REVIEW ARTICLE

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A Treat-to-Target Update in Ulcerative Colitis: A Systematic Review

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OBJECTIVES: In 2015, the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) program proposed shifting the therapeutic focus on ulcerative colitis (UC) toward altering the natural history of the disease course by regularly monitoring objective measurements of disease activity and tailoring treatment accordingly. The therapeutic paradigm shift was well received in the research community and is often cited. However, new evidence on optimal UC treatment targets continues to accumulate since the time of the STRIDE guidelines. This systematic review summarizes the evidence accrued since the STRIDE UC recommendations, discusses the barriers for adoption of treat-to-target approaches in clinical practice in UC, and suggests directions for future research.

METHODS: We systematically reviewed MEDLINE for studies from the time of the STRIDE systematic review up to March 31, 2018, that assessed the potential treatment targets identified by the STRIDE recommendations.

RESULTS: Each potential treatment target literature search returned > 200 articles, which were then reviewed by 2 independent investigators for relevant studies. Selected studies of clinical factors, patient-reported outcomes, endoscopy, histology, imaging, and biomarkers and implications on treatment targets are summarized.

CONCLUSIONS: It appears that the relative weight given to different therapeutic targets in the development and improvement of UC treatments could be optimized, with an increased emphasis on endoscopic and histological targets over clinical or symptomatic targets. For this evolution to occur, however, new research has to demonstrate that the treat-to-target approach will deliver on the promise of better long-term outcomes compared with current approaches.

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/A77 and http://links.lww.com/AJG/A194

INTRODUCTION

Ulcerative colitis (UC) is a chronic disease with a remitting and relapsing course that can progress from asymptomatic mild inflammation to extensive inflammation of the colon, resulting in frequent bloody stools, colonic motility dysfunction, potentially permanent fibrosis and tissue damage, systemic symptoms, and the need for surgery (1–5). Approximately one-third (31%) of patients with limited UC at diagnosis will have disease extension by 10 years (6). In 10%–15% of patients, UC can ultimately lead to colectomy (7). Achieving mucosal healing *via* treatment lowers the risk of requiring colectomy (7–9), which is important, because colectomy provides symptomatic relief, but no cure, and is associated with complications in up to a third of patients (10). UC management focused on symptomatic control may leave less active or smoldering disease (i.e., mucosal healing unachieved) lingering, risking future relapse (11). Despite an improving

treatment landscape, long-term colectomy rates have not declined over a 10-year period (7), highlighting the need for new therapeutic strategies.

In 2015, the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) committee defined the treat-to-target (T2T) approach for inflammatory bowel disease (IBD), which shifted the goal of UC treatment to long-term prevention of disease complications (dysplasia/cancer, hospitalizations, colectomy) and proposed monitoring of objective disease activity measurements (e.g., endoscopic evidence of inflammation) (2,12,13). The T2T approach, adapted from the rheumatoid arthritis paradigm, aims to achieve disease remission by adjusting therapy according to the achievement (or not) of predefined treatment response targets (2,9,13). The STRIDE committee proposed a composite target of normalization of bowel habits and intestinal inflammation, but evidence

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was limited for the incorporation of histology and biomarker targets (13).

Recent evidence indicates that complete mucosal healing might be the ideal therapeutic goal in UC (14). As the definition of mucosal healing continues to evolve, 2 aspects should be considered: endoscopic and histological healing because evidence suggests that microscopic features of activity may persist in macroscopically inactive disease (14,15). Unfortunately, many clinicians continue to manage patients with UC symptomatically, thus the uptake of the T2T strategy in UC appears to be lagging (16).

The aim of this study is to provide a systematic review of the current research on T2T strategies in UC, discuss barriers to implementation, and offer practical advice on their incorporation into clinical care.

METHODS

An electronic PubMed search from the time of the STRIDE systematic review up to March 31, 2018, was performed to assess accumulating evidence for the potential treatment targets of clinical factors, patient-reported outcomes (PROs), endoscopy, histology, imaging, and biomarkers (Table 1). Please see

supplemental material for detailed methods (see Supplementary Digital Content 1, http://links.lww.com/AJG/A77).

The search strings largely replicated those used for the STRIDE publication (13). Selection criteria for inclusion of relevant publications were studies in patients with UC including placebo-controlled randomized clinical trials, interventional studies, observational studies, meta-analyses, and reviews. Case reports and studies performed in patients with cancer, neoplasia, and dysplasia were excluded.

RESULTS

Evolving targets since the publication of the STRIDE recommendations

The STRIDE recommendations pointed to new IBD management standards, for UC in particular. This section highlights recent data that could help refine some of those recommendations to continue developing and improving UC treatments (Figure 1).

Clinical targets and PROs

The STRIDE committee recommended that PROs, such as resolution of rectal bleeding and bowel habit normalization, should be a therapeutic target for UC. However, including objective

Table 1. Summary of outcomes from literature review

Targets	Clinical/PRO	Quality of life	Endoscopic	Histology	Imaging	Biomarkers
Databases	PubMed	PubMed	PubMed	PubMed	PubMed	PubMed
Time limits	Mar 1, 2013–Mar 31, 2018	Nov 1, 2013–Mar 31, 2018	Mar 1, 2015–Mar 31, 2018	Jan 1, 2014–Mar 31, 2018	Jan 1, 2015–Mar 31, 2018	Jul 1, 2013–Mar 31, 2018
Main search terms	(Ulcerative colitis) AND (index OR scale OR score) AND (clinic*) NOT (microscopic colitis OR mastocytosis OR cancer OR irritable)	(Patient-reported outcomes OR quality of life OR fatigue OR disability OR productivity OR depression OR anxiety) AND (ulcerative colitis)	(Ulcerative colitis) AND (endoscopy OR colonoscopy OR sigmoidoscopy OR proctosigmoidoscopy OR endoscopic) AND (index OR score OR grade OR Baron OR Rachmilewitz OR Mayo OR Matts OR UCEIS OR Truelove OR Dick OR Marks OR Feagan OR Powell OR Lemann OR Sutherland OR healing)	(Ulcerative colitis) AND (mucosal healing OR histological healing OR histological scoring)	(Ulcerative colitis) AND (imaging OR ultrasound OR magnetic resonance OR computed tomography)	(Ulcerative colitis) AND (calprotectin OR lactoferrin OR C-reactive protein OR erythrocyte sedimentation rate OR hemoglobin OR bone mineral density OR ferritin OR prostaglandin) AND (response OR remission OR flare)
Search limits	English, humans	English, humans	English, humans	English, humans	English	English, humans
UC only	839	542	456	654	413	245
Relevant references identified	39	118	71	77	49	81
Comparison with STRIDE literature review (relevant references/total citations)	54/4,166	73/1,660	429/2,899	128/1,265	97/9,056	50/228

PRO, patient-reported outcomes; STRIDE, Selecting Therapeutic Targets in Inflammatory Bowel Disease; UC, ulcerative colitis; UCEIS, UC Endoscopic Index of Severity.

	STRIDE Consensus Targets	Accumulating Evidence	Optimized Targets
Clinical Targets and PROs	Resolution of rectal bleeding and normalization of bowel habits should be the target. Monitor every 3 months until symptom resolution and every 6 months thereafter.	Discrepancy between symptom normalization and endoscopic activity.	Validated PRO scores and tools/technologies for PRO reporting.
Endoscopic Targets	Absence of ulceration is the target (minimum score of 1). Assessments should be done every 3-6 months after start of therapy.	Utility of UCEIS and modified Mayo scores. More stringent endoscopic resolution associated with better outcomes (Mayo score = 0).	Validated UCEIS and Mayo scores. Mayo score = 0
Histological Targets	Not recommended as a target because of insufficient evidence.	Histological healing associated with endoscopic healing and can predict long-term outcomes.	Validated histological index. Nancy and Robarts scores as promising potential tools in clinical practice and clinical trials
Adjunctive Biomarker Targets	CRP and fecal calprotectin are adjunctive measures of inflammation but NOT treatment targets. Failure of CRP or fecal calprotectin normalization should prompt endoscopic evaluation.	Fecal calprotectin responsive to treatment induction and dose response.	Validated fecal calprotectin cut-off value with demonstrated specificity, sensitivity, and reliability. Home-based test development.
Novel Future Targets	Molecular evidence of inflammation (intestinal permeability) may be helpful with assessing disease activity in patients who demonstrate endoscopic healing but still experience symptoms. Methods for detecting molecular inflammation will require extensive research to demonstrate its association with disease short-term and long-term outcomes.		

Figure 1. Accumulating evidence and evolution of specific targets in the management of UC. CRP, C-reactive protein; PRO, patient-reported outcomes; UCEIS, UC Endoscopic Index of Severity.

inflammation measures as clinical study endpoints is important because the use of PROs alone has resulted in high remission rates for placebo (17). Furthermore, a small but consistent proportion of patients with endoscopic (Mayo score = 0) and histological remission may continue to report symptoms of unknown etiology (18–20). Noninflammatory mechanisms, such as small intestinal bacterial overgrowth, bile acid diarrhea, changes in motility or permeability, neurologic abnormalities, dysbiosis, or chronic fibrotic changes (21–23), may be possible causes. Conversely, around a quarter of patients who are clinically asymptomatic have endoscopically active disease (Mayo score > 1) (18). Interestingly, patients report a higher symptom burden than their healthcare providers using the same index; thus, the data collection method may be important to consider (24). Although simple surveys and/or mobile applications could improve symptom reporting by patients (24,25), these findings altogether point to the shortcomings of using solely clinical endpoints or PROs to reliably assess disease status. Given the US Food and Drug Administration's recognition of PROs as a clinical target, stool frequency and rectal bleeding remain important, although tools to monitor and quantify these measures need to be refined. Ultimately, evidence suggests that symptoms should be supplemented with objective targets.

Quality of life measures

The restoration of a patient's quality of life (QoL) was considered to be the ultimate goal by the STRIDE committee (13). There are inherent challenges in using QoL endpoints, such as the lack of standardized instruments and the subjective nature of QoL. Two prospective studies using different instruments reported high-to-moderate correlation between QoL scores and clinical drug response over a short time (26,27). The disease-specific Inflammatory Bowel Disease Questionnaire measure was dose-responsive and had a linear correlation with Mayo scores (endoscopic score of disease activity). Therefore, although evidence of active disease association with reduced QoL continues to accumulate, consensus on QoL instruments across IBD studies remains a challenge.

Some clinicians have suggested that an objective disability index may be a valuable long-term target as well. In 2012, the IBD disability index was developed according to World Health Organization disability classifications (28). The instrument has since been validated, opening the door for measuring disability in clinical trials (29). In studies investigating factors associated with disability, active disease, poor drug adherence, and corticosteroid treatment (vs biological treatment) were associated with increased disability, supporting the utility of the IBD disability index (30,31).

Fatigue is commonly reported in patients with IBD and is associated with active disease; chronic fatigue has recently been shown to be more prevalent in patients with IBD than in a reference population (32–34). Fatigue has been associated with poor QoL using both general and IBD-specific instruments, emphasizing the importance of this PRO domain (32). However, validation of objective measures of fatigue is needed before incorporating it as a target in UC.

Endoscopic targets

Endoscopic mucosal healing measurement is foundational to the indexes of disease severity and extent. The most often used endoscopic disease activity metrics are the UC Endoscopic Index of Severity (UCEIS) and the Mayo Clinic indexes (Mayo score) (13). Despite extensive research, these indexes are not fully validated and can be subject to interobserver disagreement (13,35–37). The UCEIS has shown less intra- and inter-reader variability than the Mayo score, but fewer studies of its predictive value and validity were available at the time of STRIDE (13). Since that time, studies have shown that UCEIS has a better correlation with disease severity and treatment responsiveness than the Mayo score and is more sensitive to detect deep ulcers becoming smaller and shallower, which the Mayo score overlooks (38,39). Recent Mayo score variations may surpass the original by incorporating the extent of inflammation along the colon while attempting to preserve the score's ease of use (40,41).

STRIDE preferred the Mayo score for real-world endoscopic healing evaluations in 2015, but emerging evidence supports UCEIS (13,38,39). For settings where the Mayo score is still preferred, centralization can improve interobserver agreement for the endoscopic components, and a recent study suggested that training can improve consistency in community settings (42,43).

When the STRIDE recommendations were developed, targets for the Mayo and UCEIS indexes were under debate, with a score of 1 considered the minimum target for both. Recent evidence suggests that more stringent endoscopic goals (i.e., Mayo or UCEIS score of 0) are associated with better outcomes and lower relapse risk (9.4% and 5.0%, respectively) (44–47).

Procedure type can also influence endoscopic assessments. Sigmoidoscopy is the standard technique in clinical trials, whereas colonoscopy is typically performed in clinical practice to confirm UC diagnosis and assess disease. A recent study demonstrated that sigmoidoscopy can evaluate distal colon inflammation with accuracy comparable with colonoscopy, particularly in patients with active disease (48).

Novel endoscopic imaging techniques (e.g., computed virtual chromoendoscopy, confocal laser endomicroscopy) may improve diagnostic accuracy for assessing endoscopic healing in UC (49). For example, confocal laser endomicroscopy can evaluate mucosal permeability that correlates with disease severity and treatment response (49–51). However, these imaging techniques require specialized training, and their utility in routine clinical care is still unclear.

Histological targets

In UC, histological remission, defined as microscopic normalization of colonic mucosa, is distinct from endoscopic remission, which entails the resolution of endoscopically visible disease activity (13,14). Of several histology indexes available, the Nancy index and the Robarts Histopathology Index (RHI) have been the most studied indexes (52). In a prospective observational study,

87.1% of patients with histological remission at initial assessment remained in clinical remission after 1 year (53). In addition, histological remission in patients with UC was a strong predictor of steroid-free remission and clinical recurrence after 3 years of follow-up and was associated with lower hospitalization and corticosteroid use rates over a median follow-up period of 6 years (47,54,55). In a retrospective study, histological normalization was associated with increased odds of relapse-free survival compared with endoscopic healing or histological quiescence (56). In an observational cohort, the Geboes histology grade at baseline was strongly associated with a risk of clinical relapse in patients with UC who are in clinical remission after 12 months (57). Together, these data suggest that histologic remission can predict long-term outcomes.

Thus, including histological endpoints as treatment targets should enter into consideration (47). However, a uniform validated histology index is still needed because Ponte et al. (47) used the Nancy score, whereas the other studies used different indexes.

Validation of histologic indexes could broaden the use of this mucosal healing measure beyond its current limited application (13,58,59). The RHI was developed by selecting histopathological descriptors that had intra- and inter-reader reliability across the Geboes score, modified Riley score, and a visual analog scale. RHI incorporates the level of chronic inflammatory infiltrate, lamina propria neutrophils, neutrophils in the epithelium, and any erosion or ulceration present in the mucosal tissue (59). Similarly, the Nancy index scores ulceration, acute inflammatory cell infiltrate (i.e., neutrophils), and chronic inflammatory infiltrate (i.e., lymphocytes, plasmacytes) (58). These 2 indexes correlate with clinical remission and disease activity, as well as with the Mayo endoscopic score and fecal calprotectin (FC) concentrations (60). These indexes provide an opportunity for wider adoption of simplified or reliable histological scoring systems; however, further research is needed to validate their relationship with long-term outcomes, to establish clinically meaningful cutoff points, and to explore the feasibility and reliability of their practical adoption among community pathologists (52,58,59).

In the future, molecular studies may complement tissue exams for histological evaluation in UC. In this regard, intramucosal calprotectin was found to be associated with histological, endoscopic, and clinical remission (61).

Imaging targets

Imaging modalities are an attractive monitoring alternative compared with the invasive current procedures but are not yet considered sufficient to evaluate mucosal healing in UC, novel methods notwithstanding (13). A magnetic resonance enterography disease index (magnetic resonance (MR) index of activity) was found to be viable to assess mucosal healing in a small cohort of patients with Crohn's disease (CD) (n = 48) (62). Laurent et al. (63) demonstrated that diffusion-weighted magnetic resonance imaging (MRI) using an MRI-specific index (Nancy score) accurately defined mucosal healing (endoscopically determined) in a small cohort of patients with UC (n = 29). Similarly, MR colonography was found to have a high accuracy for the diagnosis of disease activity and severity in UC (64). Further research to validate imaging modalities, indexes, and correlations with long-term disease outcomes are needed.

Ultrasound, a noninvasive radiation-free imaging modality used to evaluate the extent of disease activity (i.e., mucosal alterations, transmural involvement), was shown to have

sensitivity and specificity similar to that of MRI and computed tomography for the diagnosis of IBD (65). Before the STRIDE publication, studies had investigated the ability of contrast-enhanced ultrasound to distinguish between quiescent and active disease *via* vascular activity (65). A systematic review on the utility of ultrasound for disease monitoring found that several UC ultrasound indexes have been developed, but they generally assessed bowel wall thickness, Doppler signal, wall layer stratification, compressibility, fatty wrapping, and strain pattern (66). The authors concluded that indexes have been developed with suboptimal methodology, thus development and validation of a new index are warranted (66).

Biomarkers as targets

Although endoscopic and histological assessments are direct disease measures, they are invasive and costly, and thus non-invasive biomarkers of mucosal healing, treatment response, and/or disease flares are desirable (13). At the time of STRIDE, there was insufficient evidence supporting the use of biomarkers as surrogate endpoints for treatment optimization. However, data on the clinical utility of biomarkers, particularly FC, have been accumulating. Regular FC monitoring, with treatment escalation in patients with increased levels was associated with a reduced rate of relapse, albeit nonstatistically significant (67). In addition, mesalamine dose escalation reduced calprotectin levels to <100 μg/g, and relapse occurred sooner in patients with calprotectin level >200 μg/g (68).

New longitudinal observational studies found that escalating FC concentrations may predict relapse in patients with inactive UC as early as 3 months before the presentation of symptoms (69–75). Whether FC concentration changes can be used as surrogates of treatment response is still under investigation. Studies have reported that FC concentration reductions may be predictive of endoscopic and histological response to induction therapy and clinical remission (60,71,74,76–79). Low FC concentrations also correlate with the absence of mucosal inflammation or structural abnormalities (60,73,79). In addition, reductions in FC during treatment have been found to be dose-responsive (68,71,80,81). A meta-analysis by Mosli et al. (82) defined an optimum cutoff point for FC as 50 μg/g, but various concentration thresholds have been used across correlative studies. Thus, standardization and validation of a single FC cutoff point is needed to characterize its specificity and sensitivity as a biomarker ready for clinical practice. Because clinical data increasingly support FC as a UC biomarker, the optimal therapeutic target needs to be determined *via* well-designed disease-modification trials.

Studies are underway to identify and characterize additional promising fecal biomarkers such as leucine-rich α-2 glycoprotein, prostaglandin E-major urinary metabolite, hemoglobin concentration, M2-pyruvate kinase, lactoferrin, and high mobility group box 1 (81,83–86).

There are conflicting data on the utility of serological biomarkers as predictors of disease activity. C-reactive protein (CRP) and erythrocyte sedimentation rate were found to have low accuracy in detecting endoscopic activity in patients with UC (87). A *post hoc* analysis of a prospective clinical trial showed that CRP levels failed to discriminate between patients in clinical remission, with endoscopic inflammation and with mucosal healing (88). In pediatric patients with UC, neither marker was found to be useful in predicting clinical, endoscopic, or histological UC disease activity (89).

Challenges and considerations for implementing T2T recommendations in clinical practice

The T2T approaches in UC may require greater healthcare utilization, wider use of invasive procedures, and treatment escalation in the face of apparent symptomatic resolution, which raises potential barriers to implementation from patients, payers, and clinicians (Figure 2). Moreover, although the STRIDE consensus provided therapeutic goals, practical algorithms to reach these goals are needed. Thus, integration of T2T management into real-world UC clinical settings requires evidence generation to demonstrate its benefits and to validate therapeutic algorithms (2). In this section, we will highlight some of the implementation barriers and gaps in the evidence based on our review of the latest literature.

Clinical perspective

Demonstrating that the T2T approach can modify the disease course and prevent disability and long-term complications is critical to justify the added costs and healthcare utilization (2). Even in CD, where the CALM trial demonstrated that a tight control algorithm could improve clinical and endoscopic outcomes, long-term follow-up was necessary to evaluate the impact on disease course and support a paradigm shift in management (90). Another study along similar lines is currently underway (Enhanced Algorithm for Crohn's Treatment Incorporating Early Combination Therapy; REACT2).

For UC, based on the evidence summarized in this review, we propose an algorithm for incorporating T2T approaches into clinical care (Figure 3). However, this or any other algorithm would require prospective clinical studies to demonstrate its impact on disease outcomes and QoL.

Regarding the evaluation of endoscopic healing, the immaturity of the evidence connecting the pursuit of endoscopic targets to improved long-term outcomes represents a barrier for practical acceptance. This review captures the dichotomy between 2 disease score methods. As indicated in Figure 3, either Mayo or UCEIS can be used. In our opinion, UCEIS is the preferable score, although Mayo may be more familiar and therefore more feasible in clinical practice (for both, the target would be a score of 0). An important initial step to address current gaps, however, would be to aim for consistency in the routine adoption and recording of a disease score in patient reports, perhaps starting with Mayo, if that is the most feasible, but aspiring to eventually incorporate UCEIS as standard practice.

The incorporation of histologic scores lags behind endoscopic scores. Although it may be advisable to start considering how histologic evaluation could be integrated into routine practice, which we reflect in our algorithm in Figure 3, histologic score targets are not recommended for current practice because of the lack of prospective interventional studies demonstrating benefit of solely histologically guided therapy decisions. Given the limited number of current UC therapies, abandoning a medication in a patient with endoscopic remission and histologic inflammation only is not advisable until prospective data become available.

Because endoscopic scoring cannot be centralized in practice as it is in clinical trials, gaps in training represent another barrier to the effective adoption of endoscopic or histologic assessments. Educational initiatives or practice-centric programs guided by experts have proven useful in improving inter-reader reproducibility (42), but this is an area still in search of optimal solutions.
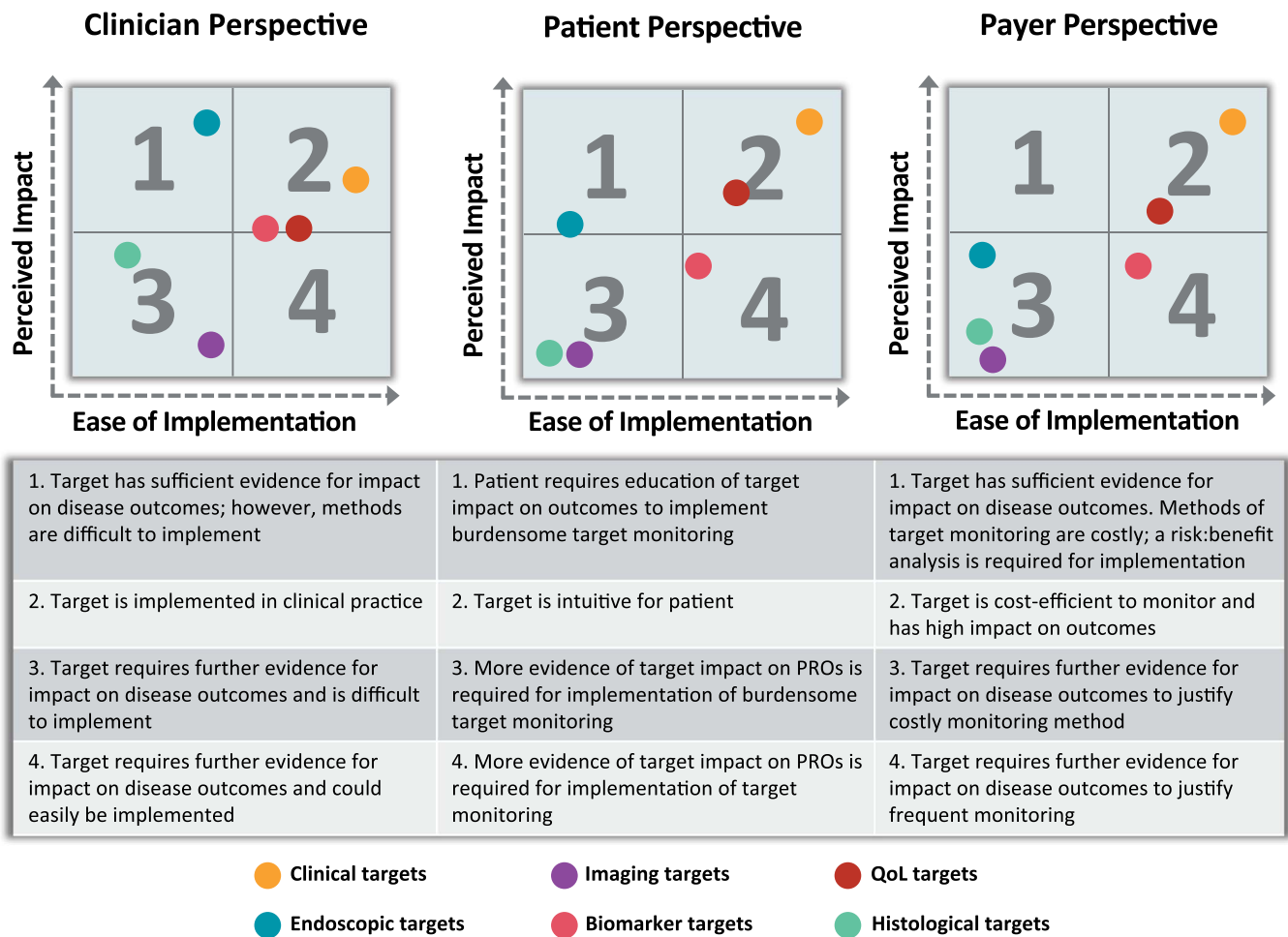
Figure 2. Feasibility of and barriers to implementation of a T2T approach. In the above matrices, the targets are placed on a scale that accounts for the ease of implementation as a treatment target (x-axis) and perceived impact of treatment target on disease outcome (y-axis). Quadrant 1 contains targets that are difficult to implement but have high perceived impact by stakeholder, quadrant 2 contains targets that are easy to implement and have high perceived impact, quadrant 3 contains targets that are difficult to implement and have low perceived impact, and finally quadrant 4 contains targets that are easy to implement and have low perceived impact. Each stakeholder will require different levels of evidence and education to successfully adopt the treat-to-target approach proposed by the STRIDE committee. Barriers to implementation are summarized under each matrix. PRO, patient-reported outcomes; QoL, quality of life; T2T, treat-to-target; STRIDE, Selecting Therapeutic Targets in Inflammatory Bowel Disease.

Given the invasiveness and cost of the monitoring procedures required, there is a need for data-driven evidence on the utility of noninvasive monitoring methods in predicting UC relapse to reduce healthcare and patient burden. At present, FC remains the most developed noninvasive means, and evidence suggests that it can be incorporated in the clinic for disease monitoring (91). A well-validated FC threshold that would indicate mucosal healing remains under investigation because clinical trials so far have used variable thresholds (13.9–261 μg/g) and correlative measures (e.g., reference data, definition of relapse) (71,81,88). Regarding practical application of FC testing, we propose that in current practice, a cutoff point of < 100 μg/g could be a target indicative of low disease activity (Figure 3). In practice, FC should be measured close to the time of an endoscopic assessment to "benchmark" the FC level to the individual patient. Furthermore, studies on home-based testing allowing patient self-measurement have reported good correlation with the classic enzyme-linked immunosorbent assay, which may help realize frequent FC monitoring with less patient burden (92). Imaging modalities offer a noninvasive method of monitoring disease activity for patients at higher risk for endoscopic disease and of tracking structural changes resulting from chronic inflammation that may be contributing to long-term complications. However, more research is required to investigate the specificity, sensitivity, and reliability of these tools.

Regarding PROs, 2 clear criteria have emerged as critically relevant for UC (rectal bleeding and stool frequency), but other QoL domains have been poorly studied (e.g., fatigue, disability) and are not consolidated into a single instrument. The increasing interest in PROs by regulators for drug development in IBD could and should propel the validation of tools following regulatory guidelines.

Payer perspective

Payers will require clear and unequivocal assessments of the favorable risk-benefit ratio for T2T approaches vs the current status quo before this paradigm enters the mainstream of coverage. Ideally, these assessments would be supported by long-term randomized controlled trials, as well as adequate cost-effectiveness analysis. Evidence will be needed demonstrating
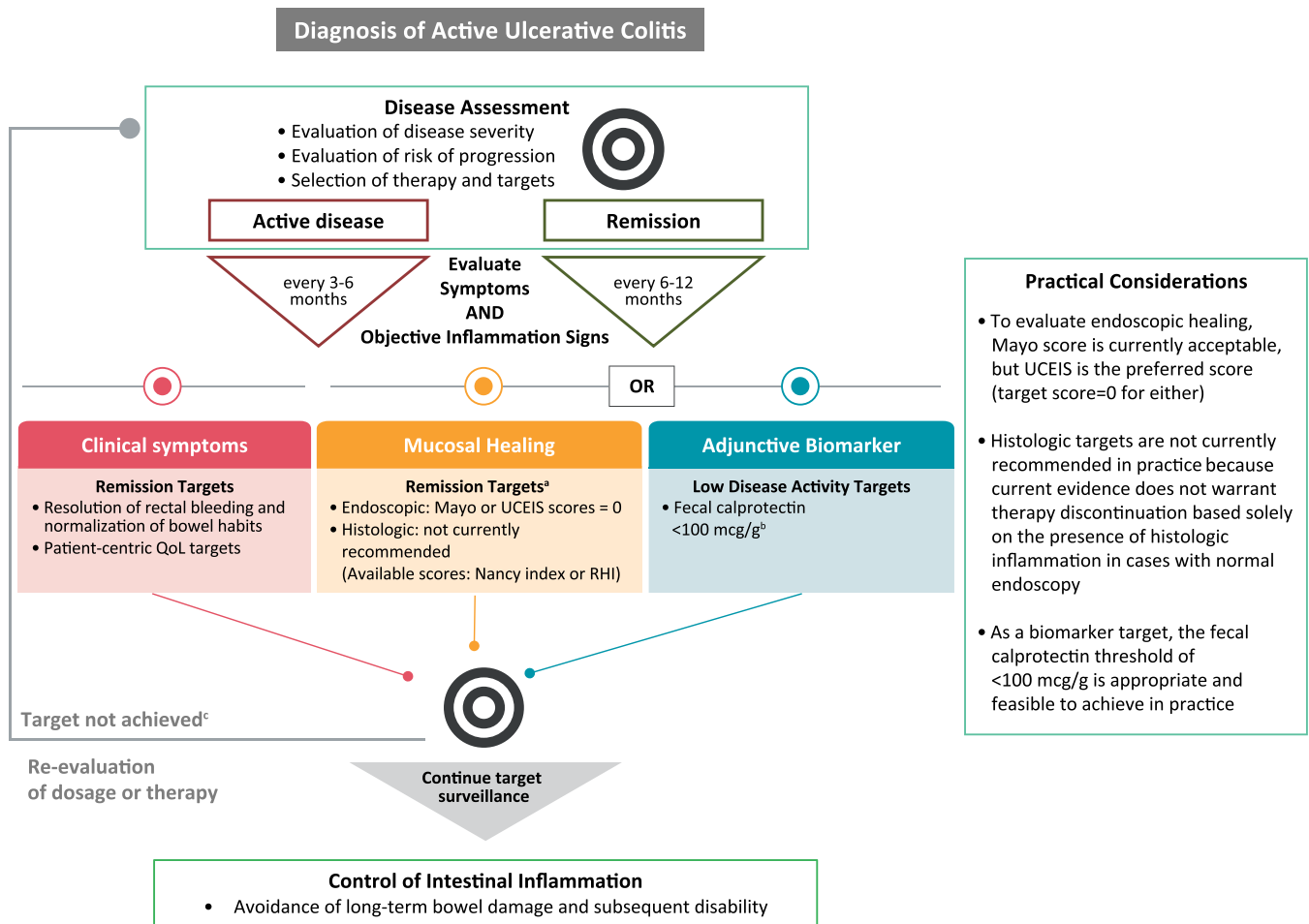
Figure 3. Proposed ulcerative colitis T2T algorithm. [a]Mucosal healing as a treatment target must involve patient decision because of the high burden of monitoring and potential need for therapy escalation despite symptom resolution. [b]Biomarker normalization as a treatment target must involve patient decision because of potential need for therapy escalation despite symptom resolution. [c]If adjunctive biomarkers are not improving or normalizing, mucosal healing targets should be reassessed. QoL, quality of life; RHI, Robarts Histopathology Index; T2T, treat-to-target; UCEIS, UC Endoscopic Index of Severity.

that earlier aggressive treatment (or alternatively a more rapid step-up approach) and frequent monitoring may be more cost-effective in the long-term despite increased short-term costs (2). Obviously, the development of less costly and burdensome monitoring strategies would also lower the barrier to acceptance.

Patient perspective

Patient considerations could be key to the success of personalized T2T approaches because motivated patients would be expected to remain adherent and compliant with protocols, even during times of disease remission and symptom resolution. Physicians should discuss specific goals that patients may have and patient concurrence with the treatment target. Patient adherence to a T2T approach will require their acceptance of dose escalation if the goal is deeper level healing or remission (histological or molecular/biomarker). Personalized regimens should consider disease severity and a patient's tolerance of aggressive treatment and possibly repeated procedures and testing, as well as the risk factors for complications, relapse, and side effects (2,93). Ideally, patient education would also foster the incorporation of lifestyle changes (dietary recommendations, etc.), which may have limited

intrinsic efficacy but could contribute to symptom improvement (94).

Ultimately, the overarching aim of a T2T approach in UC is to meaningfully modify the disease course, restoring QoL and preventing major long-term functional impairment and disability. Therefore, measuring how T2T strategies deliver against specific goals under each perspective will be critical to validate this clinical paradigm and propel its wider adoption. Undoubtedly, such validation will require studies that are ambitious in scope (encompassing measures of clinical status, surgery rates, resource utilization, cost-effectiveness, patient function, QoL, and PROs), large in size, and lengthy in duration. Real-world cohorts may offer a good platform for such studies, although the challenges of conceptualizing comparative schemas (i.e., what would the reference controls for such a study be, and would historic data be valid) and reaching investigator consensus in the definition of suitable treatment targets and outcome measures should not be underestimated. Alternatively, large prospective clinical trials investigating the benefit of a T2T approach in UC, similar to that of CALM or REACT2 in CD, could help clinicians understand the value and feasibility of meeting targets with current therapies and monitoring tools.

Future directions

As more is learned about intestinal inflammation, new tools and treatment targets may emerge. Endomicroscopy studies have developed more detailed mucosal healing criteria (including crypt numbers, crypt lumen deformity, crypt lumen leakage, and vascular leakage) (95). Further studies could determine the predictive value of endomicroscopic mucosal changes regarding clinical outcomes. The search for biomarkers is also evolving, with a recent study identifying 4 gene transcripts responsive to antitumor necrosis factor therapy and correlated with endoscopic disease activity; these molecular markers pinpoint changes in disease activity more accurately than CRP, erythrocyte sedimentation rate, and platelet count (96). Further research is needed to shed light on the underlying causes and etiology of persistent symptoms in patients with endoscopic remission (20,23). To that end, the development of a functional UC bowel damage index beyond endoscopy or histology scoring (akin to the Lémann score in CD (97)) would provide a major research and management tool.

The T2T paradigm, widely accepted in rheumatoid arthritis, is an emerging approach in IBD. This approach is currently more established in the treatment of CD, but growing evidence supports its usefulness in UC. Given the new evidence, the T2T recommendations (STRIDE) could be updated for both CD and UC (98). In the near future, we might need to look beyond the mucosa and recognize fibrosis and molecular healing as components of UC. All these factors may hold the key to avoiding long-term functional deficits and disability in UC.

Finally, we would be remiss to deny that the implementation of T2T strategies in routine practice remains challenging and requires a shift. Successful T2T implementation will require patient and physician education and communication (to create true personalized treatment plans and goals), renewed efforts in evidence generation to validate reliable and preferably noninvasive endpoints that predict favorable long-term outcomes, and establishment of the superior risk-benefit and cost-effectiveness profile of a T2T strategy over the current paradigms.

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