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Appreciating the Nuance of Daily Symptom Variation to Individualize Patient Care

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Abstract

Introduction: Improving symptoms for patients with chronic illness is difficult due to poor recall and imprecise assessments of therapeutic response to inform treatment decisions. Daily variation in symptoms may obscure subtle improvement or lead to erroneous associations between symptom changes and alteration in medication or dietary regimens. This may lead to mistaken impressions of treatment efficacy (or inefficacy). Mobile health technologies that collect daily patient reported outcome (PRO) data have the potential to improve care by providing more detailed information for clinical decision-making in practice and may facilitate conducting single subject (n-of-1) trials.

Methods: Interrupted time series to prototype mobile health enabled data collection for three patients. We recruited pediatric patients with established inflammatory bowel disease who had persistent symptoms. Based on their self-identified most troubling symptoms, patients were sent customized, daily-automated text messages to assess the extent of their symptoms. Standardized, PRO Measurement Information System (PROMIS) surveys were deployed weekly. Individual statistical process control charts were used to assess variation. Patients met with physicians regularly to interpret their data jointly.

Results: We report the experience of 3 patients with inflammatory bowel disease, each with different symptoms. Daily symptom monitoring uncovered important patterns, some of which even patients were unaware before reviewing their symptom data. Important associations were found between symptom variation and changes in medications and diet. PROMIS survey results assessed longitudinally accurately reflected changes in patient symptoms.

Conclusions: We demonstrated how PROs can be implemented in practice. Monitoring and analyzing daily symptom data, using both customized and standard PROs, has the potential to detect meaningful variation in symptom patterns, which can inform clinical decision-making or can facilitate conducting formal n-of-1 trials to further improve outcomes.

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eGEMs
Generating Evidence & Methods
to improve patient outcomes

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ABSTRACT

Introduction: Improving symptoms for patients with chronic illness is difficult due to poor recall and imprecise assessments of therapeutic response to inform treatment decisions. Daily variation in symptoms may obscure subtle improvement or lead to erroneous associations between symptom changes and alteration in medication or dietary regimens. This may lead to mistaken impressions of treatment efficacy (or inefficacy). Mobile health technologies that collect daily patient reported outcome (PRO) data have the potential to improve care by providing more detailed information for clinical decision-making in practice and may facilitate conducting single subject (n-of-1) trials.

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Introduction

Clinicians rely on patients' recall of their symptoms to adjust therapies and monitor responses, but the accuracy of patients' recall, particularly between clinic visits, is poor.[1] Patients recall recent symptoms more clearly than earlier, more remote symptoms, and more severe symptoms more clearly than mild symptoms.[2] Recognition of day-to-day variability in symptoms is also important for revealing important trends (improvement or worsening), but measuring such variability is difficult without close tracking of symptoms. Daily symptom variation is important because it may obscure the ability to detect signal (of improvement) from the noise (of random daily variation). Taken together, these challenges highlight the problems of symptom recall as the basis for making treatment recommendations, and either altering or escalating therapeutic interventions.[1,3]

Inflammatory bowel disease (IBD) causes chronic inflammation of the gastrointestinal tract, often resulting in severe symptoms. Despite optimal treatment, over 40 percent of patients continue to have symptoms that reduce their quality of life (QOL) such as persistent fatigue,[4,5] abdominal bloating, or fecal urgency.[6] Careful attention to a patient's symptomatic response to therapies using paper symptom logs is often inadequate or too cumbersome to provide sufficient evidence to guide treatment.[7] Improved methods are needed to ease symptom data collection and to facilitate conducting individual (n-of-1) therapeutic trials to improve symptoms and QOL.

Currently, 78 percent of teenage patients carry mobile devices capable of easily collecting and transmitting symptom data on a daily basis.[8] There is growing interest among patients (e.g., the "quantified self" community)[5,9,10] and physicians[11-15] in leveraging mobile technologies for improving patient outcomes.

According to a recent study by the Pew Research Center, over 40 percent of Americans who have a chronic health condition track their symptoms or health indicators such as headaches, blood sugar, blood pressure, etc.[5] But there is little evidence of the impact that frequent monitoring of self-reported data has on patient QOL or other health outcomes.[16]

While some limited progress has been made in integrating formalized patient-reported outcome (PRO) measures into clinical practice, these early efforts provide little evidence to guide the effective integration of PROs into real-world patient care setting.[16,17] Efforts at implementation are made more difficult by technical limitations (e.g., many care centers lack electronic tools to collect PROs, and completing repeated online surveys are not sustainable for most patients over time). Most published studies utilizing PROs in real-world patient care settings have demonstrated that the PROs have little or no impact on patient outcomes.[16] This may be due to a lack of validated tools to monitor patient symptoms or QOL reliably and prospectively in real time.[16]

Standardized QOL indicators for general assessment have not been studied widely for assessing patients in clinical practice. The Patient-Reported Outcomes Measurement Information System (PROMIS) survey instruments may be appropriate for this purpose, but PROMIS surveys have been validated only in population studies.[18,19] PROMIS tools have not been studied in individual patients or over short periods, and have not been broadly incorporated into routine patient care.

As part of an ongoing study exploring innovations in health care, we evaluated a prototype tool to determine if continuous symptom tracking aids in improving patients' and physicians' understanding of symptom patterns and if tracking can help patients and physicians work together to better target

treatments.[20,21] We also attempted to determine if PROMIS measures can be used in individual patients to track QOL over short periods, as opposed to populations of patients for which they were developed. We report, here, important learning from a small number of patients who completed prototype testing of this tool.

Materials and Methods

This study was conducted as part of the ongoing work of the Collaborative Chronic Care Network (C3N) project that is developing innovations to facilitate more continuous, collaborative relationships between patients and families with chronic illness and their physicians. The tools described here emerged from a structured design process involving patients, families, clinicians, and innovators that entails testing novel concepts in small-scale prototypes and larger pilot studies prior to deployment.[21] This manuscript describes the prototype testing of the novel concept. We took advantage of the collaborative network of patients, physicians, and researchers who participate in the ImproveCareNow Network to engage participants.[21]

We recruited adolescent patients with IBD who were engaged in their care and were interested in further improving their symptoms and QOL. Each patient (along with a parent if under 18 years old) met with his or her pediatric gastroenterologist and a researcher at the time of study enrollment to discuss the patient's medical history and to plan the details of the patient's individual study. Patients identified their most troubling symptoms that they wished to track and improve. The researcher and patient agreed upon a means of assessing symptoms by selecting from a list of preassembled measures. They were allowed to create their own symptom measure if none was available to fit their needs. We used a daily, automated text-message service to prompt patients to submit symptom scores via text message. We did not limit the number of questions that could be asked per day, but suggested each patient select no more than three to four. At study enrollment, the patient determined what time of day the messages were to be delivered. The questions were delivered each day at this prespecified time, and did not vary from day to day or with responses to prior questions.

We also used the PROMIS survey instruments to measure fatigue and pain interference across all patients.[22,23] These short surveys have been extensively validated in a wide range of chronic medical conditions and children.[18,19,24] The PROMIS surveys query information on specific outcomes for the preceding seven days. The results were converted to T-scores, where a score of 50 represents the mean score of the general pediatric calibration sample (standard deviation 10).[25] T-scores greater than 50 represent worse fatigue or pain interference. We deployed the appropriate PROMIS survey weekly via a web-based interface to each patient. We compared individual patients' PROMIS survey results with their average symptom scores from the same period.

We used individual-level, statistical process control methods for time-sequence data to monitor the patient's daily symptom data and weekly PROMIS survey data as they were collected over time.[26] We established each patient's individual baseline pattern of symptom variation, or "common cause variation." Symptom data points that fell outside three sigma control limits were noted as "special cause variation," or variation outside stable baseline variability.[26,27] These data, along with calculated control limits, were graphed on a Microsoft Excel spreadsheet for visual representation of data for patient and physician review. For prototype testing, we used a heavily

manual process—including creating Microsoft Excel graphs by hand and sharing data with patients and providers via email—that was possible for only a small number of patients. The purpose of this type of manual prototype was to inform more robust pilot testing facilitated by automated tools being developed by the research team.

Patients were given access to their own data and were provided with graphical displays of their data at each meeting. Physicians and patients jointly reviewed the data on a regular basis in prearranged consultations (in person or by phone, according to each family and physician's preferences). These meetings were opportunities for patients and physicians to learn from patterns of data and to make treatment decisions if they felt this was appropriate. This study did not restrict or guide treatments or any physician recommendations.

This study and the consent procedures were approved by the institutional review boards of both the University of Michigan Health System (HUM00051651) and Cincinnati Children's Hospital Medical Center (2010-3380). All adult participants provided written informed consent to participate in this study. Written informed consent was obtained from parents of minors and written assent from minors themselves for participation in this study.

Results

Eight patients were recruited for prototype testing of daily data collection. Patients tracked symptoms in order to monitor for changes in disease status, to generate hypotheses as to what makes their symptoms better or worse, or as part of a specific n-of-1 study. We present three patients who tracked their symptoms, prior to implementation of n-of-1 testing, and for whom symptom patterns led to important revelations.

Patient 1

A 19 year old with longstanding indeterminate colitis underwent proctocolectomy with ileal pouch anal anastomosis at the age of 10 years. She had frequent nocturnal stools that woke her up to six times per night and caused fatigue contributing to her poor QOL. She had been treated every eight weeks with long-term infliximab therapy by intravenous infusion.

In collaboration with her physician, she decided to track her total number of daily stools and the number of stools waking her from sleep each night. She historically awoke to have a bowel movement from three to six times per night on average. During her baseline observation period, there was a span of nine consecutive nights with fewer episodes of nocturnal stools (Fig. 1). However, she failed to recognize this nine-night interval of improved nighttime waking for stools despite the shift in symptoms that qualified as special cause variation.[26] This shift occurred immediately following an infusion of infliximab, which led her treating physician to conclude that infliximab may have played a role in her transiently improved stool pattern. However, this postinfusion improvement was not reproduced after her subsequent four infliximab infusions, during which time her daily symptoms were continuing to be recorded. She did experience reproducible improvement in her stools with repeated courses of antibiotics that were prescribed for non-IBD related symptoms by her primary care physician (previously illustrated in Kaplan et al.[20]). During those times when she experienced decreased nighttime bowel movements, she also felt less fatigued (Fig. 2). Upon reviewing these data she confirmed that she felt less fatigued and more energetic. She attributed this to improved sleep with less frequent nighttime waking for bowel movements. The patient and her physician both felt that the graphical representation of her symptom data aided in their visualization and understanding of the treatment effects.

Figure 1. Statistical Process Control Chart of Number of Stools Per Night
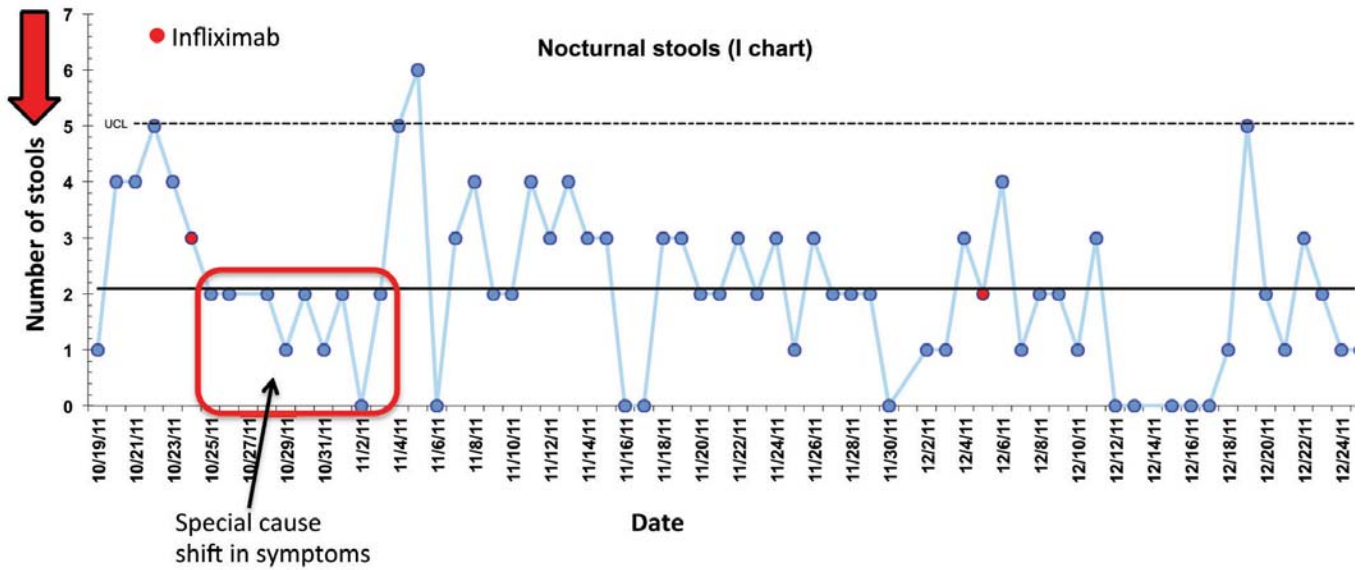
Notes: Number of nocturnal stools recorded each morning. Note shift of nine nights with fewer stools than the median number (red oval) representing special cause variation. Red dots indicate infliximab infusions. The red arrow represents direction of the patient's desired improvement (fewer nocturnal stools). UCL = upper control limit. Solid line = median line.

Figure 2. Weekly Fatigue T-Score Plotted Over Time
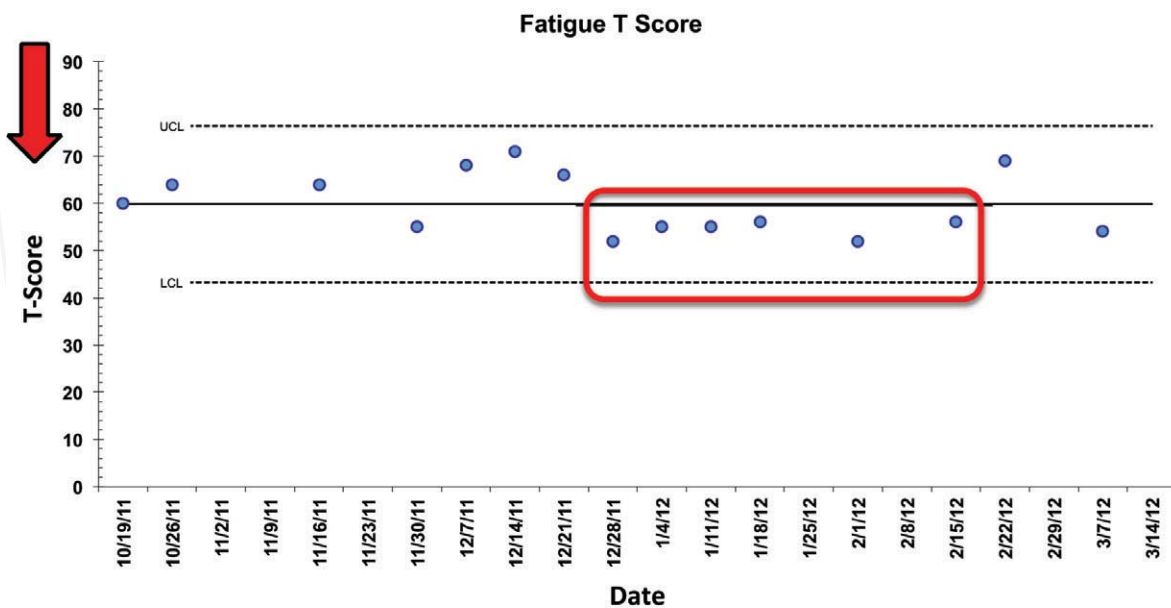
Notes: Weekly PROMIS Fatigue score. By using the T-score, we reference the patient's score against the general population. The mean Patient-Reported Outcome Measurement Information System (PROMIS) fatigue score for the general population is 50. Higher scores represent greater fatigue. A special cause occurred (red oval) as a shift of six consecutive data points below the mean, representing a significant improvement in her fatigue. The red arrow represents the direction of the patient's desired improvement (less fatigue).

Patient 2

An 11 year old with Crohn's colitis had diarrhea and fecal urgency. Both the patient's mother and her physician were interested in trying different probiotics to determine if one would be more effective than others for managing her fecal urgency. Over the course of repeated periods on and off different probiotics,[20] her fecal urgency gradually improved (Fig. 3, green dashed ovals), though there was no discernable difference during periods with or without the use of probiotics.[20] The reduction in fecal urgency over time was reflected in improved PROMIS Fatigue score (Fig. 3, green dashed ovals).

After three months of monitoring, the patient developed an exacerbation of the disease (Fig. 3, red solid ovals), with diarrhea and increased fecal urgency. This was associated with simultaneous worsening PROMIS Fatigue scores (Fig. 3, red solid ovals).

Patient 3

A 16-year-old male with Crohn's disease was a competitive runner. His primary symptom related to Crohn's disease was frequent loose stools. However, the most important issue that interested him was improving his running pace. After he was diagnosed

**Figure 3. Daily Urgent Stools and Weekly Fatigue Score**
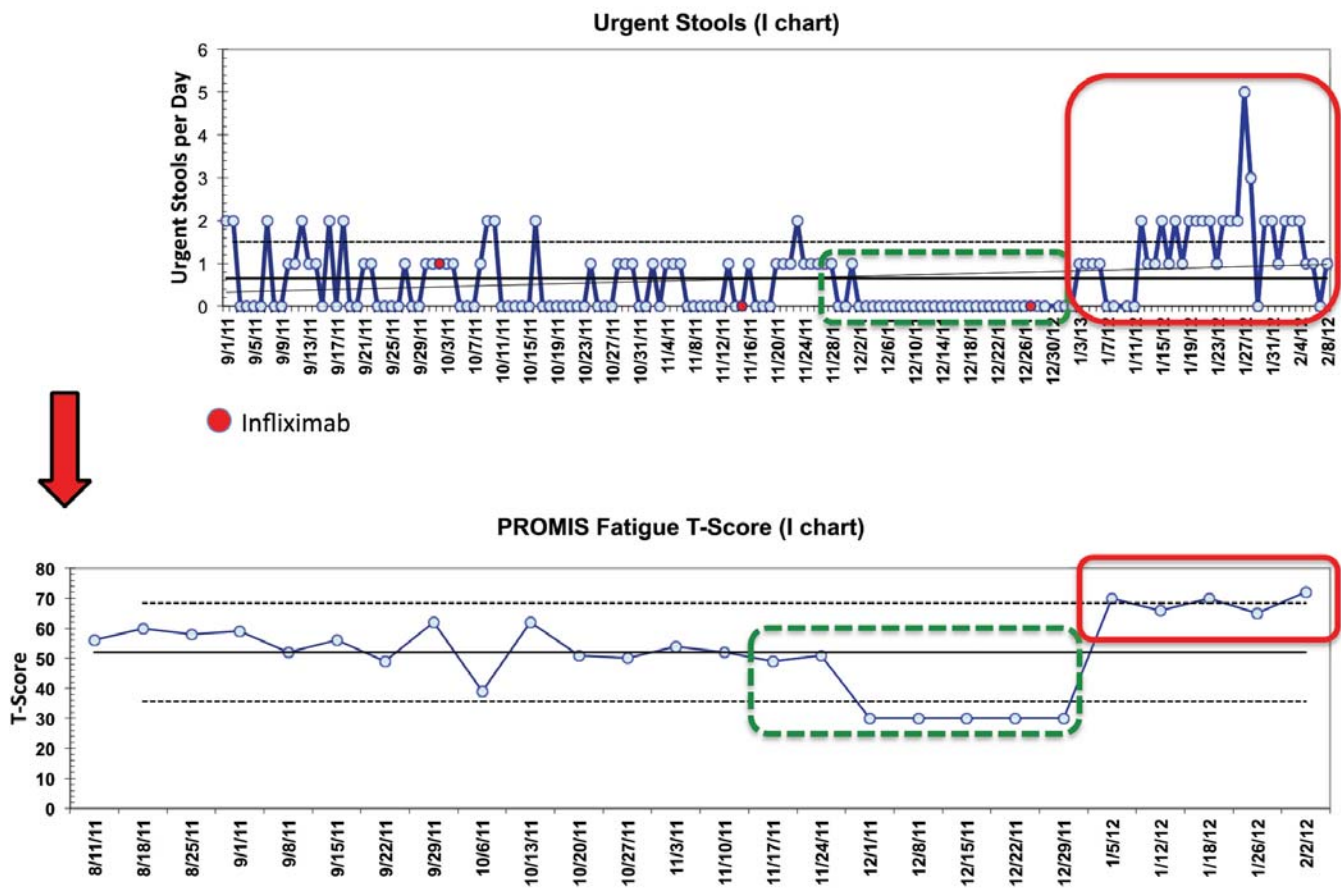
Notes: Daily urgent stools (upper chart) and weekly PROMIS Fatigue T-score (lower chart) over the same periods. Green dashed ovals represent area of improvement and red solid ovals represent area of worsening stools and fatigue. The red arrow represents the direction of the patient's desired improvement. Note the concomitant improvement, then worsening, in urgent stools and fatigue.

with Crohn's disease, his running pace decreased and had not returned to his pre-illness baseline, and he was interested in assessing his running potential after starting treatment with biological therapy. At his enrollment in this study, his baseline PROMIS fatigue T-score was 35.7, indicating that he was less fatigued than the average healthy individual. He received his first infliximab infusion on May 25, 2011, with induction regimen completed by July 6, 2011, (usually consisting of three infusions spread over six weeks). His number of daily bowel movements decreased within four days of completing the induction regimen, and attained a steady state along with a special cause (Fig. 4, oval). He also had a concomitant special cause in his stooling pattern. His running pace also improved significantly from a mean 8.4 to 7.6 minutes/mile, indicated by a special cause shift as well. This patient had identified his running pace as his most important symptom. This modest improvement in his running pace represented an important improvement in his QOL.

Figure 4. Concomitant Improvement in Stools, Running Time, and Fatigue
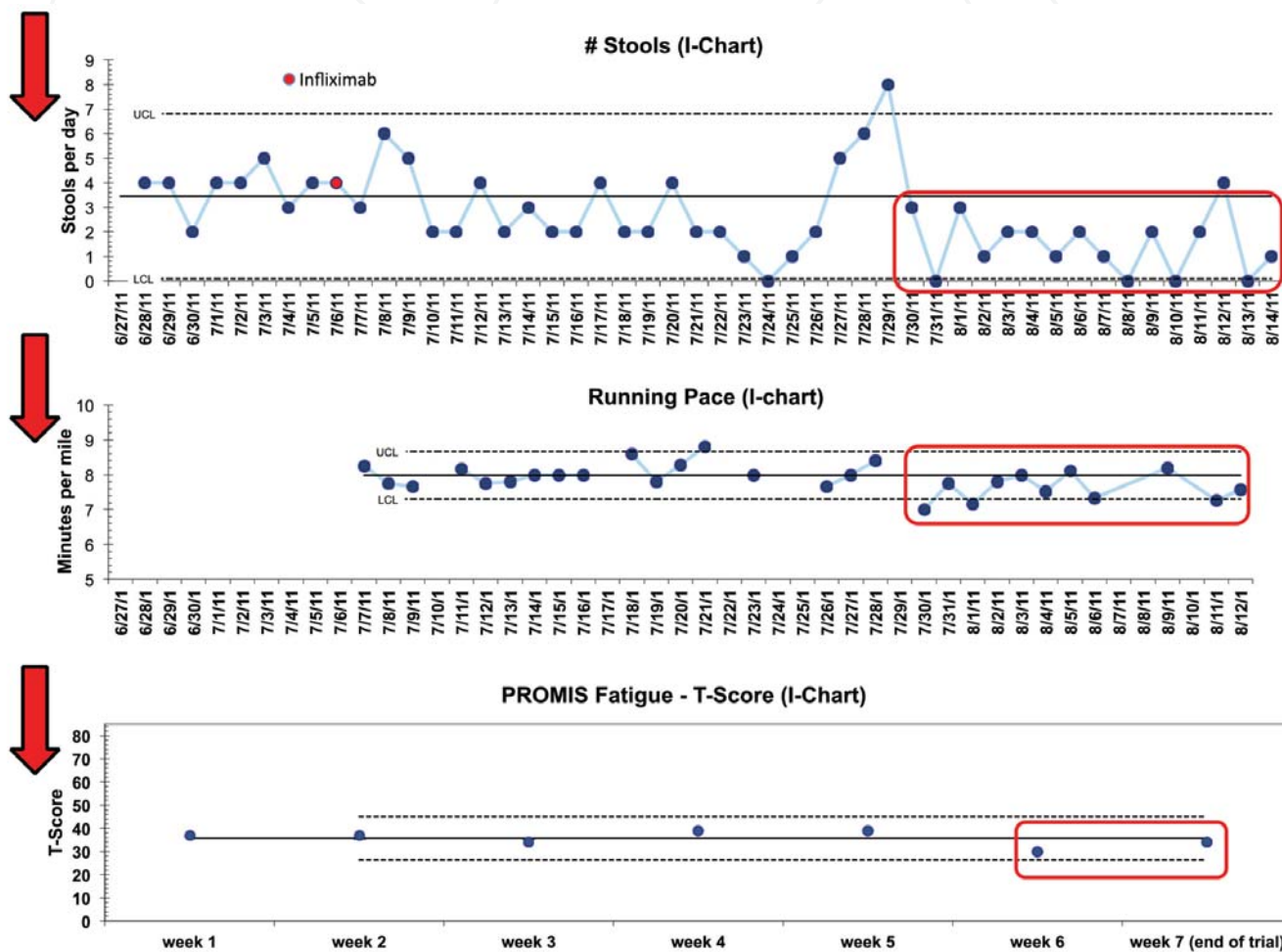
Notes: Daily number of stools (upper chart), running pace (middle chart), and PROMIS Fatigue T-score (lower chart) for the same patient over the same period. Special cause improvement is denoted by ovals. The red arrow represents the direction of the patient's desired improvement. Improvement in running pace coincides with improvement with PROMIS fatigue score. PROMIS measures represent the preceding seven days.

Discussion

We found that monitoring daily symptom data detects the daily variation in patients' symptoms. Establishing a patient's background pattern of symptom variation can serve as a baseline from which to make subsequent comparisons when making changes in diet or medications. Significant (special cause) deviations in symptoms from the baseline pattern are also associated with variation in PROMIS instrument assessments. Our data from these patients suggest that the PROMIS measures of fatigue and pain, in particular, are responsive to changes in patient symptoms over short periods and on the individual level. These findings lend face validity to daily remote monitoring of patient symptoms, and pave the way for broader use of the PROMIS instruments for use in patient-centered improvement research. Using standard PROMIS instruments, in addition to more customized patient symptoms, may enable greater learning across patients because measures are well validated and standardized in pediatric populations.

We also found that knowledge about daily symptom variation and PROMIS assessments of key outcomes may be clinically relevant. Improving patients' and physicians' understanding of symptom patterns for the purpose of tailoring treatments to the patients' needs is essential for understanding response to attempted therapies. It is also essential to measure symptoms that are important to patients in order to help patients achieve good QOL even if other traditional measures show minimal symptoms.

This work is important and expands upon the very few previous studies of the impact of daily monitoring on outcomes for chronic diseases.[16] The most widely documented evidence is for asthma in which daily monitoring is associated with improved asthma control.[28] There is also evidence that daily monitoring via mobile phone of adults with heart failure results in improved QOL, improved self-care,[12] and—in one study—decreased mortality.[29] Similarly, in insulin-dependent diabetes mellitus, daily monitoring leads to improved glucose control, more symptom-free days, and decreased perceived disease-related anxiety.[13] Despite limited evidence of benefit from mobile symptom tracking in some studies, the majority of studies do not demonstrate a measurable improvement in patient outcomes.[16] One significant issue that has not previously been addressed is the day-to-day variability of patient symptoms. As we've seen in our study, there is substantial daily variability in symptoms, which may obscure the detection of improvements, when they occur. The work reported here builds on previous studies by developing tools that enable daily symptom tracking to better understand and detect changes in patient symptoms. Understanding the nuances of symptom variation—at baseline, and in response to therapeutic challenges—is critical for targeting therapies for improvement and for determining the individual efficacy of therapeutic changes. Daily symptom data collection eliminates the problem of recall and recency bias. Comparing daily symptom data with weekly PROMIS surveys provides internal consistency of the PRO measures collected for each patient. Together, the collection of these PRO data from patients facilitates real-time feedback to patients and their physicians about the effectiveness of therapies. These methods offer substantial improvements over routine clinical practice and over prior mobile health (mHealth) studies lacking such feedback.

Our prototype study has important limitations. First, we have described our experience with only three individual patients. These were highly engaged patients who volunteered for this study (as is the case in many studies). It is possible that daily or weekly symptom measurement may not be feasible in less-engaged patients. However since 75

percent of young people have mobile phones and 88 percent of them send and respond to numerous text messages daily (typical 14 to17 year olds send and receive 100 text messages per day),[30] it remains to be determined how important engagement with care is to these assessments. There is also some concern that daily monitoring may lead to increased attention to symptoms and worsening of perceived physical health.[31] However others have demonstrated that patients with chronic constipation who monitored daily symptoms had no worse outcomes than those monitored weekly in a prospective randomized clinical trial.[32] Others found improved outcomes with daily monitoring for irritable bowel syndrome, asthma, and heart failure.[12,13,33] It will be important to determine if certain patients may benefit more from these methods and if others should avoid these methods to minimize attention to symptoms.

Note that a patient with longstanding daily symptoms may have a significant improvement in symptoms without being aware of such changes (as was seen with patient 1). Conversely, perceived improvement may not actually represent real improvement, but may be misattributed background variation—which, when graphically evaluated, represents common cause variation (as seen with patient 2). There may also be temporal associations between improvements in symptoms and other factors. This was seen with the initial improvement in nocturnal stools following infliximab infusion (patient 1), which was not reproduced after subsequent infusions. It is tempting to infer a causal relationship between two events because of their close proximity in timing, even if the association is coincidental. The accuracy of the interpretation of associations has direct implications for how most physicians and patients routinely test therapies by ad hoc trial and error. Casual symptom monitoring can easily lead to mistaken impressions of treatment efficacy

or inefficacy. It is only with careful monitoring of outcomes, and with replication (through experimentation), that we can distinguish between causal relationships or associations.[34,35]

This study also highlights the importance of tracking the symptoms that patients feel are most important to them. The example of patient 3, whose gastrointestinal symptoms and fatigue were not severe, illustrates this additional benefit of our individualized, patient-centered approach. By closely monitoring the symptom that was most important to the patient (his running pace), he and his physician were able to determine when a significant improvement occurred in the outcome that was of greatest importance to the patient.

Our findings in this early study highlight the difficulty in assessing treatment efficacy based on casual assessment of symptom relief for an individual patient. These findings are of great importance to improving the physician's ability to adequately understand their patient's disease activity and the symptoms contributing to QOL for the purpose of tailoring treatments to the needs of the patient. This applies when new therapies are initiated and also during changing, modifying, weaning off, or withdrawing therapies (as could be the case with steroid weaning for IBD treatment). These new methods offer the potential to support more collaborative decision-making and to improve clinicians' and patients' abilities to identify the right treatments both through informal learning and planned experimentation with individual patient therapeutic (n-of-1) trials.

These findings should also serve as a call to action. To improve patient symptoms we must have a clear understanding of the effects of an intervention (medical, dietary, behavioral, etc.) on the patient's symptoms. Only with a clear understanding of symptom variation, and an ability to discern a

meaningful change in symptom pattern from the background variation, can we fully understand the effects of therapies on symptoms and know with certainty whether or not a therapy improves symptoms and QOL. The new methods described here are the building blocks for transforming the doctor-patient relationship to become more collaborative and to provide improved evidence for understanding individual patient treatment efficacy for better treatment individualization.

We are continuing to develop the methods that were prototyped in this study. Based on the success of daily tracking using customized and standardized measures (PROMIS measures), and the utility of graphical display of symptoms using statistical process control, we are developing more advanced technology (Web platform and mobile app) to enable tracking and real-time visualization of this data for the patient and provider. We are also examining ways to better support patients and providers in using PRO data to enable formal n-of-1 studies of pediatric patients with IBD. N-of-1 studies are well established as a method to improve patient symptoms. However, until now these methods have been limited in their scope of use. We are currently expanding these methods that we have described here to develop the means of conducting n-of-1 studies concurrently with larger numbers of patients who may have different complaints and different treatments. These methods have the potential to benefit patients broadly and to improve patient-physician engagement and communication across a wide range of clinical settings.

Conclusion

Clinicians and patients should consider the use of mobile daily symptom data collection to improve care and outcomes. Daily symptom tracking can facilitate improved informal learning as well as rigorous n-of-1 experimental studies to objectively assess individual treatment efficacy and individualize patient care.[34,35] Prototype studies have provided proof of concept so that these methods can be further expanded to enable more robust learning designed to improve symptoms and QOL for pediatric patients with IBD and others with differing chronic health conditions.

Acknowledgements

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