | | | | B | 1.3 | 0.13 | <0.001 |
| Partial Mayo from 6 point symptom score | 134 | 0.92 | 0.92 | Constant | 0.8 | 0.08 | <0.001 |
| (1.3A+1.2B+0.8) | | | | A | 1.3 | 0.05 | <0.001 |
| | | | | B | 1.2 | 0.06 | <0.001 |
| Riley histology score from Mayo score | | | | Constant | 2.7 | 1.17 | 0.023 |
| (A+B-2C+2.4D+2.7) | 51 | 0.35 | 0.29 | A | 1 | 0.67 | 0.122 |
| | | | | B | 1.1 | 0.76 | 0.141 |
| | | | | C | −2 | 1.3 | 0.123 |
| | | | | D | 2.4 | 0.99 | 0.02 |

Statistical analysis of the four linear regression models used.



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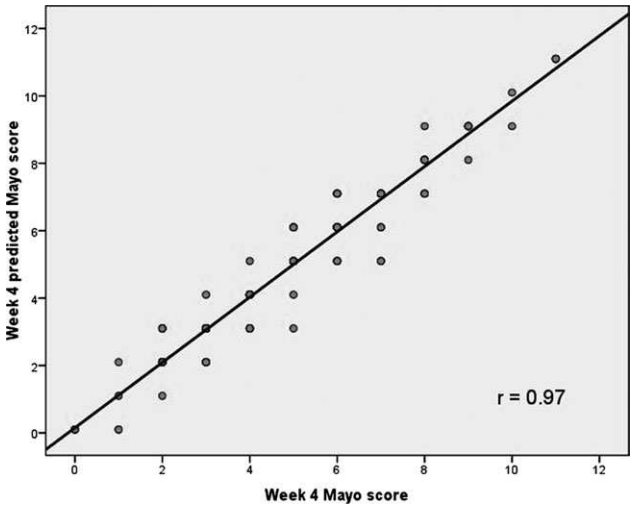


FIGURE 1. Total Mayo versus predicted Mayo score at week 4.

+ 1.3B + 1.8 (Table 2) to predict total Mayo score and 1.3A + 1.2B + 0.8 (Table 2) to predict partial Mayo score (where A is the stool frequency subscore and B the rectal bleeding subscore). There remained good correlation with the actual total Mayo score (rho = 0.89 at week 4; rho = 0.90 at week 8) and good agreement in disease severity classification (kappa = 0.61 at week 4 and 0.71 at week 8). Close correlation was also found between predicted and actual scores for the partial Mayo score (rho = 0.96 at both weeks 4 and 8).

## Factor Analysis

By factor analysis of week 4 data, the endoscopic subscore contributed the lowest amount to the overall variance of the total Mayo score (7% vs. 59% for stool frequency, 20% for rectal bleeding and 14% for physician's global assessment). At week 8, endoscopy contributes 6% to the overall variance (vs. 65% for stool frequency, 16% for rectal bleeding, and 13% for physician's global assessment).

## Histology

A significantly lower week 8 Riley index score was found in patients who achieved clinical remission at week 8 (the primary endpoint of the clinical trial; 3.8 vs. 7.1; $P = 0.04$). Similarly, the Riley index was significantly lower in those patients who achieved mucosal healing at week 8, defined as an endoscopic subscore of 0 or 1 (3.2 vs. 5.4; $P = 0.002$), compared with subjects who did not.

The Riley index score correlated reasonably well with both total and partial Mayo scores at week 4 (rho = 0.55 and rho = 0.50, respectively; Fig. 3). The correlation between the Riley index score with endoscopy subscore at week 4 was also reasonable (rho = 0.55) but does not suggest a strong predictive association. These relationships were also explored using linear regression; a model to predict histology score from total Mayo score gave the equation A + B − 2C + 2.4D + 2.7 (Table 2) (where A is stool frequency subscore, B rectal bleeding subscore, C physician's global assessment, and D the endoscopy subscore). This model correlated better with the week 4 Riley index score (rho = 0.59) but only weakly with week 8 Riley index score (rho = 0.36). A Bland–Altman test of agreement suggested poor agreement (limits from −6 to +7 points on an 18-point scale) between the predicted and actual Riley index at week 4 (Fig. 4, Table 3). Similar agreement was found using week 8 data (limits of agreement −7 to +7; Table 3). Oddly, this model showed a negative relation between physician's global assessment and histology score, which further undermines this particular model.

## DISCUSSION

The partial Mayo score can be used to accurately predict the total Mayo score and correctly classifies disease severity. This suggests the endoscopic component of the Mayo score does not contribute additional information to the score, probably because the endoscopic appearance is tightly related to other components of the Mayo score. Indeed, the week 4 endoscopic subscore correlated with week 4 partial Mayo score (rho = 0.55), suggesting there is a relationship between endoscopic findings and clinical activity. Factor analysis also demonstrated that the endoscopic subscore contributed the least to the overall variance of the Mayo score.

This observation is supported by evidence from other smaller studies of disease activity indices in 66 consecutive patients with UC.[27] Two invasive indices (St Mark's Index

**TABLE 3.** Bland-Altman Analyses

| Analysis | Sample Size | Mean | Standard Deviation | 95% Limits of Agreement | |
|---|---|---|---|---|---|
| Week 4 predicted Mayo vs. total Mayo | 139 | −0.01 | 0.59 | −1.15 | +1.14 |
| Week 8 predicted Mayo vs. total Mayo | 134 | −0.14 | 0.60 | −1.32 | +1.04 |
| Week 4 predicted vs. actual Riley histology score | 51 | 0.14 | 3.33 | −6.39 | +6.67 |
| Week 8 predicted vs. actual Riley histology score | 54 | −0.02 | 0.63 | −7.13 | +7.09 |



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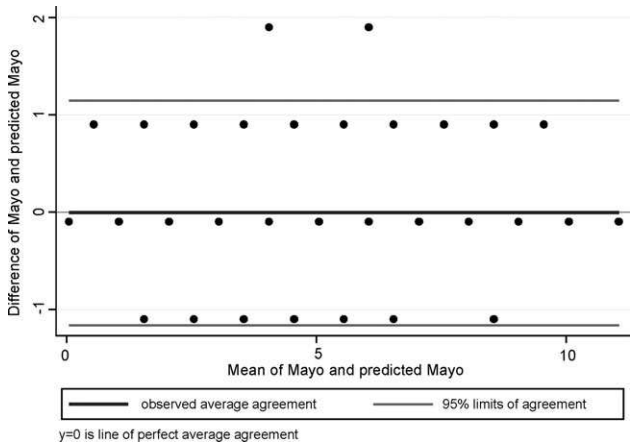


FIGURE 2. Bland–Altman plot of agreement (with 95% limits of agreement) between predicted and actual Mayo score at week 4.

and the UC Disease Activity Index [UCDAI]) were compared with two noninvasive indices (Seo Index and Walmsley Index or Simple Clinical Colitis Activity Index [SCCAI]) by Spearman's correlation. The noninvasive indices correlated well with the St Mark's index (rho = 0.87 for Seo Index, rho = 0.71 for SCCAI). Factor analysis found that the endoscopic component of the invasive scores contributed to only 0.04%–3.37% of the variance in the measurement of disease activity. The endoscopy component correlated well with overall disease activity but had little uniqueness and was made redundant with information from stool frequency and rectal bleeding scores. The authors have gone on to validate the SCCAI and Seo Index by developing a quantitative method of measurement of psychometric (whether the index captures appropriate information) and performance (reproducibility and discrimination of the index) validity.[28] This is the most rigorous validation of any UC disease activity index. Its findings suggest that, although both noninvasive indices have incomplete content validity, they are reproducible and responsive. This suggests that there is certainly room for improvement in UC disease activity scores but this study validates the use of a noninvasive index and demonstrates good consistency despite the lack of endoscopic information.

A further caveat to the use of an index with an endoscopic component is the possibility of interobserver error. The degree of interobserver agreement is related to the experience of the endoscopist, with trainees having poorer agreement than experienced endoscopists.[29,30] Even among experienced endoscopists agreement ranges from kappa of 0.51 when rating vascular pattern to 0.97 for grade of inflammation.[29] A study comparing endoscopic scores of digitally recorded colonoscopies performed in 16 patients with mild to severe UC by 10 UC specialists found that interobserver variation was greater in mild and moderate compared with severe disease activity with concordance of 25% in mild, 47% in moderate, and 76% in severe activity.[31] Endoscopy scoring systems are subjective even in experienced hands, and difficult to standardize. Scores in less severe disease should be interpreted with caution.

Interestingly, in this study histological findings could not be accurately predicted from clinical parameters although they did relate to clinical outcome. There was only a moderate correlation with endoscopic activity at week 4 (rho = 0.55). The disconnect between clinical disease activity scores and endoscopy or histology assessment has previously been demonstrated, initially by Truelove and Richards[32] and more recently by others.[13,33] This may be explained by a lag between endoscopic and histological improvement leading to higher histology scores at the week 4 timepoint.[13] Alternatively, there may have been

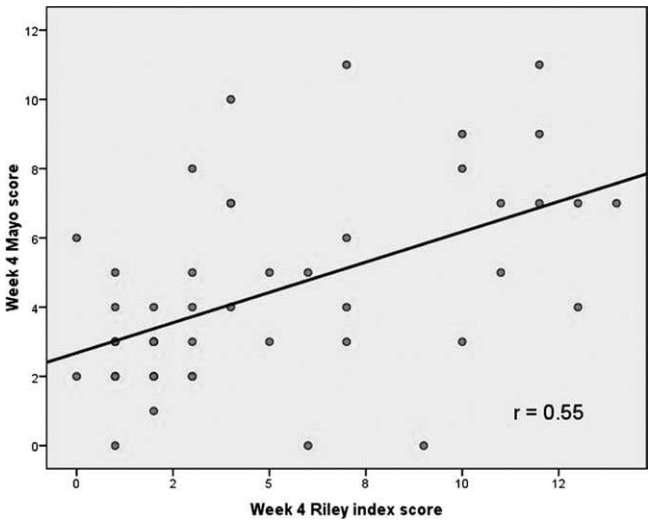


FIGURE 3. The Riley index score versus total Mayo score at week 4.

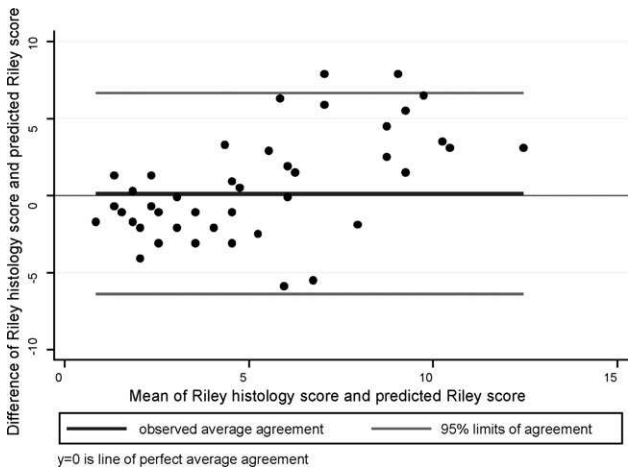


FIGURE 4. Bland–Altman plot of agreement (with 95% limits of agreement) between predicted and actual Riley index score at week 4.



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patchy histological changes[34] and sampling error may have occurred or interobserver error by the large number of endoscopists who took part in this study.

However, it is not certain whether histological healing is a more clinically relevant endpoint compared with endoscopic mucosal healing. The lack of close agreement between them suggests that they cannot be used interchangeably. Both measures have limitations: endoscopic findings are prone to variability and can be subjective[31] and can underestimate histological disease activity,[13,35] while histology is also open to sampling error, interobserver variation,[36] and the Riley index, as used in this study, has not been formally validated. We are unable to conclude from our data which is the stronger predictor of outcome but suggest further prospective comparison between them to answer this important question.

We acknowledge that this study does have limitations; in particular we note that the physician's global assessment subscore may not be completely independent from endoscopic appearance since it acknowledges the other three components of the Mayo score, including the endoscopic subscore. To address this, we used only the 6-point symptom score to construct a model for the partial and total Mayo scores and still found close correlation between the predicted and actual Mayo scores (rho = 0.90 for total Mayo and rho = 0.96 for partial Mayo at week 8) and good agreement in disease severity classification (kappa = 0.71). This shows that a truly noninvasive index, using only stool frequency and rectal bleeding subscores, can still accurately predict the invasive score. This is supported by a similar prospective comparison of this 6-point score with the Mayo score in 75 subjects with a Spearman's correlation coefficient of 0.61.[22]

Furthermore, the Riley histology index has not been formally validated, but it has been used in clinical trials with good reproducibility.[37] An alternative histology index[38] has been validated and may provide a more accurate evaluation of mucosal healing, although it is a more complex score. Similarly, the partial Mayo score has not been formally validated but has been shown to correlate best out of nine noninvasive disease activity indices with the Mayo score (rho = 0.93).[23] In addition, we are unable to perform a comparison of different noninvasive scores due to a lack of prospective data and therefore cannot confirm previous findings that the Walmsley index is the most valid and differentiating score.[23] Further studies to validate the partial Mayo score using the methods described by Higgins et al[28] in both psychometric and performance domains would also be desirable.

We recognize that mucosal biopsy will remain important within clinical trials of UC. Screening biopsies enable exclusion of other pathology such as cytomegalovirus colitis, and mucosal biopsies are valuable for assessment of mucosal drug penetration and determining mechanism of action. However, when assessing disease remission much more work is needed; the delay in achieving histological healing compared with clinical remission or endoscopic healing is problematic. It is by no means certain that histological healing should be an endpoint in clinical trials. We have demonstrated that histological appearance cannot be accurately predicted by the clinical domains of the Mayo score. Given the importance of mucosal healing as a clinical endpoint, and until noninvasive surrogate markers of inflammation have been validated, mucosal inspection is the only tool currently available to investigators to evaluate this.

In conclusion, when Mayo scores are used to determine outcomes in double-blind, randomized clinical trials, the endoscopic subscore contributes little to the overall disease activity assessment of UC. The total Mayo score could be replaced by the partial Mayo score. Further study is required to rigorously validate the partial Mayo score so this can be used consistently in future clinical trials in UC. The data also have relevance to normal clinical practice: patients and clinicians can feel confident that sigmoidoscopy is not essential to assess healing after treatment for UC, as the findings can be expected to correlate with symptoms.

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