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Rise of precision medicine: can it deliver on its promise in IBD?

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ABSTRACT

The clinical and molecular heterogeneity of IBD—both between patients and within the same individual over time—continues to pose a significant challenge to the implementation of truly personalised treatment strategies. Unlike oncology, where somatic mutation patterns define an actionable information layer, IBD lacks detectable dominant molecular drivers that can guide therapeutic choices. Although the therapeutic landscape has broadened with the advent of numerous biologics and small molecule drugs, predictive (*ex ante*) biomarkers for treatment response remain elusive. In this review, we assess the current progress and limitations of biomarker-guided precision therapy in IBD. We argue that traditional binary response definitions at single landmark endpoints fail to reflect the multidimensional and dynamic nature of therapeutic outcomes. We hence propose combined, and thus individualised, endpoints such as comprehensive disease control as a more holistic and responsive therapy goal in IBD. We propose to integrate the individual longitudinal dynamics of treatment response, and also continuous, objective monitoring of subclinical residual inflammation, analogous to the concept of minimal residual disease in oncology. In this concept, longitudinal assessment of patient-reported outcomes and molecular profiling in response to therapy may serve as early predictors of long-term outcomes, guide early therapeutic adjustments and reveal mechanisms that open new therapeutic avenues, such as adjunct or combination treatments. Adopting this dynamic, data-driven approach to treatment adaptation could shift management of IBD from reactive to proactive and substantially improve long-term outcomes with the vision to fully control a life-long disease.

KEY MESSAGES

⇒ Individual choice of therapies based on clinical and molecular heterogeneity of IBD, both between patients and within individuals over time, remains a major barrier to precision medicine.
⇒ Baseline biomarkers directing individual assignment of therapies (*ex ante* approach) remain elusive despite an expanding therapeutic repertoire.
⇒ Binary assessments of efficacy at landmark time points, while important for differentiation in regulatory trials, fail to capture the multidimensional, dynamic nature of individual treatment outcomes in IBD.
⇒ Individual response may be best characterised by assessing patient-level response dynamics over time and by using stringent, combined endpoints such as comprehensive disease control.
⇒ Development of adaptive, response-driven treatment algorithms with early therapy intensification or switching is essential to avoid the 'time trap' of prolonged use of not fully effective therapies.
⇒ Patients, once in disease control. need non-invasive surveillance to direct pre-emptive intensification of therapy. In analogy to oncology, we suggest developing a molecular or cellular monitoring of 'minimal residual disease' in patients having achieved comprehensive disease control.
⇒ New (algorithmic) clinical trial frameworks are needed to evaluate individual therapy escalations as an actionable precision medicine approach.

BACKGROUND

Inflammatory Bowel Diseases (IBDs) encompass a group of chronic inflammatory disorders primarily affecting the gastrointestinal tract, with two main subtypes: Crohn's disease (CD, OMIM #266600)[1 2] and UC (OMIM #191390).[3 4] Typically emerging between the second and fourth decades of life, IBD significantly reduces quality of life, contributes to long-term disability and increases morbidity due to disease-related complications. The diseases display a drastic rise in prevalence over the last 70 years and are strongly linked to an industrialised, urban lifestyle.[5–7] Currently, no curative treatment exists. In recent years, several advanced targeted therapies have been approved, all of which provide improvement in terms of signs and symptoms.[8–10] However, these therapies achieve sustained remission in distinctly fewer than 50% of treated patients.[11–14] Up to 30% of patients with IBD are primary non-responders, meaning they do not respond to targeted therapies at a sufficient level at all. Additionally, nearly half of the patients who initially benefit from advanced therapies lose their clinical response within the first years, requiring dose escalation or a change in treatment—an issue known as 'secondary non-response'.[15] The biological mechanisms underlying the loss of response months and years after successful induction remain unclear. In addition to molecular escape mechanisms, secondary treatment failure may also result from the development of anti-drug antibodies and patient non-compliance, which are beyond the scope of this review.

Therapeutic success is typically measured in controlled trials using endpoints with regulatory

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relevance such as clinical remission, defined by the Mayo score or the Crohn's Disease Activity Index (CDAI) in combination with endoscopic improvement.[16–18] While these definitions are validated to demonstrate therapeutic efficacy against a comparator in clinical trials, they fall short of capturing the truly meaningful goal: achieving full control of the disease process, at the clinical, morphological and ideally also at the molecular level. To reach this goal, that also should improve long-term outcomes and promote healthy ageing in the majority of patients, the prevailing paradigm of unstratified single-drug therapy in IBD will need to give way to individually tailored and adaptive treatment strategies. As a perspective, future individual therapies may even include the causal reprogramming of early immunological tipping points such as the emergence of antigen-specific T cells to permanently shut off disease processes. This is the promise of precision medicine: delivering the right therapy to the right patient at the right time.[19 20] In alignment with other initiatives in the field of precision inflammation medicine, we define this as an approach to treating patients that accounts for individual variability and environmental factors, with the goal of addressing unmet needs across all patients more effectively (box 1). In cancer medicine, this paradigm has already revolutionised treatment strategies.[21 22] The focus has shifted from stratifying patients by organ—or tissue-specific classifications to molecular markers. Basket and algorithm trials, the approval of therapies based on specific genetic mutations rather than the organ indications and consequently the establishment of molecular tumour boards, have helped precision medicine to become a reality in significant parts of cancer medicine. This reclassification of patients by mutations in the cancer genome has fundamentally reshaped clinical decision-making and regulatory frameworks, setting a blueprint for treating other chronic diseases. In this review, we explore the opportunities that precision medicine offers for the therapeutic management of IBD, while also addressing the

Box 1 Commonly used endpoint definitions

Singular endpoints

Clinical response
- ⇒ Crohn's disease (CD): Reduction of Crohn's Disease Activity Index (CDAI) by ≥70 points,[125] reduction of patient-reported outcome (PRO)2 (absolute stool frequency ×2; pain score ×5) by ≥8.[126]
- ⇒ UC: Reduction of partial/total Mayo score of ≥30% and of ≥2/3 points from baseline,[24] reduction of PRO2 (rectal bleeding and stool frequency) ≥3.[127]

Clinical remission
- ⇒ CD: CDAI <150 points.[125]
- ⇒ UC: Total Mayo score ≤2 (or stool-frequency subscore of ≤1, rectal-bleeding subscore of 0, endoscopic subscore of ≤1).[87]
- ⇒ PRO2-based definition: CD (absolute stool frequency ×2; pain score ×5) overall <8126, UC: rectal bleeding=0 and stool frequency <1.[127]

Endoscopic response/improvement
- ⇒ CD: >50% decrease from baseline in Simplified Endoscopic Score for Crohn's Disease (SES-CD).[125]
- ⇒ UC: Mayo endoscopic score of 0 or 1.[128]

Endoscopic remission
- ⇒ CD: SES-CD of ≤4 and a decrease of ≥2 points from baseline or an SES-CD ≤ 2, respectively.[125]
- ⇒ UC: Mayo endoscopic score of 0.[128]

Biomarker normalisation
- ⇒ High-sensitivity C-reactive protein <5 mg/L and faecal calprotectin <250 µg/g.

Patient level combined endpoints

Deep remission
- ⇒ Combination of clinical and endoscopic remission (both CD and UC).[129]
- ⇒ Often in combination with: SES-CD of ≤2-4, no deep ulcerations (Crohn's disease)
- ⇒ no steroid treatment for ≥8 weeks.[130]

Histo-endoscopic mucosal improvement
- ⇒ UC: Mayo endoscopic score of 0 or 1 and Geboes score ≤3.1.[125]

Histo-endoscopic mucosal remission
- ⇒ UC: Mayo endoscopic score of 0 and Geboes score <2.[131]

Disease clearance
- ⇒ UC: Combination of endoscopic, histological and clinical remission.[131 132]

Optimal disease control
- ⇒ UC and CD: Complex framework of 13 features including features of disease clearance, based on advisor and patient recommendation.[133]

Comprehensive disease control
- ⇒ UC (and CD): Combination of clinical/symptomatic, endoscopic and histological remission*, biomarker normalisation and PRO-remission*.[85 86 134]

While endpoint definitions vary considerably across academic and industry-sponsored studies, commonly used binary endpoints are summarised in the table. Notably, registration trials often employ dual endpoints—where efficacy must be demonstrated independently for each endpoint at the cohort level (eg, clinical remission and endoscopic response as a co-primary endpoint for induction of UC). In contrast, achieving a patient-level combined endpoint is more stringent, as it requires that each individual patient meets all specified criteria simultaneously to be counted as a success.
* if available.

specific challenges and pitfalls posed by the inherent complexity of chronic inflammatory diseases.

The time trap: accumulating damage and complications as a major hurdle in IBD therapy

Clinical evidence indicates that treatment efficacy diminishes with longer disease duration and prior exposure to multiple advanced therapies. A clear relationship between the number of prior advanced therapy failures and a reduced therapeutic benefit has been shown for almost all advanced drugs in both types of IBD, an observation that is potentially confounded by duration of disease and patient compliance among several other factors.[12 23–25] This is particularly well documented for second line advanced therapies following prolonged use of anti-tumour necrosis factor (TNF) agents, which often lead to fast symptomatic improvement; however, without achieving sustained disease control in many patients.[26–29] One key factor influencing treatment response is therefore pre-existing chronicity of inflammatory disease. Particularly, in patients with long-standing CD, a connection between persistent inflammation and irreversible structural damage, including strictures, fistula and fibrotic organ remodelling has been documented. Follow-up anti-inflammatory therapies are then frequently less effective at controlling symptoms and healing the mucosa.[30] The longer the disease persists, the more likely it is that inflammation-driven structural tissue dysfunction becomes an emerging factor of therapy failure.[31] A negative relationship between disease duration and therapeutic efficacy has been well documented in CD but is less well established for UC.[32]

The pathophysiological basis of repeated failure of advanced therapies beyond the impact of structural damage—often referred to as 'biologic fatigue'—remains poorly understood. Chronic suboptimal drug exposure, which includes the effect of anti-drug antibodies, is a contributing mechanism, particularly to secondary failure. Therapeutic drug monitoring thus has emerged as a distinct field but will not be further addressed in this review.[33 34] An interesting point is whether secondary treatment failures are also specifically driven by distinct underlying biological mechanisms, or whether multiple prior therapy failures in a given patient merely reflect an inherently complicated, refractory disease phenotype, characterised by a more complex and multifactorial inflammatory process, independent of the treatment applied. Evidence for pathomorphosis, that is, the evolutionary change of disease mechanisms that occur in the patient under the pressure of a specific therapy, has been suggested, for example, by showing increased interleukin (IL)-23 expression in anti-TNF failure patients with Crohn's disease.[35] Along this line, several molecular baseline signatures for prediction of development of a complicated disease course have been identified in adult and paediatric patients, which could guide the early use of targeted therapies in the disease course.[36–38] The recent PROFILE (PRedicting Outcomes For Crohn's disease using a moLecular biomarker, ISRCTN11808228) trial has shown the difficulty of translating such markers into a clinical utility. Although previously replicated, the prospective use of the tested marker set failed as a guide to identify complex patients, which would particularly benefit from an early combination therapy (ie, at diagnosis) with anti-TNF and an oral immunosuppressant. One can speculate that the study failed to reach its primary endpoint due to a large efficacy signal of the combined top-down therapy even in unselected adults with newly diagnosed active CD in contrast to stepping up via a standard therapy algorithm.[39] Taken together, current evidence supports the existence of an early therapeutic window for optimal chances to reach disease

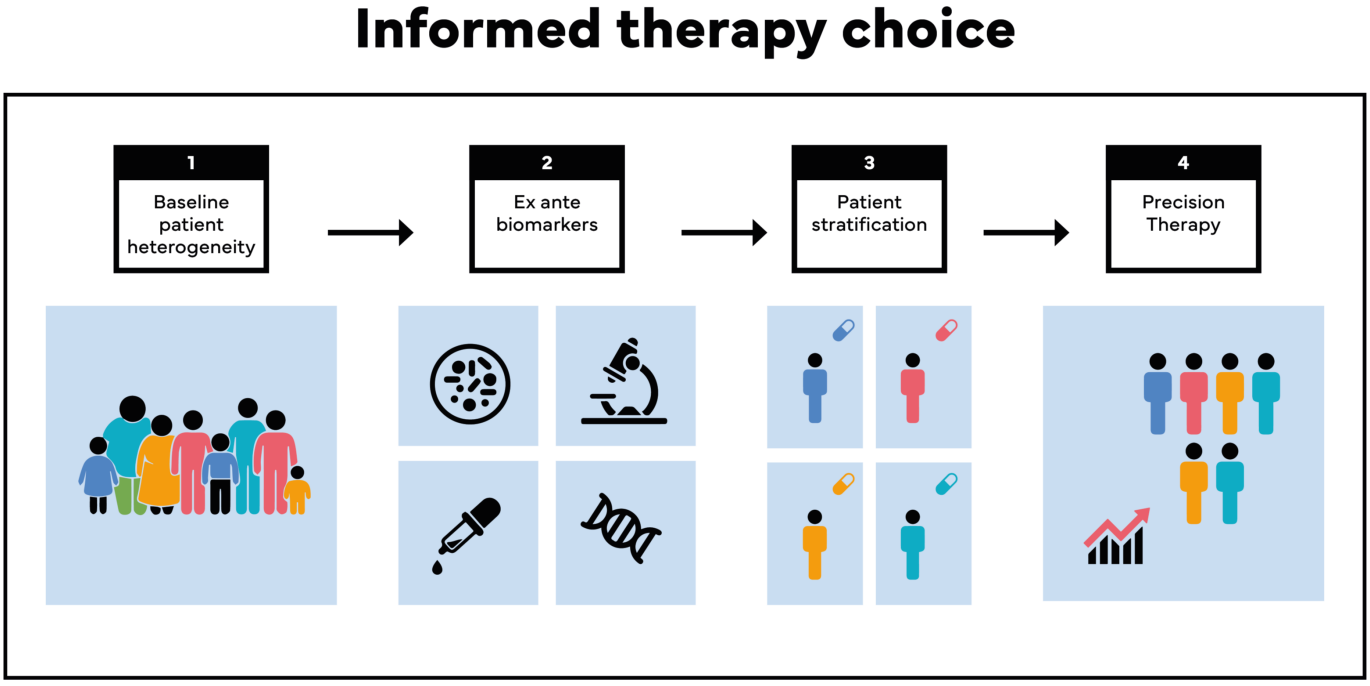

Figure 1 Ex ante biomarker strategy: informed therapy choice in IBD?
Recent efforts to develop a precision medicine approach for IBD have focused on characterising interindividual heterogeneity at baseline. The overarching goal is to identify *ex-ante* biomarkers—including genetic variants, microbiome composition, epigenetic patterns (eg, methylome), transcriptomic signatures, histopathological features and clinical metadata—that can inform patient stratification and guide therapeutic decision-making. This biomarker-driven approach aims to tailor interventions to individual patient profiles, ultimately improving treatment efficacy and long-term outcomes in IBD. (Icon source: The NounProject).

control which should be leveraged to avoid disease progression and complications. Prolonged inadequate inflammation control likely allows the development of end-organ damage and diminishes future treatment efficacy, highlighting the need for early, precisely chosen, molecularly guided interventions and a holistic approach to disease management to prevent a prolonged continuation of partially ineffective therapies.

Baseline biomarkers to increase efficacy of targeted therapies

The substantial dissatisfaction with the long-term efficacy of targeted therapies in all-comers has prompted interest in defining subpopulations, in which therapeutic efficacy of a particular drug class would be higher than in the overall population (eg, 'ideal anti-TNF patients' or 'ideal anti-IL-12/23 patients'). The underlying assumption is that individual disease heterogeneity (eg, fixed immune network states)[40 41] leads to variable responses to different mechanisms of actions (MOAs) (figure 1). This concept allows to explain why small subgroups of patients appear to respond to treatments, which appear ineffective or even detrimental at the overall patient population level (eg, directed against IL-17 antibodies[42] or Cytotoxic T-Lymphocyte-Associated protein 4 (CTLA-4)).[43 44]

In oncology, baseline biomarkers have played a crucial role in increasing therapeutic efficacy by guiding therapeutic strategies based on predicted efficacy of particular drugs.[45] Prognostic biomarkers, including genetic and serological markers, have become integral to clinical practice, aiding in the identification of patients at risk for aggressive disease progression. They facilitate early intervention with advanced therapies and help predict treatment failure, leading to more informed and proactive therapeutic decisions. Why is the situation in IBD still different?

Since the first clinical use of an anti-TNF agent for CD,[46 47] a plethora of studies have explored potential biomarkers to predict which patients with IBD are most likely to respond to specific MOAs. Most of these studies have focused on baseline biomarkers (prior to the first administration of the biological agent) under the premise that patient-intrinsic factors may determine therapeutic responsiveness. Early investigations in anti-TNF therapy investigated laboratory markers of inflamation such as C-reactive protein (CRP), perinuclear anti-neutrophil cytoplasmic antibodies and anti-*Saccharomyces cerevisiae* antibodies.[48 49] Other efforts attempted to link genetic predisposition to treatment response, suggesting single nucleotide polymorphisms in genes implicated in IBD pathogenesis as predictors of therapeutic success.[50–52] Several studies have examined alterations in inflammatory signalling pathways, such as nuclear factor kappa B,[53] apoptotic cascades[54–56] and mitogen-activated protein kinases.[57 58] Not surprisingly, differential expression of target genes for the respective therapy has been suggested to predict better treatment response, especially if these represent generic elements of the inflammatory pathophysiology. High levels of TNF expression are associated with a benefit from anti-TNF agents such as infliximab or adalimumab, whereas those with elevated IL-23 signalling respond better to secondary use of IL-12 and/or IL-23 inhibitors.[59] Additionally, high pretreatment mucosal expression of IL-8,[60] IL-7R[61]or activation of oncostatin M (OSM)[62] were linked to primary non-response to anti-TNF therapy in patients with IBD. Low TREM1 serum levels have been suggested as a marker for non-response to anti-TNF in case series but failed to replicate in the prospective SERENE (Studies of a Novel Approach to Induction and Maintenance Dosing With Adalimumab in UC, NCT02065622 and CD, NCT02065570) studies.[63 64] Elevated IL-6 and IL-8 levels were also reported to be associated with non-response to vedolizumab.[65] Most of the observations were made in small , monocentric cohorts either lacking replication or —if replicated—prospective determination of a meaningful effect size that allows use on the individual level. Observations often failed to account for confounding effects introduced by unintended stratification based on varying levels of inflammatory load, too. It is thus possible that some of the reported associations only broadly reflect general inflammatory activity in a similar way as CRP or faecal calprotectin (FCP).

With advancements in high-throughput, hypothesis-free profiling technologies ('omics analyses')—including transcriptomics, serum proteomics and microbiome analyses—the search for predictive biomarkers has expanded beyond predefined candidate pathways. These include peripheral blood as well as biopsy messenger RNA profiles.[66–70] Likewise, baseline microbial signatures linked to favourable or unfavourable response have been suggested for several biologics.[71–75] Single-cell RNA profiling has identified a distinct immune cell cluster characterised by IgG plasma cells, macrophages, activated T cells and stromal cells being associated with disease persistence and resistance to anti-TNF therapies.[76] Recently, more complex computational models incorporating multimodal molecular datasets have been developed.[77 78] Unfortunately, all like all other *ex-ante* biomarker signatures these approaches suffer from small positive or negative individual predictive values and/or lack larger scale replication. As a result, the promise of baseline biomarkers directing patient selection to prevent prolonged exposure to partially effective treatments and to minimise adverse effects currently remains unfulfilled in the context of personalised clinical practice.

Holistic treatment goals versus endpoints used in clinical trials

This prompts the question of why even modern research technologies still struggle to identify robust biomarkers for effectively stratifying patients with IBD and guiding therapy. The basis of current biomarker discovery strategies is the clinical classification of patients into responders and non-responders based on a specific therapeutic endpoint (eg, clinical remission or endoscopic improvement). However, typical biomarker identification studies so far have been conducted in research settings, where a detailed, prospective phenotype assessment is often not available for the patients donating samples for analysis. As a result, heterogeneous—often self-defined—classifications of response/non-response have guided sophisticated molecular discovery campaigns. Variations in inclusion criteria, small cohort sizes, inconsistent sampling and differences in endpoint timing have further confounded such analyses. Unsurprisingly, the power to detect relevant biomarkers is low because the detail and quality of the phenotype definition is far away from the depth of the molecular analysis.

Large, prospective trials offer the most reliable classification of therapy response due to their prospective and well structured design and to rigorous endpoint monitoring. However, even in such trials, therapeutic success is typically defined as a binary event that is only assessed at predefined landmark time points, such as the end of the induction phase or after completing a 1-year maintenance period. Endpoint definitions in industry sponsored clinical trials (see Box 1) correspond to regulatory criteria that combine a symptomatic improvement parameter (eg, CDAI remission with<150 points in CD or a rectal bleeding score of "0" in conjunction with a stool frequency score of "0" or "1" and a decline by 1 point as subscores of the partial Mayo

clinical score in UC) with an objective measure, such as endoscopic response (eg, a drop of the Simplified Endoscopic Score for Crohn's Disease by 50% or a Mayo endoscopic score of 0 or 1 without friability in UC). However, these do not represent endpoints that capture complete remission or comprehensive disease control (which should be regarded as 'therapeutic success' in the context of disease biology), but rather operational definitions of substantial disease improvement primarily designed for proofing clinical efficacy of a particular therapy against a comparator.

Binary endpoint definitions at landmark timepoints are inherently limited in scope, as they neither capture the extent to which an endpoint is achieved, nor the speed or dynamics of response. Emerging evidence indicates that deeper levels of remission—as reflected by more stringently defined (combined) endpoints—are associated with improved long-term outcomes. Newer measures of deep remission have been proposed, particularly within the STRIDE II (Selecting Therapeutic Targets in Inflammatory Bowel Disease II) initiative.[79] STRIDE-II and even more STRIDE-III emphasises more stringent, time-bound outcome definitions, specifying not only the nature of the endpoint but also the timeframe within which it must be achieved. With refined criteria derived from systematic review of clinical studies - encompassing sustained remission, mucosal healing and long-term prevention of complications - the STRIDE targets clearly etend beyond conventional regulatory endpoints. Thresholds for laboratory markers of inflammation (ie, FCP and serum CRP) as well as for histological activity (ie, Geboes,[80 81] Robarts or Nancy index,[82] respectively) that are employed as secondary endpoints in clinical trials have been defined and emphasized.[83]

The notion of single combined endpoints, while not explicitly defined in the STRIDE II framework, has subsequently evolved into constructs such as deep remission, disease clearance, optimal disease control, and comprehensive disease control (CDC) (see box 1). While these definitions are partially overlapping, they differ in components and complexity, and some have been developed specifically for either CD or UC, rather than being uniformly applied across both conditions. 'Optimal disease control' represents a multifaceted concept, incorporating symptoms, functional outcomes, objective and markers of inflammation, which was designed in an iterative process with physician advisors and patients. The term 'disease clearance' has been adopted from dermatology, where this is used as a low-level endpoint as it does not include assessment of joint inflammation and has been suggested in IBD as a patient-level combination between response in histology, endoscopy and clinical symptoms. Notably, adding more endpoints to a combined outcome like CDC saturates the discriminative power. For example,

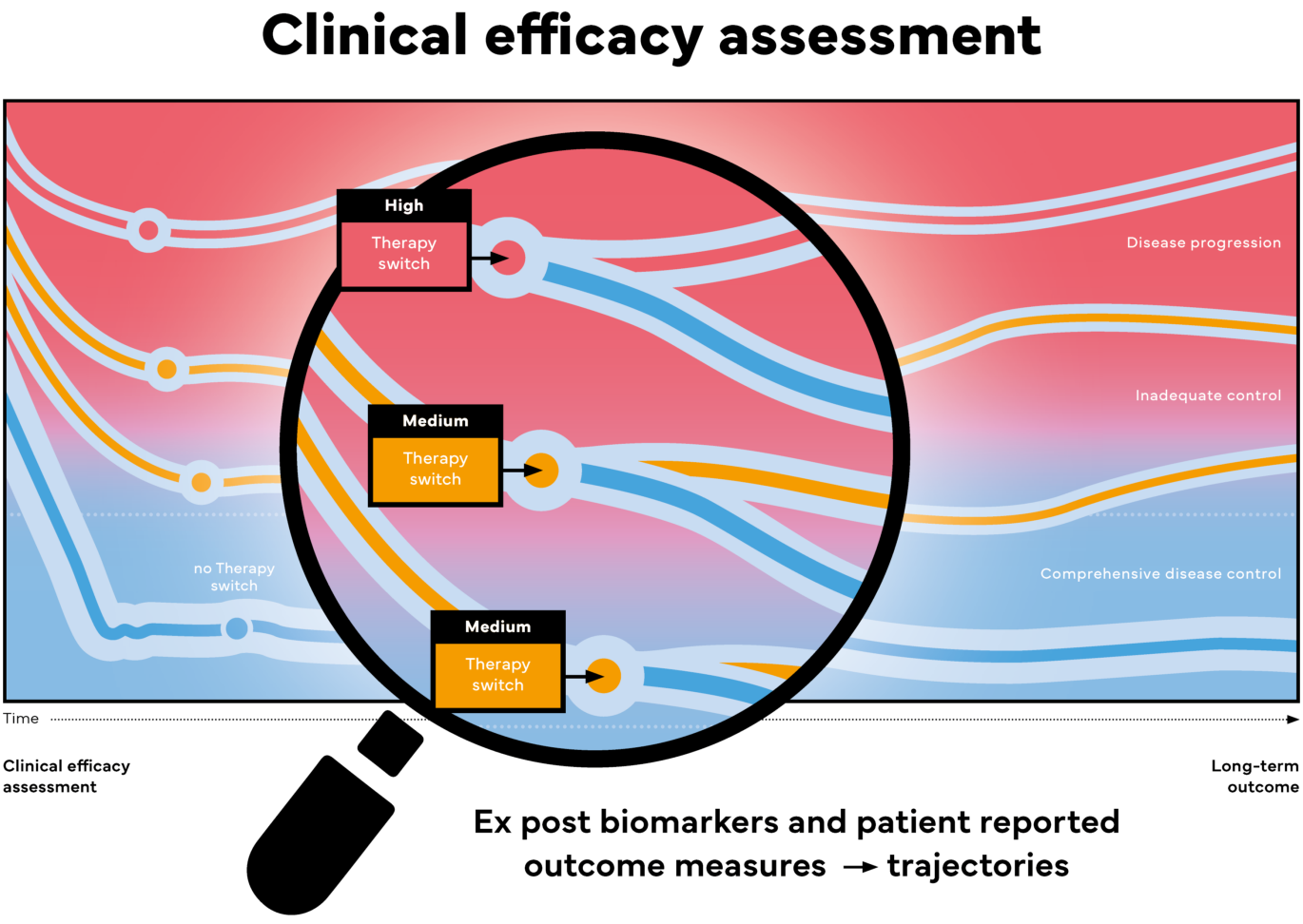

Figure 2 Treatment response trajectories reveal differences in response dynamics, helping to identify patients more likely to achieve long-term success. Clustering of individual treatment response time series—currently based on daily patient-reported outcomes—uncovers distinct responder populations defined by their response dynamics. Fast responders (blue line) have an increased likelihood to reach deep long-term endpoints (eg, comprehensive disease control). Patients on less favourable (ie. slower) treatment response trajectories might benefit from early therapy switches or introduction of a combination therapy, which needs to be examined in prospective clinical trials.

when endoscopic, symptomatic, and biomarker remission are combined with remission in IBD-specific quality of life (IBDQ), the resulting patient population closely mirrors that identified by substituting histological for IBDQ remission—representing roughly 20% of patients with ulcerative colitis reaching this target under advanced therapies in clinical trials. In a retrospective analysis of the SELECTION (Study to Evaluate the Efficacy and Safety of filgotinib in the Induction and Maintenance of Remission in Adults With Moderately to Severely Active Ulcerative Colitis, NCT02914522) trial investigating filgotinib in UC,[84 85] those patients who met CDC also had a significantly higher rate of normalisation in general quality-of-life measures (ie., short form health survey (SF)-36, Euro Quality-of Life-5 Dimensions (EQ-5D)).

In the following, we focus on the term comprehensive disease control (CDC), which has been defined as the combination of clinical remission, endoscopic remission, normalisation of laboratory biomarkers of inflammation and histological remission and was validated in a co-creation process involving patients.[86] While originally developed as a combined endpoint in UC, it is currently also explored for CD. For the sake of simplicity and consistency, we will use the term CDC throughout this perspective paper to refer to both UC and CD, unless otherwise specified.

Application of CDC in a re-analysis of the VARSITY trial[87] (An Efficacy and Safety Study of Vedolizumab Intravenous Compared with Adalimumab Subcutaneous in Participants With Ulcerative Colitis, NCT02497469) demonstrated that combined endpoints provided a much clearer distinction between the treatments (45.9% disease control in vedolizumab vs 31.3% adalimumab) than the overall 9% difference observed when using Mayo score-based remission definition as the primary endpoint.[88] Taken together, clear evidence suggests that combined stringent endpoints such as CDC will allow clearer differentiation between therapies in head-to-head trials and, on a patient level, describe the ultimate benefit of halting the disease process. Early identification of patients on a symptom response trajectory toward CDC is therefore becoming increasingly important, alongside the development of strategies to adjust treatment for those less likely to reach this state with current therapy.

Individualised assessments of therapy response trajectories

An exclusive focus on landmark endpoints fails to capture the clinical dynamics and temporal patterns of therapeutic response. To fully understand the individual patient's path to eventually reaching CDC and thereby identify those achieving it at the earliest possible time point, it is essential to assess the heterogenous and dynamic nature of individual therapeutic responses. In most studies, cohort level data of response over time (ie, decrease in CDAI, partial Mayo Score or PRO2) are reported aggregated over the entire cohort at landmark timepoints ignoring the heterogeneity of indivdual differences in response levels between patients and lacking the connection of individual patient response trajectories to end-of-maintenance endpoints. To better understand and characterise individual patterns of treatment response, continuous recording and analysis of patient reported outcomes (PROs) as individual connected time series data emerges as an important approach towards a more comprehensive view of therapeutic effects (figure 2). While currently such analyses are mostly based on daily PRO-2 scores from diaries,[89] this may also be extended to sequentially recorded objective measures such as data from wearables,[90 91] laboratory biomarkers of inflammation (eg, FCP, CRP, including home-based tests and emerging sensor technologies)[92 93] or ultrasound assessments. Statistical techniques, such as group-based trajectory modelling or *k*-means clustering, can be applied to examine individual time series data and examine whether patient clusters emerge—a technique which has long been employed for modelling progression and response to therapy in other non-communicable, non-malignant diseases.[94 95] As a final step, individual patient-level (combined) outcomes can be mapped to different individual response trajectories to explore the relationship between dynamics of individual treatment response and long-term disease improvements.

We have applied this concept to the filgotinib data from the SELECTION trial in patients with moderate-to-severe UC.[84 85] Five distinct response clusters were identified based on their response dynamics: super-responders, fast responders, delayed responders, slow relapsers and fast relapsers. Most interestingly, patient subpopulations could be defined that not only differed clearly in the speed of response, but (super)fast responders had a significantly higher rate of CDC than slower responders who almost all failed such a stringent endpoint. This phenomenon has been replicated in multiple additional datasets, including phase 3 trials for ozanimod,[96] etrolizumab,[97] etrasimod, ustekinumab, mirikizumab,[98] vedolizumab and adalimumab in UC,[99] as well as for subcutaneous infliximab[100] and mirikizumab[101] in CD. Across all datasets, a strong relationship has been observed between the speed of response to therapy and favourable long-term outcomes, including the achievement of individual composite endpoints such as CDC.[102] However, the clinical or molecular factors underpinning individual CDC achievement remain unclear and are subject to intense exploration.

The link between the rapidity of treatment response and clinical outcomes is well established across diverse medical disciplines and therapeutic indications. A rapid response to antibiotic therapy in infections, such as pneumonia, is widely regarded as a strong positive prognostic factor, indicating effective bacterial eradication and a lower risk of complications, prolonged hospitalisation or mortality.[103] Similarly, in sepsis, early and effective antibiotic administration is directly linked to improved survival rates, emphasising the critical role of response dynamics in predicting outcomes.[104] Likewise, in oncology, the dynamics of response to anti-cancer therapies—including chemotherapy, targeted therapies and immunotherapies—have significant predictive value. In some cancers, such as acute leukaemia, achieving early molecular remission within the first few treatment cycles is a key individual predictor of sustained remission and overall prognosis.[105] The same concept is now gaining recognition in IBD, where early response dynamics to advanced therapies may similarly serve as a timely indicator of deeper and more durable disease control in the further course of disease.[28] Importantly, this observation does not preclude that slower responders may still achieve CDC, but they will do so at much lower rates and, in the end, may be more likely to benefit from therapy modification.

The question of whether it is always the same patients producing most favourable responses to different therapies or whether super(fast) response represents a specific interaction between a particular intervention and the individual pathophysiology is still being explored. Mucosal transcriptome analyses supplementing the definition of subpopulations by symptom response trajectories have been conducted in two clinical trial datasets evaluating filgotinib[106] and vedolizumab/adalimumab in UC, respectively. In both studies, the different response trajectory groups strikingly differed by signatures of upregulated and downregulated genes in mucosal biopsies when comparing baseline to the first endoscopic assessment at 10 weeks (filgotinib)

and 12 weeks (vedolizumab/adalimumab).[107] The marked differences in regulated pathways between therapies further support the view that rapid responders achieving CDC are not necessarily the same individuals across different treatments, but rather those whose disease mechanisms align particularly well with the specific mode of action of a given therapy. In addition, an analysis of baseline confounders was performed across patient-level data from the active therapy groups of multiple randomised controlled trials in UC. Although biological naivety and lower disease activity were associated with super-fast responses, these factors alone were far from sufficient to statistically explain the phenomenon.[102] Together, this underscores two subsequent implications: (1) the need for dynamic, easily accessible (bio) markers predicting and monitoring CDC, and (2. the importance of early, stringent individual therapy optimisation strategies to improve suboptimal response trajectories and promote achievement of CDC.[108]

A path for dynamic re-organisation of therapies

To improve outcomes and achieve CDC in most patients, we must rethink how we use early response information to individually optimise therapy sequences. The dynamic nature of IBD further underscores the need for real-time, adaptable treatment strategies rather than overall predictive models. The underlying systems medicine concept is that targeted therapies specifically disrupt disease processes based on their mechanism of action,[109] revealing hidden molecular differences between individuals, which are currently missed, for example, by static baseline measurements. To systematically discover and monitor individual response trajectories for different therapy principles, it is essential to conduct prospective studies with serial molecular profiling together with high resolution patient phenotyping to fully capture the longitudinal dynamics of response. Ultimately, this approach may yield dynamic biomarkers that supplement or even replace symptom-based response trajectories, enabling more precise definition of critical time points for early therapy adjustment and thereby increasing the overall likelihood of achieving the long-term goal of CDC (figure 2).

In the search for individual markers of favourable therapy response, we demonstrated that serial transcriptomic and DNA methylome markers from peripheral blood not only reveal distinct mechanisms of action and pharmacodynamics between anti-TNF and anti-integrin therapies but also enable early prediction of treatment outcomes—specifically, remission at week 14—based on dynamic molecular changes observed as early as week 2. Machine learning-based dynamic features that differentiated

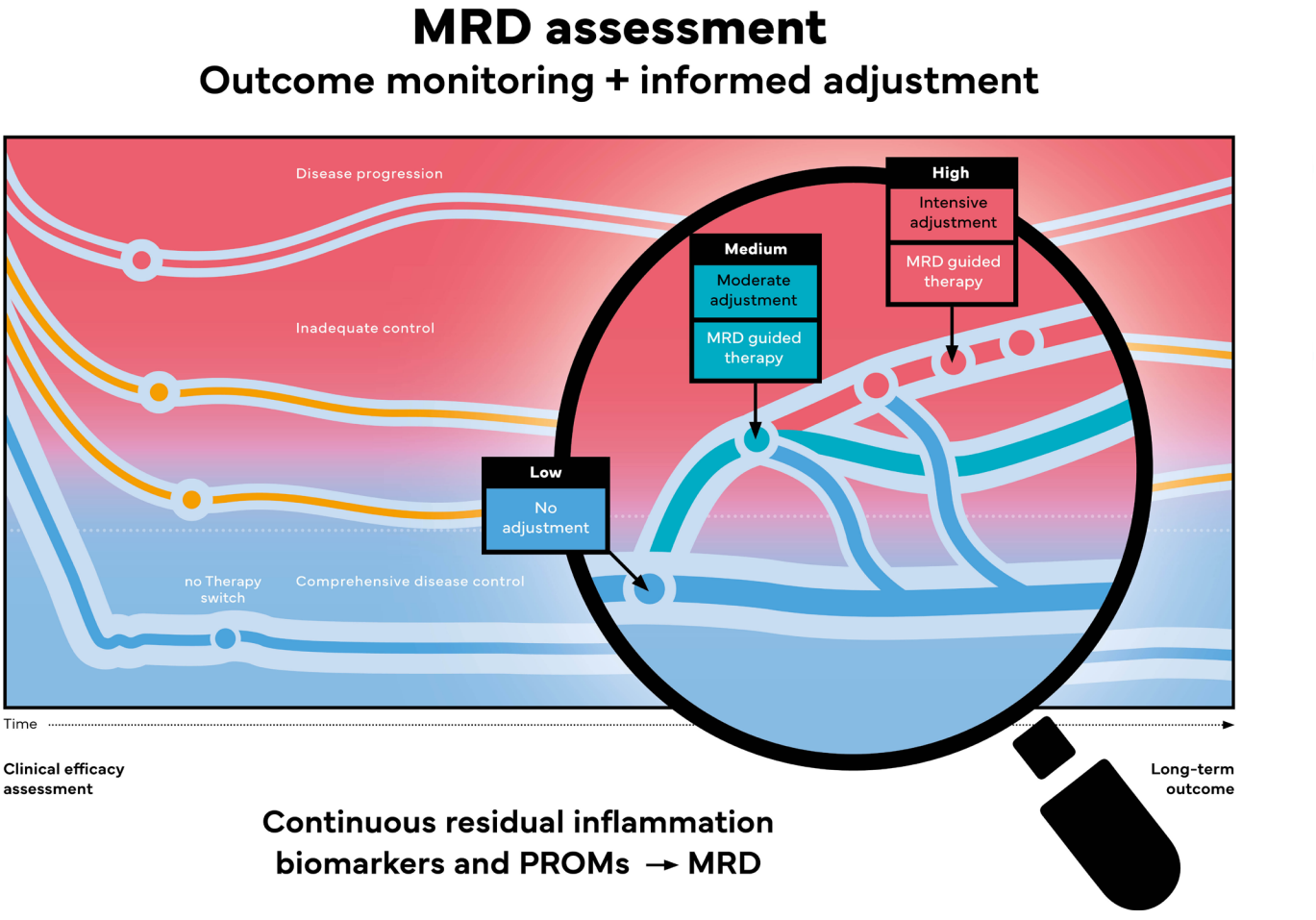

Figure 3 Monitoring minimal residual disease (MRD) in IBD and long-term outcome. Patients in (comprehensive) disease control (ie, without clinically or morphologically detectable disease activity) receive monitoring of MRD that in analogy to cancer would be best carried out by a cellular or molecular test from accessible biomaterials (eg, from stool or capillary blood). Minimal residual disease measures the remaining 'molecular' signature of inflammation in the absence of clinical or morphological measures of disease activity. This would reduce the need of monitoring of disease in deep remission (ie. CDC) by invasive and complex diagnostic techniques. The development of such defined molecular signatures of MRD is yet to come and may result from a systems analysis of individual Omics layers with spatial integration.

responder from non-responder trajectories were robustly validated in an independent cohort, underscoring their reproducibility and potential as predictive biomarkers.[110] The study identified upregulation of type II immunity markers as an early indicator of non-favourable therapeutic outcome, suggesting that non-response reflects not merely insufficient control of inflammation, but the presence of an active, alternative immune pathway that may counteract treatment efficacy. Importantly, this study used only regular definitions of clinical endpoints (ie. clinical remission and endoscopic response), mandating further studies that couple multimodal molecular profiling with dense patient phenotype information (including diary recordings of PRO measures (eg, PRO2)[111] and/or objective performance-based outcomes (eg, recorded by wearables)[90 112] and stringent endpoints like CDC.

Defining a minimal residual disease concept in IBD

Long-term control of inflammation in the maintenance phase in IBD closely mirrors the oncology paradigm of full clinical remission, which has prompted the concept of a minimal residual disease (MRD) signature for surveillance, that—if changes

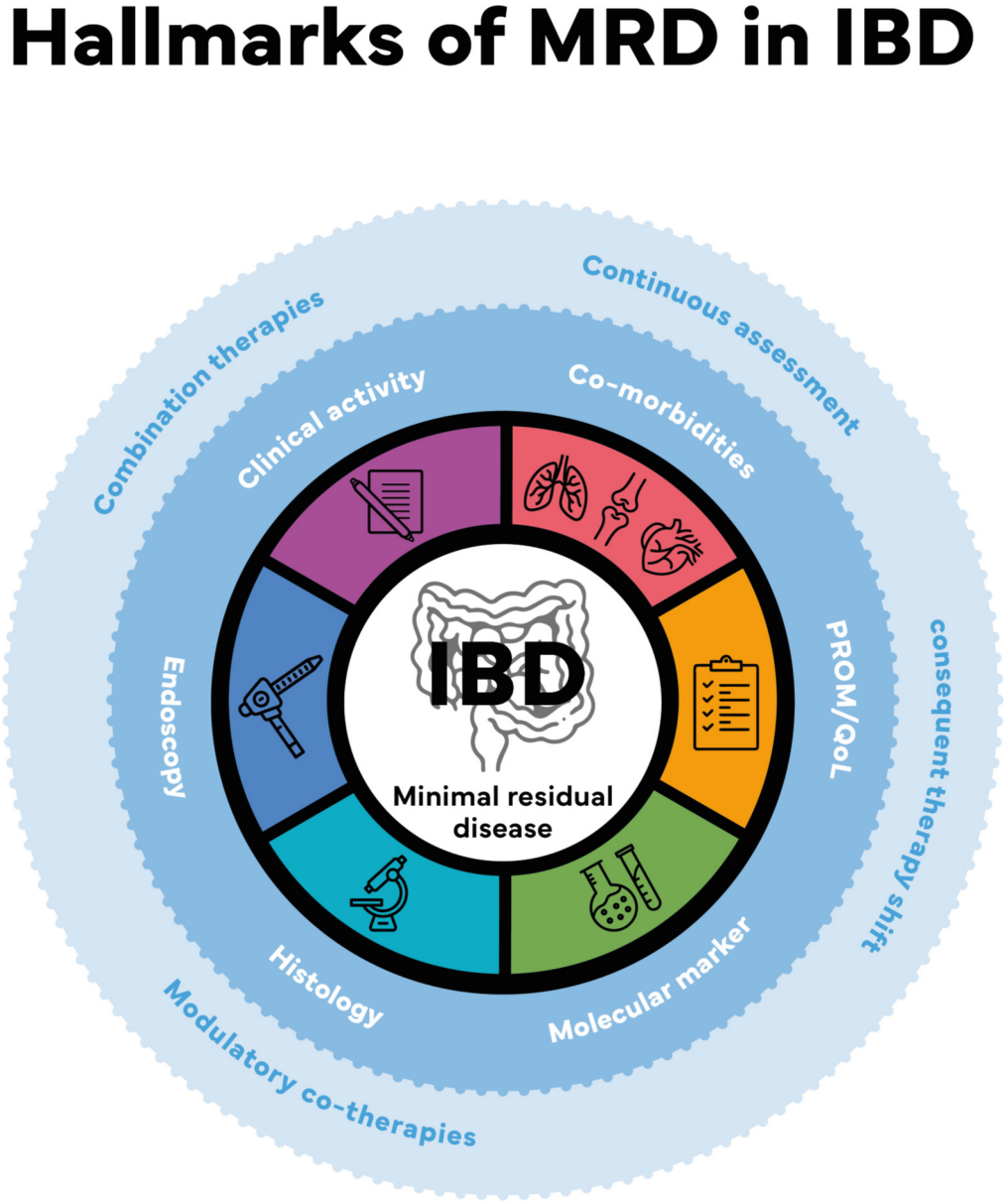

Figure 4 Hallmarks of a minimal residual disease concept in IBD. The outer circle (light blue) represents the overarching clinical requirements necessary to achieve sustained and comprehensive control of inflammatory activity in IBD. The inner circle (darker blue) outlines clinical assessment tools, including standard measures for evaluating disease control, such as clinical indices, endoscopy, conventional histology and biochemical (laboratory) markers of inflammation. In this framework, MRD is characterised by molecular biomarkers derived from easily accessible biospecimens (eg, blood, stool), along with additional high-resolution patient-centred data streams (including objective assessments for example from wearables or biosensors). These surrogate markers are monitored frequently and can reduce the need of invasive, intervention-based assessments (such as endoscopy and histology) for maintenance surveillance. Importantly, while such non-invasive monitoring enhances temporal resolution and sensitivity of disease tracking, it will still require periodic tissue-based validation to confirm remission status and guide long-term therapeutic decisions. I/con source: The NounProject. MRD, minimal residual disease; PROMs, patient-reported outcome measures; QoL, quality of life).

Box 2 Selected large precision medicine consortia focusing on therapy response in IBD

Precision Medicine in Chronic Inflammation (https://www.precisionmedicine.de)
⇒ 3TR (https://3tr-imi.eu)
⇒ ImmUniverse (https://www.immuniverse.eu)
⇒ Methylomic (https://methylomic.eu)
⇒ PerPrev-CID (https://www.perprev-cid.eu)
⇒ IBD Plexus (https://www.crohnscolitisfoundation.org/research/plexus)
⇒ Clinnova (https://www.clinnova.eu)
⇒ IBD-Response (https://www.ibd-response.co.uk)
⇒ 1000 IBD project (https://1000ibd.org)

The table presents a selection of publicly-funded academic consortia dedicated to advancing precision medicine strategies aimed at improving therapeutic outcomes in UC. While many of these large-scale initiatives are supported by the European Commission, several national programmes—such as those listed in the UK and Germany—are also actively contributing.

occur—prompts timely therapeutic intervention. MRD has emerged as a critical tool in haematology and oncology, revolutionising the way patients with cancer are managed.[113 114] MRD refers to the dynamic presence of a small number of residual cancer cells that may persist in a patient's body even following a most successful treatment, when clinical and radiological assessments indicate morphologic absence of the tumor. Recent technological advances—such as deep sequencing of liquid biopsies for mutational load[114] and detection of circulating tumour cells[115]—have translated this theoretical concept into clinical utility. Achieving and controlling MRD has become a desirable target in haematology and oncology, and it has been linked to favourable long-term outcomes such as tumour-free and overall survival. Changes in MRD activity allow for the early identification of patients at high risk of relapse. Even when patients appear to be still in clinical remission, fluctuations in MRD levels may timely prompt therapeutic adjustments. Pre-emptive therapy adjustments before visible tumour progression therefore use the predictive power of monitoring MRD to transforme a deadly disease into a controlled, dormant chronic state. Applying MRD as a concept to IBD would supplement the holistic clinical treatment goal of achieving CDC and may serve as an important interim step on the path towards reprogramming immune responses and ultimately achieving a cure for IBD.

In contrast to the *ex-ante* use of baseline biomarkers, the *ex-post* approach taken by the MRD concept should incorporate dynamic markers associated with different individual patient trajectories (figure 3). The necessary marker sets, that still need to be developed, should offer objective indicators of residual (subclinical) inflammation despite clinical achievement of CDC. The additional quality added to CDC parallels the monitoring of MRD stabilising the therapeutic impact in oncology. One

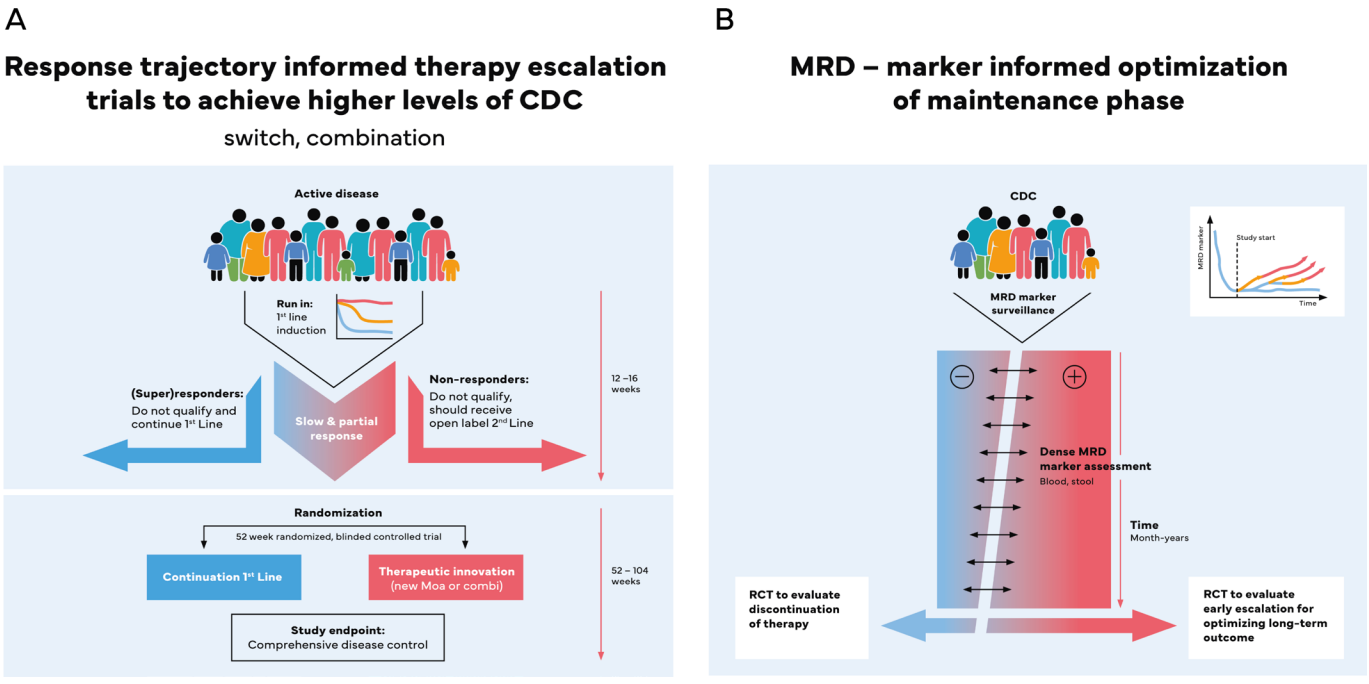

Figure 5 Potential trial designs to modify outcome based on individual response trajectory and MRD information. (A) Patients showing slow response dynamics have a low likelihood of achieving CDC. The trial design includes a run-in period (eg, on a first-line biosimilar) during which individual estimates of disease trajectories are obtained. Super-responders continue treatment and are exluded as well as primary non-responders, who should seek alternate therapies. The remaining patients, who are not on ideal trajectories (approximately 70–80% of the population), are randomised to either a therapy change (switch or introduction of a combination agent) or continuation of the initial therapy (RCT). Prospective data are obtained to determine the optimal time point for a therapy change and to demonstrate efficacy in comparison with continuation of the primary therapy. (B) Patients in CDC exhibit only a MRD signature, which may be detected through molecular assessments from liquid biopsies (blood or stool). Patients who deviate from the MRD signature through subclinical disease reactivation are randomised to a pre-emptive therapeutic intervention or placebo (RCT). This design will assess the clinical significance of immunological disease reactivation in the MRD signature in the absence of overt symptoms and evaluate the effectiveness of a pre-emptive intervention. (CDC, comprehensive disease control; MOA, mechanisms of action; MRD, minimal residual disease; RCT, randomised controlled trial).

would anticipate that molecular signatures of MRD in IBD are generic and not therapy specific. The likely benefit of monitoring biomarkers as a molecular tool to quantify remaining inflammation during response and maintenance is underscored by clinical observations, for example, in the CALM (Effect of tight control management on Crohn's disease outcomes, NCT01235689) study, where clinical activity, CRP and FCP as proxy indicators for intestinal inflammation were used to direct anti-TNF treatment escalation leading to an improvement of the primary endpoint of endoscopic healing at week 48.[116] Further confirmatory trials of this concept (eg, VERDICT trial, The actiVE ulcerative colitis, a RanDomIsed Controlled Trial, NCT04259138) are under way.[117] Deeper profiling in fully quiescent patients (ie, having achieved CDC)—ideally from easily accessible liquid biopsies such as blood or stool, or directly from the target organ—bears the promise of discovery of high-resolution, actionable MRD markers with high predictive power. This approach has been exemplified by the study by Argmann *et al*,[118] who analysed 2400 intestinal biopsies from patients with CD, UC and controls to identify inflammation-associated gene expression signatures. Using these data, they developed a biopsy-based molecular inflammation score, and a corresponding circulating score derived from blood transcriptomes to non-invasively reflect intestinal molecular inflammation.

Unlike in oncology, where MRD is defined by a quantifiable cellular or molecular parameter (eg, leukaemic cell count), the concept of MRD in IBD is likely to be more complex—extending beyond a single metric or even a composite inflammation biomarker derived from a biopsy. To capture the dynamics and extent of therapeutic control of residual inflammation, it can be anticipated to comprise a multilayered assessment of combined clinical activity and molecular parameters (molecular markers and additional patient-centric objective parameters, eg, measured by wearables or apps). Given the challenges of intensive monitoring through interventional assessments, developing molecular MRD signatures from accessible biomaterials such as blood and stool will be essential to inform routine clinical surveillance strategies of CDC (figure 4 Hallmarks of MRD). This concept is inherently dynamic—much like the hallmarks of cancer[119 120]—and will continue to evolve with the emergence of new biomarkers and patient-centred assessments. Importantly, other patient dimensions such as extraintestinal manifestations, fatigue or sexual and mental health, all of which have a biological basis in active IBD and may be independently modulated by specific therapies, might prove critical for a comprehensive definition of MRD-informed monitoring of CDC that truly reflects disease burden and patient well-being.

Perspectives and requirements

Clinically, the envisioned development of an individualised and adaptive IBD precision medicine strategy will require four main points: (1) Structured continuous assessment: Assessment of patients must integrate at present clinical, endoscopic, histological and laboratory inflammation assessments in a longitudinal manner, at a high density after therapy start, to guide care decisions. In the future, a continuous biomarker that may correspond to a yet-to-be-defined MRD-marker signature may reduce the need for clinical monitoring once disease control is achieved and could be supplemented by patient-reported data from electronic diaries and wearables. (2) Consequent adaptation of therapies: Development of treatment algorithms reflecting adaptive, response-driven care strategies with early and stringent therapy intensification or therapy shifts guided by objective classifcations of response threshold is needed to avoid the 'time trap' through prolonged use of ineffective or only partially effective therapies. (3) Development of modifying adjunctive therapies: Adaptation of therapies should include the development of adjunctive therapies that can be added for short intervals or permanently to modulate immune or epithelial pathways enhancing the effectiveness and durability of primary treatments. The microbiome has emerged as a particularly promising target of co-immunomodulation; while this is a clearly emerging field in oncology, for example, with several clinical trials using fecal microbiota transfer (FMT) to increase efficacy of checkpoint inhibition,[121 122] early evidence in IBD also points to its potential in reshaping host responses and influencing treatment outcomes.[73 74 123] (4) Rational choice of combinations in therapies: MOA-specific biomarkers may supplement the guidance by dynamic response assessments for a rational combination to overcome treatment resistance and achieve CDC in the majority of patients.

Translating these insights into clinical practice will be a long and complex process. Several large-scale consortia have been formed, including 3TR, ImmUniverse, Methylomic, IBD Plexus, the DFG Excellence Cluster Precision Medicine in Inflammation and the newly formed EU Horizon PerPrevCID project (box 2). Each of these projects covers unique aspects of the challenges mentioned above, involving the assembly of new large longitudinal treatment cohorts. However, it seems clear that the path towards precision medicine in IBD requires enormous, sustained efforts that can only be achieved through coordinated, international collaboration. The prevailing siloed research model, in which success is defined by individual achievements rather than societal benefit—and often defended on the grounds of data privacy—remains a major barrier to clinical translation. With the emergence of privacy-preserving deep learning methods, such as swarm learning,[124] we for the first time have tools at hand that allow defined collaborative research on clinical and molecular data that includes patient level data from cohorts from industry representing pivotal clinical trials, while ensuring data safety and maintaining individual ownership of data. Other important issues comprise the necessity of large real-world observation cohorts of individuals at risk and long-term clinical trials, many of which may not align with today's interests of pharmaceutical companies. However, such efforts may unlock new opportunities for future pharmaceutical innovation by enabling earlier lines of therapy and supporting the development of new treatments that help a greater proportion of patients achieve CDC.

To move precision medicine into practice, we must persuade funding agencies and pharmaceutical industry alike to support large clinical trials comparing systems-guided therapies in IBD to standard care—both for induction and early switch algorithms as well as MRD marker-guided, presymptomatic intensification of treatment in maintenance phase (figure 5). Induction trials designed to translate individual response trajectory assessments into actionable therapeutic strategies should aim to identify patients exhibiting slow response dynamics. As these patients consequently have a markedly reduced likelihood of achieving CDC, it should be investigated whether therapeutic adaptation, such as the introduction of a combination agent or early switching, can improve their response trajectory and increase the proportion achieving CDC (figure 5A). Once CDC is achieved, ongoing monitoring through regular assessment of a MRD signature may support early, pre-symptomatic detection of returning subclinical disease activity, before an actual clinical relapse. Future trials should assess the prognostic relevance of asymptomatic disease reactivation and determine

whether early pre-emptive intervention in such cases can sustain long-term CDC by therapeutic suppression of MRD activity (figure 5B).

A co-creation process with our patients should become mandatory not only to capture the most meaningful parameters of individual disease control but also to drive understanding and acceptance of intensified monitoring and therapeutic efforts. In the end, our approaches must be globally accessible for patients in different jurisdictions and operate with low complexity as clinical practice will always prioritise fast turnaround times and low cost-to-benefit ratios. Drawing a parallel to technological advances that have transformed imaging modalities such as MRI and sonography, and rendered genome sequencing a routine clinical tool, we are confident that what once seemed unthinkable is now within reach: the clinical implementation of precision medicine in IBD.

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