Disease Monitoring in Inflammatory Bowel Disease

Gastroenterology 2022;■:1–20

Disease Monitoring in Inflammatory Bowel Disease: Evolving Principles and Possibilities

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Inflammatory bowel disease is a progressive and debilitating condition. Early and effective treatment using a treat-to-target approach is key to improving patient outcomes. Therefore, proactive monitoring is essential to ensure that treatment strategies are working and targets are being met. In this review we discuss the current monitoring tools available to us and how they can be used. We also discuss the importance of monitoring during key phases of the disease and propose an optimum treat-to-target monitoring strategy for Crohn's disease and ulcerative colitis. Regarding the advent of new technology, we discuss how this may improve our monitoring capabilities and how we envisage future monitoring strategies of inflammatory bowel diseases.

Keywords: IBD; Disease Monitoring; Biomarkers.

Ulcerative colitis (UC) and Crohn's disease (CD) are progressive in nature and, without timely and effective treatment, can result in irreversible long-term complications.[1] Historic treatment strategies have focused on the resolution of symptoms, but there is a clear disconnect between symptoms and active mucosal inflammation in inflammatory bowel disease (IBD).[2–4] In an attempt to modify the natural history of the disease and improve long-term outcomes, the concept of treat to target (T2T) has been adopted.[5] Treatment strategies now aim to treat beyond symptoms to normalization of objective markers of inflammation with the goal of mucosal healing and holistic remission. Time-dependent objective treatment targets have been set out in the updated Selecting Therapeutic Targets in IBD (STRIDE-II) recommendations (Figure 1).[6] In addition, resolution of inflammation early in the disease course is key to mitigating the risk of disease progression and improving prognosis.[7–9]

CD and UC are highly heterogeneous conditions. Some patients have aggressive disease, cycling through numerous therapies, while approximately one-third have a benign disease course.[10–13] Our ability to predict treatment response or disease course is currently poor. Therefore, robust, and effective monitoring strategies become pivotal in the management of IBD. Appropriate monitoring allows us to establish when to make correct treatment choices and helps us to achieve and maintain remission. Effective monitoring also highlights when our treatment choices are not working, conferring the opportunity to change approach in a timely manner so that disease complications can be minimized. Therefore, who, when, and how often should we be monitoring to make the largest impact on our IBD patient population?

In this review we will provide an overview of the tools available for disease monitoring, with a focus on fecal calprotectin (FC). We will discuss the thresholds for decision making for our various monitoring modalities and the ideal monitoring strategies that we can adopt in the present time, and finally, we will look at evolving principles and possibilities for how future monitoring strategies could overcome the current limitations and unmet needs.

Abbreviations used in this paper: **AI, artificial intelligence; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CDEIS, Crohn's Disease Endoscopic Index of Severity; CE, capsule endoscopy; CGM, continuous glucose monitoring; CRP, C-reactive protein; FC, fecal calprotectin; IBD, inflammatory bowel disease; IUS, intestinal ultrasound; MaRIA, Magnetic Resonance Index of Activity; MRI, magnetic resonance imaging; POC, point of care; PRO, patient-reported outcome; QOL, quality of life; RCT, randomized controlled trial; SCCAI, Simple Clinical Colitis Activity Index; STRIDE, Selecting Therapeutic Targets in Inflammatory Bowel Disease; T2T, treat to target; TDM, therapeutic drug monitoring; UC, ulcerative colitis.**

0016-5085
https://doi.org/10.1053/j.gastro.2022.01.024

Current Monitoring Tools in IBD

The role of monitoring is to ensure that our patients feel well as well as to ensure resolution of mucosal inflammation, because that is what ultimately leads to disease complications. We have a variety of monitoring tools at our disposal to help diagnose, assess, and monitor our patients with IBD, including clinical symptoms and patient-reported outcomes (PROs), serum biomarkers, stool biomarkers, imaging modalities, and ileo-colonoscopy. To allow for objective and standardized assessment, numerous scoring systems have been developed, primarily for use in clinical trials, although a number of them have been simplified and can be adopted in routine clinical practice. The recent STRIDE-II recommendations have also proposed updated formal treatment targets for patients with IBD (Figure 1). In this section, we focus on the monitoring tools that are validated and available to us in our current day-to-day practice. We will also highlight some of the scoring systems available to us and discuss how they can be used to determine our treatment targets are being met.

Clinical Symptoms and Patient-Reported Outcomes

Clinical symptoms have been the foundation of our monitoring strategies for decades. In the REACT trial (Randomized Evaluation of an Algorithm for Crohn's Treatment; NCT01030809), early initiation of combined immunosuppression guided by a symptom-based algorithm resulted in a reduced risk of serious CD-related complications.[14] However, the main limitation is that symptoms correlate poorly with endoscopic inflammation, especially in CD.[2–4] Furthermore, the CALM study (Efficacy and Safety of Two Treatment Algorithms in Adults With Moderate to Severe Crohn's Disease; NCT01235689) demonstrated that a treatment strategy based on symptoms alone resulted in inferior rates of mucosal healing compared with one based on a composite strategy of symptom and biomarker assessment (C-reactive protein [CRP] and FC).[15] Nonetheless, monitoring of symptoms in conjunction with monitoring of inflammation is still essential. We need to ensure that our patients are feeling better, and if not, we need to be able to determine whether symptoms are due to active disease or driven by alternative pathology. For patients, resolution of symptoms also remains one of the most important therapeutic outcomes.[16] This is acknowledged by the STRIDE-II recommendations, which suggest clinical response and clinical remission as important short-term and intermediate treatment goals, respectively. Definitions of clinical response and remission are proposed and based on symptom scoring systems that include the Harvey-Bradshaw Index in CD and the partial Mayo Score in UC (Table 1). These scores can easily be performed in day-to-day clinical practice and used to monitor symptoms. Although several other scoring systems exist (eg, Crohn's Disease Activity Index [CDAI]), they can be cumbersome to perform, and their use is limited to clinical trials.

Recently, there has been a move toward assessing and monitoring patient-reported outcomes (PROs). This is on the basis that patients' perception of their disease and symptoms may differ greatly from that of the treating physician.[16] PROs have been shown to correlate with quality of life (QOL).[17] As such, the FDA has provided guidance on the development of PROs and necessitated their assessment as a primary outcome in randomized controlled trials (RCTs) investigating drug treatments in IBD.[18] In the interim, empirically derived clinical PRO scores have been developed with the most used being the PRO-2.[19] The STRIDE-II recommendations also include a definition of clinical response and remission based on the PRO-2 score for both CD and UC (Table 1).

C-Reactive Protein

The main serum biomarker used for monitoring inflammation in IBD is CRP. CRP is easy to measure and cheap to perform with a rapid turn-around.[20] Therefore regular measurements can be obtained during the disease course. CRP has a short half-life (19 hours) so will rise and decrease rapidly at onset and resolution of inflammation.[21] Its correlation with endoscopic activity in IBD is at best moderate, with CRP showing a high specificity but low

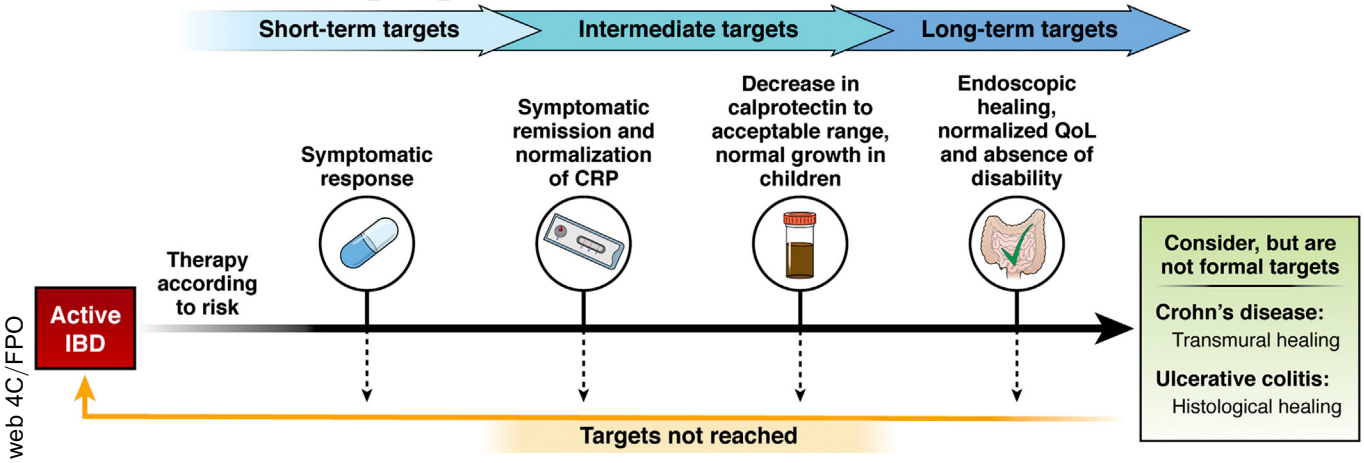

Figure 1. Treatment targets in Crohn's disease and ulcerative colitis per STRIDE-II recommendations.[6]

Table 1. Comparison of various monitoring and scoring tools with accepted definitions of outcome measures in CD and UC (based on STRIDE-II recommendations)[6]

	Outcome measure	Accepted definition	Limitations
Clinical symptoms and PROs			
Harvey-Bradshaw Index[a]	Clinical response Clinical remission	Decrease ≥3 points ≤4 points	• Poor sensitivity and specificity for endoscopic inflammation related to IBD • No assessment of disease extent • No assessment of complications associated with IBD
SCCAI[b]	Clinical response Clinical remission	Decrease >30% ≤2 points	
Partial Mayo Score[b]	Clinical response Clinical remission	Decrease >2 points <3 & no sub score >1	
PRO-2	Clinical response Clinical remission	1) Decrease ≥50% in abdominal pain and stool frequency score[a] 2) Decrease ≥50% in rectal bleeding and stool frequency score[b] 1) Abdominal pain score ≤1 and stool frequency score ≤3[a] 2) Rectal bleeding score 0 and stool frequency score 0[b]	
Serum biomarkers			
CRP	CRP response Normalization of CRP	Decrease >50% <5 mg/L or less than upper limit of normal	• Poor sensitivity and specificity for endoscopic inflammation related to IBD • No assessment of disease extent • No assessment of complications associated with IBD •
Fecal biomarkers			
FC	Reduction in FC to acceptable range	<250 μg/g (post-operative CD <150 μg/g)[a]	• Inter-/intra-individual variability • Therapeutic thresholds not clearly established • Poor specificity for endoscopic inflammation related to IBD • No assessment of disease extent • No assessment of complications associated with IBD • Poor acceptability of performing stool test
Cross-sectional imaging/CE			
MRE[a]—MaRIA score	Mucosal healing	<7	• Inability to perform biopsies • Lack of centralized reading increases inter-/intra-individual variability of scoring
IUS[a]—Simple Sonographic Score/ Simple Ultrasound Score–CD	Absence of inflammation	0 points	• Limited validation in clinical trial or real-world settings • Lack of access • Inability to perform biopsies

Table 1. Continued

Outcome measure		Accepted definition	Limitations
CE[b]—Lewis Score	Mucosal healing	<135 points	• Risk of capsule retention • Poor tolerability of bowel preparation • Lack of access • Inability to perform biopsies • Limited ability to assess disease complications • Lack of centralized reading increases inter-/intra individual variability of scoring
Ileo-colonoscopy			
CDEIS[a]	Endoscopic response	Decrease >50%	• Risk of complications associated with procedure (eg, perforation) • Poor tolerability of bowel preparation • Costly procedure • Unable to assess bowel proximal to TI • Lack of centralized reading increases inter-/intra-individual variability of scoring
	Endoscopic healing	No ulcers and score <3	
SES-CD[a]	Endoscopic response	Decrease >50%	
	Endoscopic healing	Ulcer sub-scores = 0	
UCEIS[b]	Endoscopic response	Decrease ≤2 points	
	Endoscopic healing	0 points	
Mayo Endoscopic Sub-score[b]	Endoscopic response	Decrease ≤1point	
	Endoscopic healing	0 points	
Quality of life and disability			
IBDQ	Clinical response	Increase ≥16 points	• Poor correlation with objective markers of endoscopic inflammation • Scores can be cumbersome to perform in clinical practice
	Clinical remission	≥170 points	
	Normalization	≥220 points	
SIBDQ	Clinical response	Increase ≥9 points	
IBD-DI	No disability	0–20 points	

CD, Crohn's disease; CDEIS, Crohn's Disease Endoscopic Index of Severity; CE, capsule endoscopy; CRP, C-reactive protein; FC, fecal calprotectin; IBD, inflammatory bowel disease; IBD-DI, Inflammatory Bowel Diseases Disability Index; IBDQ, Inflammatory Bowel Disease Questionnaire; IUS, intestinal ultrasound; MaRIA, Magnetic Resonance Index of Activity; MRE, magnetic resonance enterography; PRO, patient-Reported Outcomes; SCCAI, Simple Clinical Colitis Activity Index; SES-CD, Simple Endoscopic Score for Crohn's Disease; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; STRIDE, Selecting Therapeutic Targets in Inflammatory Bowel Disease; UC, ulcerative colitis; UCEIS, Ulcerative Colitis Endoscopic Index of Severity.

[a]Applicable to CD.

[b]Applicable to UC.

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sensitivity for endoscopically active disease (pooled specificity 0.92, 95% CI 0.72–0.96; pooled sensitivity 0.49, 95% CI 0.34–0.64).[22] In CD, low levels of CRP are associated with a reduced risk of clinical relapse.[23–25] CRP can also predict treatment response. In the post hoc analysis of the ACCENT-1 trial (A Safety and Efficacy Study of Infliximab (Remicade) in Patients With Moderate to Severe Active Crohn's Disease; NCT00207662), patients with CRP levels <5 mg/dL at week 14 were more likely to maintain response compared with patients with levels >5 mg/dL (56.6% vs 37.2%).[26] CRP has also been shown to predict risk of relapse following treatment discontinuation.[27] Compared with those with CD, patients with UC have a more modest and sometimes absent CRP response, possibly attributed to the fact that UC is confined to the mucosal layer.[28] As such, data on the value of CRP in assessing disease course and outcome in UC are limited. It is also important to remember that more than 15% of patients may not mount a CRP response.[22] Other factors that may influence CRP response include age, sex, and genetic polymorphisms.[29,30] Currently, STRIDE-II recommends that normalization of CRP (to values under the upper limit of normal or <5 mg/dL) should be considered as a mandatory short- to medium-term goal, but it is an insufficient long-term goal.

Fecal Calprotectin

Fecal calprotectin is one of the most well characterized and commonly used noninvasive biomarkers in IBD. Calprotectin is a cytoplasmic protein predominantly released from neutrophils that have been recruited to the bowel.[31,32] Levels of FC are stable in the stool for 72 hours and can be measured with the use of quantitative enzyme-linked immunosorbent assays.[32] FC can accurately distinguish between active and quiescent endoscopic disease, in both UC and CD , making it an excellent surrogate marker of mucosal inflammation.[22] It can also be used as a tool to help monitor response to treatment. FC is superior to other biomarkers at predicting mucosal inflammation in IBD (FC area under the receiver operating characteristic curve [AUC] 0.89 [95% confidence interval (CI) 0.86–0.91] vs CRP AUC 0.72 [95% CI 0.68–0.76]).[22] This, in combination with its ease of use and relatively low cost, makes it one of the best tools available to us for monitoring IBD (Box 1).[33]

The CALM study was the first prospective randomized controlled trial to demonstrate that a T2T strategy based on biomarkers including FC (dose escalation based on FC ≥250 μg/g, CRP ≥5 mg/L, CDAI ≥150, or prednisolone use in the previous week) resulted in superior mucosal healing rates at 1 year compared with a treatment strategy based on clinical symptoms alone (CDAI decrease of <100 points compared with baseline or CDAI ≥200, or prednisone use in the previous week).[15] A FC value ≥250 μg/g was also the main failure criterion driving treatment optimization in the tight control arm.[15,34] These data have established the role of longitudinal monitoring of FC but also its use as a formal treatment target in IBD. Combining FC with serum biomarkers has been shown to increase accuracy of detecting active disease as well as its predictive performance.[35] In the post hoc analysis of the CALM study, CRP <5 mg/dL in combination with FC <250 μg/g at week 48 was the best predictor for achieving the primary end point of mucosal healing (Crohn's Disease Endoscopic Index of Severity [CDEIS] <4 and absence of deep ulcers).[15,34]

A widely accepted and well studied cutoff for the presence of active inflammation in both UC and CD is 250 μg/g (Table 1).[22,36] However, some studies have shown a weaker correlation between FC and active endoscopic disease in isolated ileal CD compared with colonic disease.[37–39] Similarly, our group has previously shown that an FC level of >145 μg/g predicted severe disease on magnetic resonance imaging (MRI) with 69.3% (95% CI 57.6%–79.5%) sensitivity and 71.4% (95% CI 53.7%–85.4%) specificity.[40] Other scenarios where cutoffs may differ are in the context of post-operative CD. In the post hoc analysis of the POCER trial (Post-operative Crohn's Endoscopic Recurrence Study; NCT00989560), an FC value of >100 μg/g best predicted endoscopic recurrence after surgery.[34] More stringent cutoffs have also been associated with end points such as histologic and transmural healing.[41–45] Other caveats to the use of FC include lack of specificity for IBD, intra-individual variability, lower patient acceptance compared with other serum biomarkers or imaging modalities, and assay variability.[46–53] In Box 2, we provide some "tips and tricks" on how to use FC in practice and help mitigate some of its limitations.

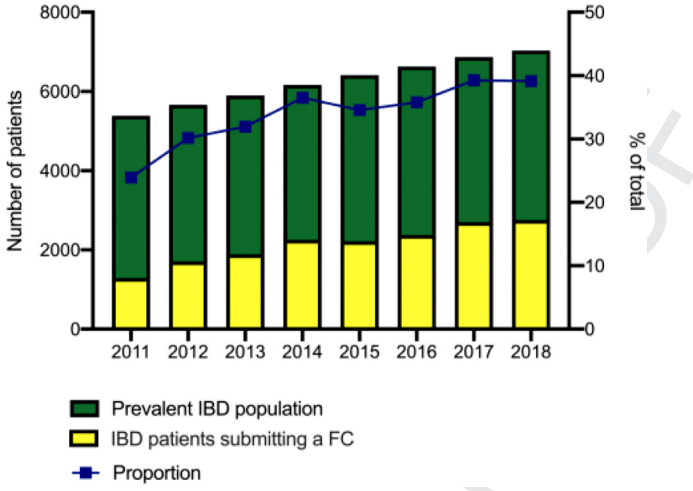
Cross-Sectional Imaging

Cross-sectional imaging plays a key role in the assessment and monitoring of IBD.[54] It can be used to assess for mucosal healing and transmural healing, and to monitor treatment response in patients.[55,56] Not only does imaging allow examination of the entire gastrointestinal tract, it can also help in evaluating disease complications (eg, progression to stricturing or penetrating disease) as well as patients with perianal disease.[54] Imaging is also noninvasive and thus an appealing test for patients. MRI is the most established and commonly used imaging modality in CD.[54] Alternatives include computed tomographic enterography although its use is somewhat precluded by the exposure to ionizing radiation.[57] In an attempt to help standardize MRI assessment in CD, scoring systems like the Magnetic Resonance Index of Activity (MaRIA) score, Clermont Index, and Nancy Score have been developed and correlate well with the presence of mucosal inflammation. However, these scoring systems are impractical for routine use (Table 1).[58,59] Although the STRIDE-II recommendations suggest using the MaRIA score to help define resolution of inflammation on MRI, a more simplified version of the score is now available (Table 1).

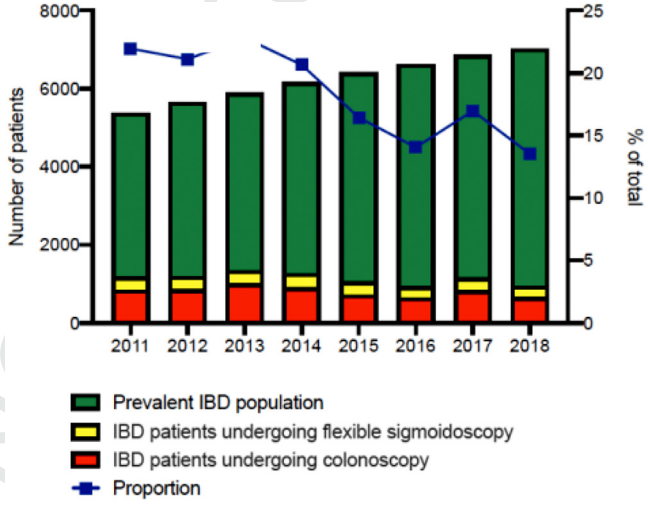
Some of the limitations of MRI are that it requires timely access to imaging facilities, its cost, and that requires interpretation by specialist radiologists.[54] Many of the scoring systems can be labor intensive to perform. Thus, its ability to be used as a regular test for monitoring is somewhat limited. Recently, the use of intestinal ultrasound (IUS)

Box 1. The Edinburgh Inflammatory Bowel Disease (IBD) Unit: Case Study of Fecal Calprotectin (FC) Monitoring

Figure A. Number and proportion of prevalent IBD population in Lothian, Edinburgh, submitting a stool sample for FC from 2011 to 2018. **Figure B.** Number and proportion of prevalent IBD population in Lothian, Edinburgh, undergoing flexible sigmoidoscopy or colonoscopy from 2011 to 2018.[162,163]



- The Edinburgh IBD Unit serves a prevalent IBD population of ~8000 patients in addition to 2500 nonprevalent patients.[5]
- FC has been used routinely in the Edinburgh IBD unit since 2009 using the same ELISA assay since 2005 (Bühlmann fCAL).[39]
- The cost of performing 1 assay at the unit is ~£20 (~$27 US)[100]
- To date >88,000 FC assays have been performed.[39]
- The proportion of the prevalent IBD patients in Edinburgh undergoing FC monitoring has increased over the years with a mirrored reduction in sigmoidoscopy and colonoscopy (Figures A and B).



- Patients are sent kits via post or given kits during hospital interactions. Written instructions are given to patients, and they are asked to return samples to the hospital directly or via their primary care practice.
- It is common practice for clinicians at the unit to request an FC assay at every patient interaction/contact.
- FC is requested routinely and proactively at baseline and subsequently every 2–3 months in the majority of patients.
- Further FC samples are requested at certain key points if timing falls outside the 2–3-month interval (eg, after treatment initiation, change, or cessation; disease flare; acquisition of therapeutic drug monitoring).
- Patients are empowered to ask about their FC results.

Box 2. Tips and Tricks for Fecal Calprotectin (FC) Monitoring

- Provide clear written instructions to patients on the importance of performing FC measurements and on the practicalities of doing so.
- FC should be performed alongside "gold standard" tests (eg, ileo-colonoscopy and small-bowel magnetic resonance imaging [SB-MRI]) at times of active disease as well as remission so that FC values can be calibrated to the specific patient and clinical scenario. One important example of this is in isolated small bowel Crohn's disease, where values may be lower.[37–40]
- To minimize intra-individual variability, patients can be advised to take the stool samples at similar times during the day when possible (eg, first stool of the morning) and to return samples to the hospital or laboratory as soon as possible. If there is any delay (>3 days) in returning samples, they can be stored in the refrigerator for up to 7 days.[47]
- Clinicians should be aware that FC values obtained from diluted (watery or mixed with urine) stool may be unreliable.[164]
- Treating clinicians should be aware of variability between assay results. In the absence of standardization, clinicians need to ensure that they are aware of their assay-specific cutoffs and aim to use the same assay throughout their practice.[52,53] In practice, if you encounter a value out of keeping with the clinical picture then consider repeating the test or further evaluation before initiating any treatment change.
- Action should be based on FC trends in an individual rather than isolated values, especially if the result is raised and out of keeping with clinical picture.
- Persistently elevated FC in the absence of inflammation on ileo-colonoscopy and/or SB-MRI warrants further investigation for the presence of proximal disease.
- FC values can be raised due to other pathologies, including gastrointestinal infections, diverticulitis, appendicitis, microscopic colitis, celiac disease, peptic ulcer disease, and colorectal neoplasia or medications, such as nonsteroidal antiinflammatory drugs.[50,51,165]

to assess disease activity has gained popularity.[60,61] Benefits of IUS are that it can be used as a point-of-care (POC) test to assess the gastrointestinal tract, thus aiding rapid decision making. [60,61] Validated scoring systems also are becoming available.[62,63] However, assessment of the proximal small bowel and rectum are limited, and access is restricted to specialist centers though uptake is increasing rapidly.

Ileo-colonoscopy

The criterion standard for assessing and monitoring IBD is macroscopic evaluation of the mucosa via ileo-colonoscopy.[64] Mucosal healing has been shown to reduce disease relapse, hospitalizations, and surgical rates.[8,65,66] As such it is one of the core treatment targets in IBD.[6] Several scoring systems have been developed to help stratify endoscopic severity. The most used are the CDEIS and Simple Endoscopic Score for Crohn's Disease in CD and the Ulcerative Colitis Endoscopic Index of Severity and Mayo Endoscopic Sub-score in UC (Table 1).[67–70] Recently, the concept of deep remission has also emerged, which necessitates resolution of symptoms in addition to mucosal healing. Patients in deep remission have been shown to have better outcomes compared with patients with only mucosal healing.[8] Other benefits of ileo-colonoscopy include the ability to obtain biopsies allowing for assessment of histologic activity. Although the benefit of mucosal healing is established, prospective studies using treatment algorithms based on ileo-colonoscopy are limited. The REACT2 study (NCT01698307) is currently underway and is looking to compare an enhanced top-down treatment algorithm based on ileo-colonoscopic findings vs a step-care algorithm based on symptoms alone.[71] The main drawbacks of ileo-colonoscopy include cost, it is an invasive test that carries risk, the need for sedation/general anesthetic, and it is poorly tolerated by patients.[64]

Capsule Endoscopy

Capsule endoscopy (CE) is an important noninvasive tool that can be used to accurately visualize the small bowel mucosa. Benefits of CE are that it is relatively safe and well tolerated, so repeated tests can be performed with limited impact.[72] In CD, it can be used to assess disease activity and mucosal healing as well as evaluate proximal areas of the small bowel not reached by conventional ileo-colonoscopy.[72–75] The latter is important because patients with jejunal disease are at an increased risk of a more complicated disease course.[76,77] CE is useful in assessing patients where there is a discrepancy between clinical/biochemical parameters and endoscopic/cross-sectional findings (eg, symptomatic with raised FC but normal ileo-colonoscopy/MRI).[72] It can also have a role in detecting post-surgical recurrence.[78] The main score used to determine small bowel activity based on CE is the Lewis Score (Table 1).[79] Limitations of CE include capsule retention,

Box 3. Baseline Assessment in Inflammatory Bowel Disease[166]

We recommend that all patients should have assessment of the following at baseline:

- Clinical symptom assessment: objective symptom scores (eg, Harvey-Bradshaw Index/Patient-Reported Outcomes—2).
- Serum assessment: C-reactive protein, albumin, platelets, hemoglobin, liver function tests, urea and electrolytes.
- Stool biomarker assessment: fecal calprotectin.
- Mucosal assessment: ileo-colonoscopy (capsule endoscopy or balloon enteroscopy in patients where ileo-colonoscopy is not adequate or feasible).
- Transmural assessment in Crohn's disease: small-bowel magnetic resonance imaging/computed tomographic enterography.
- Psycho-social assessment: objective quality of life, disability, depression/anxiety, and resilience scores (eg, Inflammatory Bowel Disease Questionnaire, Connor-Davidson Resilience Scale).
- Nutritional and dietary assessment: anthropometric measurements, hematinics, B_{12}/folate, micronutrient screen, vitamin D levels, food frequency questionnaires/food diaries.
- Immunization assessment: immunization status should be checked and vaccination considered for routinely administered vaccines as per national guidelines. In addition, patients should be considered for the following vaccines (ideally before initiation of immunosuppression): hepatitis B, pneumococcal, varicella zoster virus (VZV; no history of chickenpox/shingles and VZV serology negative), human papilloma virus, and influenza.
- Infection screening: blood-borne virus serology (hepatitis B/C, human immunodeficiency virus), Epstein-Barr virus serology, assessment for latent tuberculosis (interferon-γ release assay/chest X-ray).
- Pharmacogenetic biomarker assessment: if available, consider thiopurine s-methyltransferase and human leukocyte antigen genotyping to help guide therapeutic drug monitoring strategy.

If the above comprehensive assessment is not possible, then ensure that you have a baseline assessment using the modality you wish to monitor with so that you can detect change and/or resolution.

cost, limited access, and specialist training required for reporting.[80] The future of CE is promising, and colon and pan-enteric capsules (PillCam; Medtronic) are now available with data supporting their ability to assess mucosal inflammation in UC and CD, respectively.[81,82] In the advent of artificial intelligence (AI), machine learning algorithms are also being used to help automate reporting and improve diagnostic performance.[83]

QOL and Disability

It is well recognized that IBD can have a significant impact on one's physical and psychosocial wellbeing.[84] Low levels of QOL and high levels of disability are associated with increased indirect medical costs related to IBD.[85] QOL and disability measures correlate weakly with objective markers of disease activity, especially in CD.[86,87] Therefore, in our aim toward holistic remission, we must proactively monitor these parameters in conjunction with objective markers of disease. STRIDE-II recommendations include normalization of QOL and reduction in disability as formal long-term treatment targets in IBD.[6] Currently, the most widely used QOL scoring tool is the IBD Questionnaire, although this has been primarily developed for clinical trials. A shortened version is now available that can be used in clinical practice (Table 1). [88] The IBD Disability Index is the only validated disease-specific scoring system available for assessing and monitoring disability in IBD, but it is not suitable for routine use in clinical practice (Table 1).[89] Other important aspects to monitor include mood, sleep, fatigue, food-related QOL, and sexual function, but again, simple everyday scoring systems are lacking, so current monitoring is limited to more subjective assessments.[84]

The Ideal Monitoring Strategy for IBD in the T2T Era

The ideal monitoring strategy keeps people well and allows for detection of active disease and intervention before disease flare and occurrence of complications. Therefore, monitoring of IBD should be proactive, not reactive. The STRIDE-II recommendations not only set out updated treatment targets for IBD, but also give guidance on timing of when these treatment targets should be achieved (Figure 1).[6] If these targets are not being met, then a change in therapeutic approach is warranted. Here we discuss what an ideal monitoring strategy for IBD may look like in the era of T2T, using the tools that re readily available to us in the clinic today.

Importance of Baseline Assessment

In any monitoring strategy, a comprehensive baseline assessment is key. This not only allows for risk

stratification, aiding appropriate treatment choice, but also provides a benchmark to gauge whether your patient has objectively improved. It also allows for personalized calibration of biomarkers to your patient (eg, benchmarking FC at time of endoscopy/MRI to help clarify FC thresholds). Finally, it helps you to establish appropriate treatment targets for your patient. In Box 3 we highlight some key parameters that we feel should be assessed in all patients at baseline.

Turbo-Charged T2T in IBD

Following baseline assessment and initiation of treatment, patients should be monitored proactively regardless of whether or not they are symptomatically well. This provides the opportunity to intervene in a timely manner before symptomatic disease flare. As previously discussed, when monitoring mucosal inflammation, the lack of specificity and sensitivity of clinical symptoms and serum biomarkers such as CRP make them sub-optimal monitoring tools. Again, repeated endoscopic assessment is invasive, poorly tolerated, and carries risk, while imaging modalities like small-bowel MRI are costly, user dependent, and limited for timely access. In contrast, FC provides a reliable, quick, and cheap noninvasive method for objectively monitoring inflammation in IBD. Figure 1 depicts what we have termed a "Turbo T2T" strategy for IBD. The strategy presented is based on proactive monitoring predominantly using FC. This is similar to the protocol used in the CALM study.[15,34] Of note, in patients with perianal disease or penetrating complications, a more intensive monitoring regime is required with more use of cross-sectional and endoscopic modalities.

Histologic Healing

Particularly in UC, histologic healing has gained traction as studies have observed benefits regarding long-term remission and a reduced risk of surgery as well as colorectal cancer.[90–93] Scoring systems, such as the Nancy and Robarts Indexes, have been developed to try to assist with assessment of histologic activity in UC (Table 1) but are almost exclusively used in the context of clinical trials.[94] However, to date there is no consensus on the definition of histologic remission, and the number needed to treat to achieve improved outcomes over mucosal healing is likely very high. Current available therapies also have limited effectiveness in achieving the target of histologic healing, especially in CD. Studies, including the VERDICT trial (Determination of the Optimal Treatment Target in Ulcerative Colitis; NCT04259138), are currently underway to try to establish the role of histologic healing as a treatment target in IBD.[95] However, as per the STRIDE-II recommendations, further data is required before histologic healing is recognized as a formal treatment target in IBD (Figure 1).[6]

Transmural Healing

CD is a transmural disease, and many patients with endoscopically inactive disease may have ongoing transmural inflammation.[45] Studies have shown that patients with transmural healing may have better outcomes than those with endoscopic healing. Although transmural healing is not recognized as a formal treatment target in the STRIDE-II recommendations, it has gained traction as an adjunctive treatment target in CD.[6,96] Owing to the progressive nature of CD, scoring systems like the Lémann Index have been developed to help with assessment of the cumulative structural bowel damage in CD.[97]

Real-World Uptake and Limitations of a T2T Strategy

Despite clear target recommendations, implementing a tight T2T strategy in real-world practice can be challenging. It requires clinician buy-in, adherence, adequate resource, and implementation within a health care system. [98] In a large real-world cross-sectional study by Bryant et al, only one-third of UC patients achieved the proposed treatment targets, highlighting the disparity between remission rates seen in clinical trials vs the real world.[98] The greatest challenge to implementing T2T was due to clinician-dependent practice behaviors, such as lack of performing endoscopic evaluation. [98] Interestingly, clinician perception of achieving treatment targets in their own practice was overly optimistic compared with actual outcomes.[98]

Concerns have also been raised that intensive monitoring strategies entail significant cost implications. However, in a follow-up cost-analysis study of CALM, the authors were able to show that although total costs were higher in the tight control arm, these costs were offset by a reduction in hospitalizations and a gain in quality-adjusted life-years.[99] Great regional variation also exists regarding costs of tests; for example, in the UK, enzyme-linked immunosorbent analysis of FC is cheap and can be performed for approximately £20 per assay (about $27 US) whereas costs are much higher in the USA.[100,101]

Patient Acceptability and Perceived Utility of Monitoring

Studies have shown that there is a clear disconnect between perceptions of what physicians deem an acceptable test vs what our patients find acceptable. Buisson et al performed a national survey that demonstrated that although all of our monitoring tools (venipuncture, stool collection, IUS, flexible sigmoidoscopy, magnetic resonance enterography, wireless capsule endoscopy, and colonoscopy) are considered to be highly useful by patients with IBD, acceptability can vary greatly.[102] For example, in CD, they showed that venipuncture and IUS were the most acceptable tools for monitoring and recto-sigmoidoscopy was the least.[102] The primary reasons for this were the need for rectal enemas and abdominal discomfort related to the procedure.[102] In the UK, a study by Sellinger et al also showed that up to one-third of patients were not convinced of the benefit of a T2T approach.[103] Therefore, patient acceptability should be considered when setting out monitoring strategies for our patients, because repetitive invasive tests may have a significant negative impact on patients' QOL. Ultimately, clear communication, education on the importance of monitoring, and joint decision making

are paramount to empower our patients and to help keep adherence high.

Disease Monitoring Depending on the Phase of Disease

The reality is that many of the monitoring tools available to us are intrusive to patients, are expensive to perform, and carry a significant administrative burden on clinical teams. The results of monitoring tools require documentation and action taken in a timely manner. As such, not all patients can be monitored with the same intensity, nor is it appropriate. Although picking up inflammation and ensuring resolution at any time point during the disease course is key, strategies need to be pragmatic and consider increasing pressures on health care systems. Monitoring methods and intensity need to be flexible and fluid depending on the stage of the disease, and, importantly, remain responsive to any changes that may occur. However, there are some points during the disease where the data are overwhelmingly in favor of a higher monitoring intensity, notably during early disease and when assessing response to therapy (Figure 2).

Disease Monitoring in IBD to Prevent Disease Progression

In CD, the clock starts ticking at the time of diagnosis and probably well before. Left untreated, a significant proportion of patients will develop disease complications with time.[76,77,104] More than 50% of CD patients develop stricturing or penetrating complications by 5 years.[105] Data from a pooled analysis of several phase III RCTs of adalimumab showed that patients with early disease had higher response and remission rates compared with non-early patients.[106] In the recent SEAVUE study (Safety and Efficacy of Adalimumab Versus Ustekinumab for One Year; NCT03464136), where the median disease duration was 2.58 years, high mucosal healing rates were observed in both the ustekinumab and the adalimumab arms at week 52.[107] Furthermore, early "top down" treatment and use of T2T strategies have been shown to result in increased rates of mucosal healing and ultimately improved long-term outcomes.[15,108] Thus, the therapeutic window to try and alter the natural history of the disease is early in the disease course. As such, a key time to monitor patients is in the early phase of disease. In the long-term follow-up study of the CALM trial, where median disease duration was 0.2 years (interquartile range 0.1–0.8 years), patients who achieved deep remission at 1 year (defined as CDAI <150, CDEIS <4 with no deep ulcerations, and no steroids for 8 weeks) had a significantly lower risk of disease progression (composite of new perianal disease, progression of Montréal behavior classification, hospitalizations, or surgery) over a median of 3 years of follow-up.[8] Similarly, our group has shown that normalization of FC (<250 μg/g) within 12 months of diagnosis of CD is associated with a significantly lower risk of disease progression (composite of new perianal disease, progression of Montreal behavior classification, hospitalizations, or surgery).[7] These data support the notion that early resolution of inflammation is essential and that FC can be a surrogate for endoscopy and can help prognosticate our patients. Therefore, a proactive monitoring strategy (Figure 2) early on in the disease course, with timely intervention if targets are not being met is key. For the reasons previously discussed, we think that repeated ileo-colonoscopy and MRI for monitoring during this time is not practical. A better approach may be to use FC after diagnosis to objectively monitor response, remission, and maintenance of resolution of mucosal inflammation and performing ileo-colonoscopy and MRI at 1 year to ultimately confirm that your treatment targets are being achieved. In some cases, where the disease course is complicated (eg, perianal disease or stricturing disease) or there are signs of persistent inflammation, there is an argument to perform additional ileo-colonoscopy and MRI earlier (Figure 1). IUS may also prove to be a useful tool for early monitoring of disease, but the data on using IUS as a treatment target and whether it improves long term outcomes are still limited.

Despite UC being progressive, the impact of early disease control on the natural history of the disease is not as clear.[91,109–111] In the early IBSEN (Inflammatory Bowel Disease in Southeastern Norway) studies, UC patients achieving mucosal healing at 1 year after diagnosis had a significant reduction in future risk of colectomy.[13] Even though the window of opportunity may not be as clear in UC, we know that prolonged periods of inflammation are what ultimately lead to disease complications.[1] Therefore, it seems appropriate that early monitoring strategies like those proposed for CD should also be adopted in UC.[1]

"Time in Target" to Prevent Disease Flare and Progression

Ongoing inflammation in IBD results in progressive bowel damage and the development of complications with time. One good example of this is in UC, where a higher cumulative inflammatory burden has been shown to increase the risk of developing colorectal neoplasia.[91] Therefore, our monitoring strategy should ensure not only that targets are being met early, but also that they are maintained throughout the disease course. The concept of "time in target" has been used in the field of diabetes, where continuous glucose monitoring (CGM) allows clinicians to determine the time in which their patients have maintained their target glucose range,[112] and a higher time within target range has been associated with improved outcomes.[113] Furthermore, CGM with patient feedback has been shown to increase patient empowerment.[114] This concept is very much applicable to the field of IBD. Although continuous monitoring of inflammation in IBD is not possible at present, tight monitoring can be achieved by proactively assessing inflammation with the use of a combination of biomarkers such as FC, imaging, and endoscopic modalities to ensure that the time in target is high, and if not, that appropriate and timely intervention can occur.

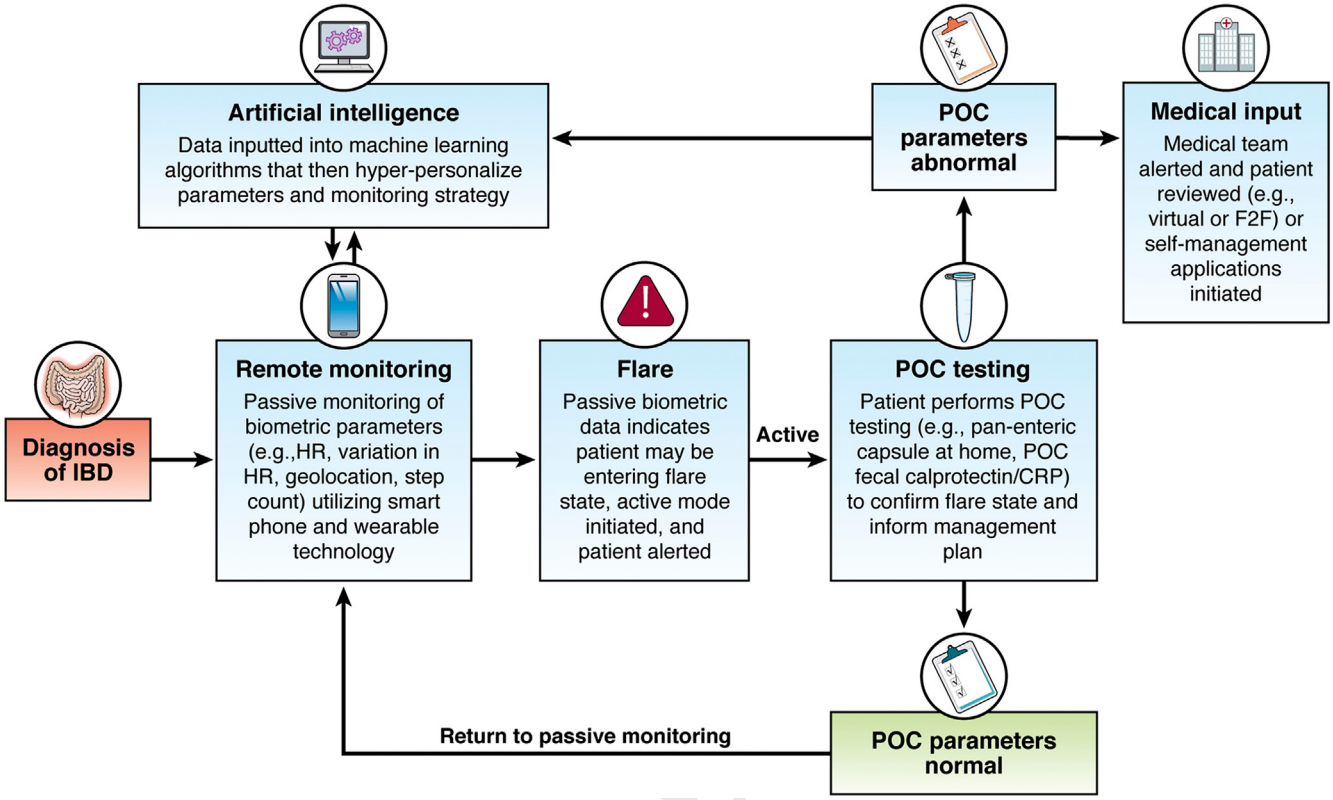


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Figure 2. Turbo treat-to-target monitoring strategy for patients with inflammatory bowel disease (IBD). See Table 1 for accepted target definitions. *For patients with Crohn's disease. CD, Crohn's disease; CRP, C-reactive protein; FC, fecal calprotectin; Hb, hemoglobin; HBI, Harvey-Bradshaw Index; PRO-2, Patient-Reported Outcomes—2; SB MRI, small-bowel magnetic resonance imaging; TDM, therapeutic drug monitoring; UC, ulcerative colitis.

Monitoring Response to Therapy

Monitoring response to therapy is essential in ensuring that patients improve symptomatically but also have objective evidence of improvement of intestinal inflammation. Response also needs to be determined in a timely fashion so that therapy can be optimized or changed without delay. Despite the numerous RCTs and prospective trials that have shown significant reductions in clinical indexes following induction therapy, the disconnect between symptoms and mucosal inflammation means that monitoring symptoms alone to assess therapeutic response is inadequate.[2–4] Normalization of CRP after initiation of treatment has been associated with clinical and endoscopic improvement; therefore, changes in CRP provide useful rapid information.[26] Unfortunately, as discussed above, the accuracy of CRP for detecting mucosal inflammation is low.[22] Mucosal healing is the goal, so endoscopic assessment to determine improvement or healing is the gold standard.[6] However, time to mucosal healing can vary, and premature or delayed assessment may lead to under- or over-treatment. Repeated endoscopic procedures are also invasive and poorly tolerated.[64]

Image modalities such as MRI and IUS may offer a less invasive approach to monitoring treatment response, although access can be an issue. In a prospective study by Ordas et al, CD patients receiving steroids or and anti–tumor necrosis factor α (TNF) had a significant reduction in MaRIA scores at week 12.[115] Furthermore, MRI detected ulcer healing and endoscopic remission at week 12 with accuracies of 90% and 83%, respectively. [115] In the TRUST-UC study (Transabdominal Ultrasonography of the Bowel in Subjects With IBD to Monitor Disease Activity With UC), IUS parameters were shown to improve significantly after treatment intensification.[116] These changes were also observed as early as 2 weeks and preceded clinical improvement. [116]

Arguably, FC is the best tool we have to monitor response to treatment. Several studies have clearly demonstrated the association between post-induction FC values and 1-year outcomes. In CD, Sollelis et al showed that a FC value <300 μg/g or a 50% decrease in FC at 12 weeks after initiation of anti-TNF was associated with steroid-free remission at 1 year.[117] Similarly, in both UC and CD, post-induction FC values ≤ 168 μg/g and $\leq 121 \mu$g/g, respectively, were shown to accurately predict sustained clinical response (83% sensitivity, 74% specificity) and mucosal healing (79% sensitivity, 57% specificity) at 1 year.[118] Thus, monitoring of FC after induction can help us determine response in a timely manner. Again, specific FC cutoffs to predict treatment response vary from patient to patient and on the clinical scenario. Therefore, observation of trends may be a better approach to determining response.

An important question is timing and frequency of monitoring. One needs to give enough time for treatments to work before considering any change, especially as efficacy appears

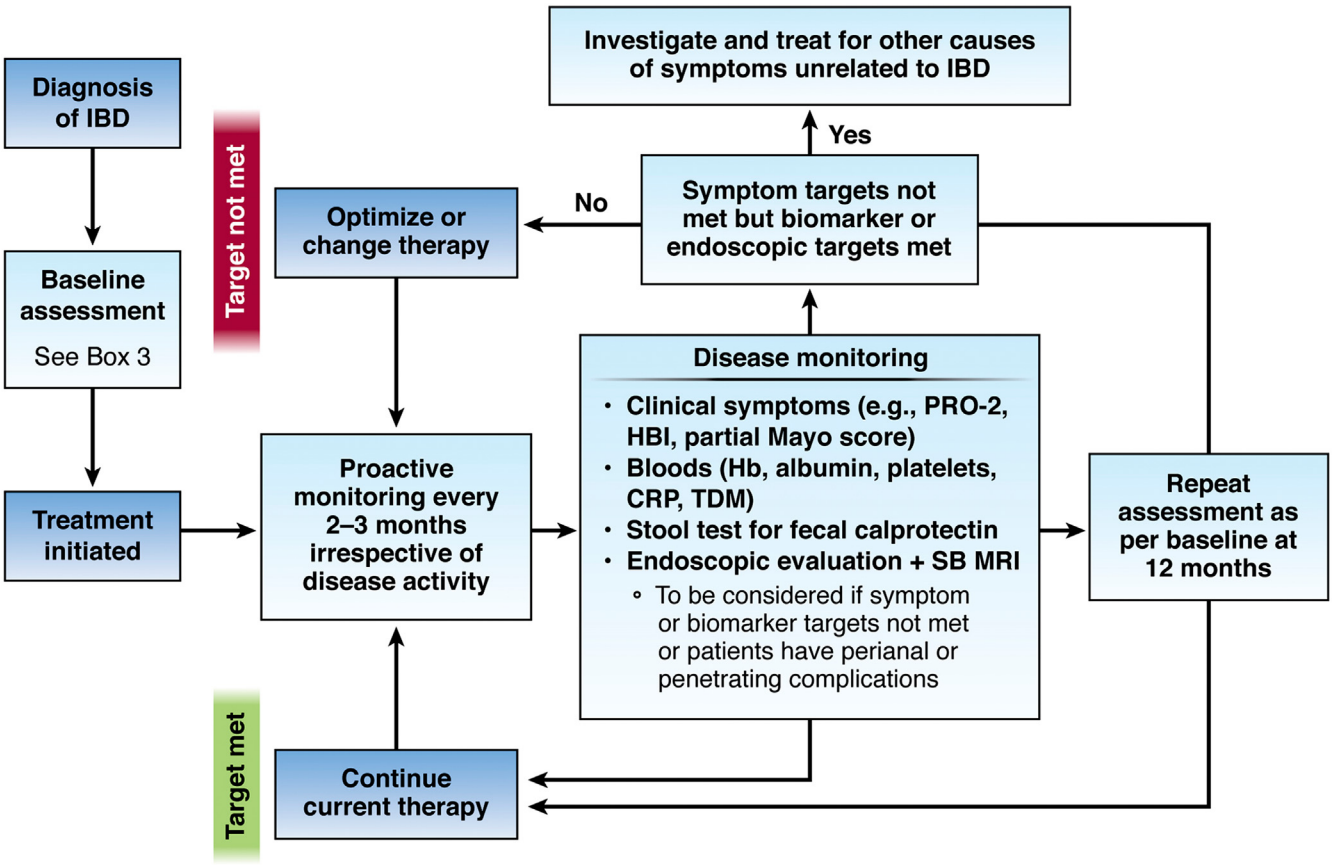

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Figure 3. Disease monitoring of the future with the use of remote monitoring, wearables, and point-of-care technology. CRP, C-reactive protein; F2F, face to face; HR, heart rate; IBD, inflammatory bowel disease; POC, point-of-care.

to drop with sequential biologic therapies. However, we must also ensure that nonresponse to therapy can be picked up early so that timely changes can be made before complications ensue. One example of this is using steroids to induce remission with a view to establishing thiopurine monotherapy to maintain remission. Thiopurines are not induction agents, so if a timely assessment of response to steroids is not made, patients' risk being initiated on a therapy that will ultimately fail. In this scenario, the Canadian clinical practice guidelines for UC recommend assessment of steroid response within 2 weeks of commencing therapy.[119] The STRIDE-II recommendations have offered some guidance on the time required to achieve treatment goals in UC and CD based on various treatment modalities (Supplementary Table 1).[6] However, it is important to remember that these time scales are based on expert opinion of the available literature, and in the absence of head-to-head controlled studies, comparisons between drugs cannot be made. Ultimately, we need to be aware that timing of assessment and monitoring will differ from patient to patient and be dependent on the treatment modality we are using.

Early Flare Detection With the Use of FC

It is important to be able to identify patients who develop active disease as early as possible to allow timely intervention. This may be in patients who are in remission or following drug de-escalation/discontinuation. Currently the best noninvasive monitoring tool for this remains FC. One of the key features of FC is its ability to predict disease flare even in asymptomatic patients. In a prospective multicenter study by de Vos et al, FC levels were determined at 4-weekly intervals in UC patients receiving infliximab therapy who were in clinical remission.[120] Patients who experienced disease flare had significantly higher FC levels up to 3 months before a symptomatic flare.[120] Furthermore, 2 consecutive FC measurements >300 μg/g, 1 month apart, was the strongest predictor of disease flare (61.5% sensitivity, 100% specificity).[120] A systematic review of 6 studies demonstrated that in asymptomatic patients with IBD, consecutive FC measurements above predefined FC cutoffs had a pooled sensitivity and specificity for predicting relapse within 2–3 months of 78% (95% CI: 72–83) and 73% (95% CI 68–77), respectively (AUC 0.83).[121] This supports the role of pro-active longitudinal monitoring of FC to detect early disease flare.

Post-operative Crohn's Disease

The established monitoring strategy after resectional surgery and ileo-colonic anastomosis for CD is based on endoscopic evaluation at 6–12 months.[122] Evaluation of the anastomosis can be made with the use of the Rutgeerts Score, which can help predict symptomatic recurrence of

disease.[123] A score of ≥i,2 should trigger initiation of treatment or escalation of existing therapy.[122] Recent data also have demonstrated that FC has good accuracy at predicting anastomotic recurrence, and therefore could be used as a tool to help detect early recurrence or prioritize patients for endoscopic assessment.[124]

Early Psychosocial Intervention and Monitoring

Data from a large population-based study in Sweden demonstrated that not only do IBD patients have a higher incidence of psychiatric disorders compared with the general population, but also that the highest risk of overall psychiatric morbidity was seen in the first year after the diagnosis of IBD (hazard ratio 1.4, 95% CI 1.2–1.6).[125] IBD patients were also observed to have an increased risk of suicide attempts, and completed suicide was associated with CD and elderly-onset (>60 years of age) IBD. [125] Low levels of resilience have also been associated with higher disease activity, more surgery, and lower QOL in IBD.[126] The GRITT method (Gaining Resilience Through Transitions), a resilience-based care coordination approach developed at Mount Sinai, New York, has been shown to improve levels of resilience, resulting in a reduced number of emergency attendances and hospitalizations.[127] Thus, early monitoring of psycho-social well-being with timely intervention is arguably just as important as monitoring of objective markers of inflammation.

What Does Disease Monitoring of the Future Look Like?

The complex lifelong and incurable nature of IBD makes it a challenge to monitor. Future monitoring tools and strategies need to be frictionless, passive, responsive, and adaptive. Current monitoring strategies are ultimately intrusive and costly and require considerable active input from patients. Consequently, with the advancement of technology, new ways of disease monitoring are emerging with a view to reducing the burden on patients and health care providers. These include but are not limited to remote monitoring via POC testing, telehealth and teleconsultations, development and integration of mobile-based applications and wearables, and implementation of AI for endoscopy and as a decision-making support tool. Considerable work is also being done to try to identify more accurate biomarkers of disease activity. Furthermore, with the growing evidence of the role of the gut microbiome in IBD, novel medical or dietary therapies will likely adopt a microbiome-modulating approach to treatment. As such, monitoring strategies will look to incorporate assessment of not only inflammation and physiologic and psychosocial parameters (eg, depression/anxiety, resilience, sleep, fatigue, QOL), but also parameters related to diet and the gut microbiome.

Remote Monitoring: Point-of Care Testing and eHealth

This aspect of remote monitoring and POC testing is covered extensively in a review by Maaser et al. Some key points to highlight are that to enable tight and timely monitoring for IBD we need proactive regular monitoring of patients before disease flare with the use of tools providing rapid turn-around. Patients may be seen in the clinic only 2 or 3 times per year, so developing remote monitoring strategies is essential for tight disease control. Technologic advances have resulted in the availability of rapid POC testing for CRP, FC, and therapeutic drug monitoring (TDM), all of which can be performed in an outpatient or home setting.[128–130] Various eHealth solutions now also exist, including virtual clinics, web-based tools for tracking symptoms and PROs, and advanced systems that incorporate POC testing of biomarkers at home and give treatment and monitoring advice to patients. Several studies have demonstrated the benefits of adopting eHealth strategies, but uptake is limited to only a few specialist centers.[131–134] Furthermore, cost, liability, and data security are all issues that need to be addressed when considering the use of eHealth solutions.[135] There is also a gap in technology to allow us to adopt these strategies reliably and at scale.

Remote Monitoring With the Use of Mobile-Based Applications and Wearables

Remote monitoring and mobile technology have the potential to revolutionize the treatment of IBD. It also confers the opportunity of access to monitoring for hard-to-reach populations in developing parts of the world where the incidence of IBD is increasing rapidly.[136] Approximately 80% of the world's population own smartphones.[137] There has also been a boom in the development of mobile-based health applications, including apps for IBD. Typically, these apps contain features such as symptom and PRO tracking, medication alerts, food/nutrition diaries, and disease-related information. Examples of commercially available apps include GI Monitor, GI Buddy, and myIBD.[138,139] However, research on the validity and benefit of these commercially available apps is lacking. Current apps are also limited by the lack of integration and ability to transmit data to health care providers. However, there are several validated noncommercial apps available. One example is the HealthPROMISE app, which was developed at Mount Sinai and tracks PROs as well as quality of care measures. It can also integrate into patients' medical records. Use of this app has been shown to result in improved QOL as well as perceived quality of care in patients with IBD.[134] Another example is the UCLA eIBD app, which measures a validated 4-question PRO that correlates with disease activity in IBD.[140]

One of the key issues with mobile-based applications is that they are only effective if users input data. Many apps fail due to lack of "stickiness," ie, patients do not fully engage. When patients are well, they are less inclined to input data, or many may avoid using the app because it serves as a constant reminder of their underlying diagnosis. The ideal app needs to be able to alert us as to when a patient is entering a flare state, ideally before symptom onset. This allows monitoring to be enhanced and therapy to be adjusted accordingly. We have discussed the utility of FC

in this setting; incorporating POC FC may be one solution, but that remains expensive, and repeated measurements can become impractical for patients.[46,141]

The real unmet need is for passive monitoring systems that continuously and unobtrusively collect data in the background. Wearable technologies may play a key role here. Wearable technologies come in many different forms, the most common being fitness bands or watches. These wearables can passively monitor and collect data on physiologic parameters, including heart rate, heart rate variability, step count, activity levels, sleep, and geolocation. Many of these parameters are pertinent to IBD. For example, in a large online survey performed in more than 3100 patients with IBD, patients with CD in clinical remission who had poor sleep (as determined by means of the National Institutes of Health PROMIS [Patient-Reported Outcomes Measurement Information System] questionnaire) had a significantly increased risk of active disease within 6 months.[142] Other studies have shown a correlation between poor sleep and endoscopic activity as well as an increased risk of hospitalization.[143,144] In a prospective study at the University of Chicago, patients with IBD were given Fitbit devices and data on step count, heart rate, and sleep in addition to CRP and FC were collected.[145] The study showed that the number of daily steps was predictive of having an elevated CRP or FC measured within 7 days (AUC 0.70, 95% CI 0.65–0.75),[145] suggesting that physical activity, assessed by step count, may be a useful predictor of disease activity in IBD. Technologic advances have also allowed the development of wearable biosensors that can passively detect levels of CRP and interleukin-1β in sweat.[146] A patient survey by Hirten et al showed that patients with IBD feel that wearables can provide important information on their health and that they would be willing to wear them for monitoring purposes in both clinical and research settings.[147] In our goal for holistic remission, wearables may also be used to monitor other aspects of IBD such as mood or extra-intestinal manifestations. Machine-learning algorithms also can be developed and trained on data collected via these methods. Ultimately, further prospective studies are needed to help validate the role of wearables in monitoring IBD.

Novel Biomarkers and Monitoring the Gut Microbiome in IBD

With the advent of "multi-omics" and the development of advanced computational methods to analyze data, we have gained an increased understanding of the genetic, molecular, microbial, and metabolic pathways that underpin IBD.[148] Several studies have identified numerous putative biomarkers of IBD that could potentially be utilized in the diagnosis and monitoring of the disease. These include biomarkers from serum, stool, urine, and exhaled breath.[149–154] Unfortunately, to date none of these "new" biomarkers have been shown to be clinically superior to the currently available tests, primarily FC. Nonetheless, there is a need for more accurate and accessible biomarkers for monitoring our patients with IBD. Another area of great interest is the gut microbiome. Studies have demonstrated that IBD is associated with a reduction in diversity of the gut microbiota.[155,156] Thus, there is a growing interest in developing and utilizing microbiome-modulating therapies as possible treatments for IBD.[157] Future monitoring strategies will likely look to incorporate assessment of the gut microbiome through either indirect or direct measures (eg, dietary intervention).

AI in Monitoring IBD

The AI revolution in health care is here and already being adopted in the field of gastroenterology.[158] In endoscopy, studies have demonstrated that AI algorithms increase polyp detection when deployed across existing colonoscopy platforms.[159] Its application to IBD care is an area of great interest and explored in detail in a review by Stidham et al.[160] In monitoring, one way that AI could greatly assist is by performing standardized and automated scoring for imaging and endoscopy. Pilot studies have already demonstrated the ability of AI to automatically grade endoscopic activity in UC with results similar to expert reviewers.[160,161] Implementation of these systems into clinical practice would allow meaningful assessments to be made and comparisons in individuals over time. AI could also be used to develop decision support tools that are hyper-personalized for individual patients.

Turbo-Charged T2T of the Future

An example of how we may approach disease monitoring of IBD in the next 10 years is shown in Figure 2. First, when our patient is well, data are collected passively via wearable technology. Algorithms then can detect physiologic variables outside the patient's designated range and alert the user. The user can then log symptoms via the app and be prompted to check POC parameters (eg, FC, TDM, CRP, pangenetic capsule at home). If parameters come back as normal, the system informs the patient of "false alarm" and goes back to passive mode. However, if parameters are abnormal, the medical team is alerted, and appropriate action is taken. During this process, data are continuously being inputted into machine-learning algorithms that can then hyper-personalize the monitoring strategy at every phase of disease. A number of these tools exist now; we are just in desperate need of data from large perspective cohorts to help develop and validate their use.

Conclusion

Early and effective treatment, adopting a T2T approach with optimum monitoring strategies, is key to improving long-term outcomes in IBD. With the advent of technologic advances and a better understanding of IBD, we will likely see a huge shift in the way we monitor these conditions. Future monitoring strategies should empower patients, be less invasive physically and mentally, be more cost-effective for health care providers, minimize unnecessary patient attendance to hospital, and ultimately help improve clinical outcomes.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of Gastroenterology at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2022.01.024.

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Received October 12, 2021. Accepted January 18, 2022.

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CRediT Authorship Contributions
NP and CWL wrote the original manuscript, revised the manuscript, and approved the final version.

Conflicts of interest
NP has served as a speaker for Janssen, Takeda, and Pfizer. CSL has received research support from Abbvie and Gilead; acted as a consultant to Abbvie, Janssen, Takeda, Pfizer, Galapagos, MSD, Hospira, Pharmacosmos, GSK, Gilead, Topivert, Vifor Pharma, Dr Falk, Oshi Health, Trellus Health, and Iterative Scopes; and has received speaking fees and travel support from Pfizer, Janssen, Abbvie, Galapagos, MSD, Takeda, Shire, Ferring, Hospira, Warner-Chilcott, and Dr Falk. Q10

Funding
Charlie Lees is funded by a UK Research and Innovation Future Leaders Fellowship, "Predicting Outcomes in IBD."

Supplementary Table 1. Times (mean number of weeks) required for achieving goals after starting treatment (adapted from STRIDE-II recommendations)[6]

	Clinical response	Clinical remission	Normalization of CRP	Decrease of FC	Mucosal healing
Crohn's disease					
Oral steroids/EEN	2	4	5	8	13
Budesonide	3	6	8	10	15
Thiopurines	11	15	15	17	24
Methotrexate	9	14	14	15	24
Anti-TNF	2–4	4–6	9	11	17
Vedolizumab	11	17	15	17	24
Ustekinumab	7	13	11	14	19
Ulcerative colitis					
Oral 5-ASA	4	8	8	10	13
Oral steroids	2	2	5	8	11
Locally active steroids[a]	3	8	8	9	13
Thiopurines	11	15	15	15	20
Adalimumab	6	11	10	12	14
Infliximab	5	10	9	11	13
Vedolizumab	9	14	14	15	18
Tofacitinib	6	11	9	11	14

5-ASA, 5-aminosalicylic acid; CRP, C-reactive protein; EEN, exclusive enteral nutrition; FC, fecal calprotectin; TNF, tumor necrosis factor α.
[a]Beclomethasone diproprionate, Budesonide MMX.