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A clinician's guide to treat-to-target in Crohn's disease: a comprehensive review

Treat-to-target in Crohn's disease

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Abstract

The modern-day treat-to-target (T2T) approach in patients with Crohn's disease pursues the goal of optimising long-term outcomes through the principles of early intervention and tight disease control. The STRIDE-II guidelines specify short, intermediate, and long-term treatment goals, documenting specific treatment targets to be achieved at each of these timepoints. Scheduled appraisal of Crohn's disease activity against pre-defined treatment targets at these timepoints remains central to determining whether current therapy should be continued or modified. Consensus treatment targets in Crohn's disease, as defined by the updated STRIDE-II guidelines, comprise combination clinical and patient-reported outcome (PRO) remission, in conjunction with biomarker normalisation and endoscopic healing. Although the STRIDE-II guidelines endorse the pursuit of endoscopic healing, clinicians must consider that this may not always be appropriate, acceptable, nor achievable in all patients. This underscores the need to engage patients at the outset in an effort to personalise care and individualise treatment targets. The use of non-invasive biomarkers such as faecal calprotectin in conjunction with cross sectional imaging techniques, particularly intestinal ultrasound, hold great promise; as do emerging treatment targets such as transmural healing. Two randomised clinical trials, namely CALM and STARDUST, have evaluated the efficacy of a T2T approach in achieving endoscopic endpoints in patients with Crohn's disease. Findings from these studies reflect that patient subgroups and Crohn's disease characteristics likely to benefit most from a T2T approach, remain still to be clarified. Moreover, outside of clinical trials, data pertaining to the real-world effectiveness of a T2T approach remains scarce, highlighting the need for pragmatic real-world studies. Despite the obvious promise of a T2T approach, a lack of guidance to support its integration into real-world clinical practice has the potential to limit its uptake. This highlights the need to describe strategies, processes and models of care capable of supporting the integration and execution of a T2T approach in real-world clinical practice. Hence, this review seeks to examine current and emerging

literature to provide clinicians with practical guidance on how to incorporate the principles of T2T into routine clinical practice for the management of Crohn's disease.

Key Words: treat to target; inflammatory bowel disease; Crohn's disease; treatment targets; endoscopic remission; transmural healing; time to response; intestinal ultrasound

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Core Tip: A treat-to-target (T2T) approach applies the principles of early intervention and tight disease control to optimise long-term outcomes in Crohn's disease. This is achieved through scheduled assessments of disease activity, wherein progress is measured against pre-defined treatment targets, to inform whether current therapy should be continued or modified. Despite its obvious promise, a lack of guidance to support the integration of a T2T approach into clinical practice has the potential to limit its uptake. This review seeks to examine the current and emerging literature, to provide clinicians with practical guidance on how to incorporate the principles of T2T into routine clinical practice, as they apply to the management of Crohn's disease.

INTRODUCTION

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The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) committee, supported by the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD), first endorsed the paradigm shifting concept of treat-to-target (T2T) in Crohn's disease and ulcerative colitis in 2015.^[1] This paradigm shift was driven by an understanding that even in the absence of clinical symptoms, cumulative insults to the bowel can result in progressive disease complications; highlighting the need for a proactive target driven approach supported by timely clinical assessment and intervention. This is particularly relevant to Crohn's disease wherein uncomplicated

inflammatory disease can progress to stricturing (18%) and penetrating/fistulising (70%) disease complications without effective treatment to control inflammation.^[2]

The modern-day T2T approach in Crohn's disease pursues the goal of optimising long-term outcomes through tight disease control.^[3] This is achieved through scheduled assessments of disease activity, wherein progress is measured against pre-defined treatment targets to determine whether treatment goals have been achieved, and thus whether current therapy should be continued or modified. It also remains important to acknowledge that the treatment goalposts in Crohn's disease have shifted away from targeting clinical remission and quality of life measures alone, toward integrating both clinical and objective assessments of disease activity when appraising treatment response.^[4] Consensus treatment targets in Crohn's disease, as defined by the updated STRIDE-II guidelines, comprise combination clinical and patient-reported outcome (PRO) remission, in conjunction with biomarker normalisation and endoscopic healing.^[4] These targets prioritise symptom resolution and restoration of quality of life in patients with Crohn's disease with a view toward reducing long-term disease sequelae and disability.

Despite the obvious promise of a T2T approach, a lack of guidance to support its integration into real-world clinical practice has the potential to limit its uptake.^[5] Hence, this review aims to provide clinicians with practical guidance regarding the clinical application of a T2T approach in the context of managing patients with Crohn's disease. Evidence supporting current and emerging treatment targets, as well as systems, processes, and models of care necessary to support the integration of a T2T approach, will also be examined.

TOWARD A PERSONALISED APPROACH

An essential component of enacting a T2T approach in clinical practice is to ensure that the treatment strategy adopts a shared decision-making model between the IBD-patient

and the IBD-clinician.^[6] Although the STRIDE-II guidelines endorse the pursuit of endoscopic healing, clinicians must consider that this may not always be appropriate, acceptable, nor achievable in all patients. This emphasises the need for clinicians to engage patients at the outset in an effort to personalise care and individualise treatment decisions.

A. DEFINING TREATMENT GOALS

KEY POINTS

- > Explain principles and objectives of a T2T approach to patients at Crohn's disease diagnosis
- > Acknowledge that clinicians and patients may have different goals and objectives
- > Define treatment goals that are acceptable, achievable and clinically meaningful to both parties

Patient 'buy-in' to the T2T philosophy remains critical in reducing anxiety and cultivating acceptance of therapeutic changes on the basis of scheduled disease assessments, that may not always correspond to patient perceived deterioration in symptoms or wellbeing. A recent study by Selinger and colleagues found that only 66.2% of 298 patients with IBD who were in steroid-free clinical remission, appraised a T2T approach focused on achieving the absence of mucosal inflammation, to be acceptable (Likert scale ³ 8/10).^[7] Instead, patients were more likely to prioritise avoiding clinical flares, hospitalisation, surgery, and colorectal cancers, as acceptable treatment goals. This implies that a third of patients remain unconvinced by the objectives of a T2T approach; highlighting the need for clinicians to spend more time explaining the rationale behind a T2T approach to patients, and appreciate that treatment targets espoused by STRIDE-II may not be acceptable to all patients.

In light of this, it remains important that IBD clinicians consult with patients to discuss and document treatment goals early on in their disease course. These goals need to be

acceptable, achievable and clinically meaningful to both parties. A patient-centric approach may also lead to greater patient 'buy-in' and thereby reduce non-adherence which has been associated with unfavourable outcomes.^[8-11] Moreover, the need to personalise treatment goals are exemplified by real-world clinical dilemmas associated with initiating, continuing and escalating immunosuppression in those with significant comorbidities, polypharmacy, prior malignancy history, older age, and class or dose-specific medication intolerances.^[12, 13] Thus prioritising symptomatic relief and quality of life measures with a view towards preserving functional independence may be more appropriate than striving to achieve endoscopic healing in specific IBD populations, such as the elderly and those with significant co-morbidity.^[14] Hence, a single treatment target such as endoscopic healing may not be universally applicable across all patients; highlighting the need to personalise treatment goals.

B. INDIVIDUALISE TREATMENT DECISIONS

KEY POINTS

- > Adopting a shared decision-making model that empowers patients to participate in the therapeutic decision-making process should be encouraged
- > Personalising choice of advanced medical therapy is important

Once therapeutic goals have been established, it is important to consider which therapy is best suited to achieve agreed upon treatment targets. While therapeutic effectiveness represents an obvious consideration, several other factors related to the patient, disease, safety, cost, and drug availability, are also likely to influence the choice and sequencing of medical therapies.^[15] Therapeutic sequencing, that is the order in which advanced medical therapies are prescribed, represents an emerging concept borne out of the ever-growing therapeutic armamentarium in Crohn's disease, with several newer therapies also on the horizon.^[16] This is exemplified by data indicating that second and third line biologic therapies may not be as effective as first-line therapies.^[17] Although anti-TNF therapy remains the consensus first-line choice of medical therapy in perianal Crohn's

disease, consensus regarding the sequencing of medical therapies in uncomplicated inflammatory Crohn's disease remains still to be clarified.^[18]

The advent of highly effective biologic medicines, including the recent emergence of small molecules, have proven integral to achieving more favourable clinical outcomes. However, it remains important to acknowledge that the pursuit of more stringent endpoints, such as endoscopic healing, radiologic remission, and normalisation of inflammatory biomarkers, may require early and intensive therapy, which represents an important concept to discuss with patients. This was exemplified by findings of a recent study involving patients with Crohn's disease, who were candidates to receive immunomodulator and/or biologic therapy, which reported that using a shared-decision making model, between the IBD-patient and IBD-clinician, resulted in more patients (25 v 5%, $p < 0.001$) choosing combination (biologic-immunomodulator) immunosuppression over immunomodulator monotherapy.^[19] Additional benefits such as lower decisional conflict ($p < 0.05$), and greater trust in the treatment provider ($p < 0.05$) were also associated with the shared-decision making intervention. This highlights the value of adopting a collaborative approach to therapeutic decision-making that encourages patient participation.

C. TIMING ASSESSMENTS OF RESPONSE

KEY POINTS

- > Assess the right target at the right time for the right therapy
- > Know time to response of the therapy that you prescribe
- > Differentiate between short, medium and long-term treatment targets per STRIDE-II

Therapy specific considerations

Once treatment targets have been agreed upon and a specific IBD therapy has been chosen, an awareness and understanding of the anticipated time for the chosen therapy to induce clinical, biochemical, and endoscopic improvement, is vital in determining the

optimal timing of clinical follow-up, assessments of response, and defining treatment futility.^[20] This is particularly important given that there appears to be significant variability in the time to response between different IBD therapies. In Crohn's disease, therapies such as corticosteroids, exclusive enteral nutrition, anti-TNF therapies, janus kinase inhibitors (JAK-I), and interleukin 12/23 inhibitors have been associated with clinical improvement within 2 mo; while agents such as methotrexate, thiopurines and vedolizumab may take several months to demonstrate maximal response.^[20] In recognition of this, the STRIDE-II recommendations provide guidance on ³ estimated time to response, albeit based on judgemental estimation of findings from an IOIDC survey and a systematic review.^[4] These principles should be used to guide timing of assessments of response, and have been summarised in Figure 1 and Table 1.

Treatment target specific considerations

Identifying appropriate treatment targets remain central to a T2T strategy, as is determining suitable timepoints at which to evaluate whether or not these targets have been achieved. As an example, if a treatment target were to be evaluated too soon, it remains possible that an inappropriate therapeutic change may be initiated; conversely, if a treatment target were to be evaluated too late, it remains possible that a therapeutic change may be inadvertently delayed. Both of these situations have the potential to lead to adverse patient and disease outcomes. In light of this, the STRIDE-II guidelines distinguish between short, intermediate, and long-term treatment targets.^[4] In fact, IBD experts involved in developing the STRIDE-II guidelines identified clinical remission as the most important short-term treatment objective, closely followed by clinical and endoscopic response.^[4] Normalisation of inflammatory biomarkers such as C-reactive protein, erythrocyte sedimentation rate (ESR), and faecal calprotectin were identified as short-to-intermediate treatment targets, while endoscopic healing endures as the consensus long-term treatment target in Crohn's disease.^[4]

EXAMINING CONSENSUS TREATMENT TARGETS

Several treatment targets have been endorsed by the STRIDE-II committee (Table 2). The following section will review the evidence supporting their recommendation, discuss how to incorporate them into routine clinical practice, and highlight any potential limitations in their real-world application.

A. CLINICAL TARGETS

KEY POINTS

- > Clinical symptoms correlate poorly with mucosal inflammation
- > Patient reported outcome measures (PROMs) to be integrated into routine clinical care
- > **Short term (< 3 mo): *Clinical response: 50% reduction from baseline PRO2***
- > **Medium term (3-6 mo) : *Clinical remission defined by PRO2***
- > **Long-term (6-12 mo): *Absence of disability & normalisation of health-related quality of life***

Patient reported outcome measures

Clinical symptoms have been demonstrated to correlate poorly with mucosal inflammation in Crohn's disease. [21] In fact, it is not uncommon to find substantial mucosal inflammation in the setting of clinical remission. Symptoms have, however, been shown to correlate with patient perceived disease control and quality of life; indicating that symptom control represents an important treatment goal from the patient perspective.[22] Patient reported outcomes measures (PROMs) have since become a standard measure of patient wellbeing. As a cheap, inexpensive and easily reproducible method of evaluating clinical symptoms, PROMs can, and should, be evaluated as part of routine clinical care. The most frequently used PROM is the PRO2 which incorporates two items from the Crohn's disease activity index (CDAI), namely the weighted daily stool frequency and abdominal pain.[23] The STRIDE-II definition of short-term clinical response and intermediate-term clinical remission are made solely on the basis of PRO2 assessments; with response defined as a 50% reduction from

baseline, and remission defined as an abdominal pain ≤ 1 and stool frequency ≤ 3 . Moreover, at these short-term (< 3 mo) and intermediate (< 6 mo) timepoints, the STRIDE-II guidelines advocate that treatment changes can be made if these targets have not been achieved.^[4] Nevertheless, despite the importance of incorporating PROMs such as PRO2 into routine clinical care, they need to be used in conjunction with objective measures of inflammation.^[4, 22]

It would be remiss not to acknowledge the impact that IBD has on a patient's mental and emotional wellbeing.^[24] This is also reflected by the STRIDE-II guidelines which endorse improving quality of life and IBD related disability as key long-term treatment targets.^[4] Validated questionnaires and tools such as the IBD disability index and the IBD disk should also be utilised to evaluate IBD related disability and quality of life in this context.^[25, 26]

Limitations of clinical targets

Similar to patients, clinicians also value and recognise the importance of symptom control as a treatment target. This was reflected by ³ most experts in the STRIDE-II Delphi group advocating that symptom relief, that is clinical response followed by clinical remission, represent short and intermediate term treatment goals in Crohn's disease, respectively.^[4] However, one of the inherent limitations of using CDAI as a marker of intestinal inflammation in Crohn's disease, is that the CDAI may be ³ similarly elevated in patients with Crohn's disease and irritable bowel syndrome.^[27] Moreover, patients who achieve clinical response and remission on the basis of CDAI may not always achieve biomarker and endoscopic normalisation, both of which represent intermediate and long-term target targets per the STRIDE-II guidelines, respectively. This was evident in the CALM trial which indicated that treatment escalation on the basis of clinical symptoms alone led to lower rates of endoscopic healing than escalating on the basis of a composite strategy of combined clinical and biochemical (faecal calprotectin *plus* C-reactive protein (CRP)) activity.^[28] Similarly, the SONIC trial found that more than 50% of infliximab-azathioprine treated patients who were in clinical

remission had persistent biomarker and/or endoscopic inflammation.^[29] In view of the frequent discordance between clinical symptoms and objective assessments of inflammation, the STRIDE-II guidelines do not advocate that clinical response and remission represent long-term treatment targets.^[4] Hence, while PROMs such as PRO2 should be integrated into routine clinical care, PROMs are best used in conjunction with objective measures of inflammation to guide therapeutic decision-making.^[4, 22]

B. NON-INVASIVE BIOMARKER TARGETS

KEY POINTS

> Medium term (3-6 mo) : *Normalisation of CRP < upper limit of normal (ULN) and faecal calprotectin < 250 ug/mL*

> Normalisation of both CRP and faecal calprotectin may be of greater utility in terms of endoscopic outcomes, than normalisation of either biomarker in isolation

The ideal biomarker for inflammatory Crohn's disease activity should be accurate, minimally invasive, inexpensive, and acceptable to patients.^[30] Unfortunately, no single biomarker fulfils all of these criteria. Nevertheless, non-invasive biomarkers such as CRP and faecal calprotectin are frequently used in clinical practice. The STRIDE-II consensus guidelines support normalisation of both of these parameters as medium-term treatment targets.^[4]

CRP

Non-invasive serum biomarkers such as CRP are easily accessible, and thus frequently utilised as part of serial monitoring of disease activity in patients with Crohn's disease. However, in view of CRP being neither disease or bowel specific, limitations in using CRP as the sole basis for treatment decisions must be acknowledged. This is exemplified by findings that up to 20% of patients with active ileal Crohn's disease will have a normal CRP, and that CRP concentrations correlate poorly with clinical symptoms which can, at times, make its bed-side interpretation challenging.^[31-33]

Similarly, published data implies that CRP correlates moderately with endoscopic activity in Crohn's disease, with a normal CRP demonstrating a high specificity but low sensitivity for endoscopically active Crohn's disease.^[34-37] Moreover, although a cut-off of 5mg/dL is frequently used to differentiate between normal and abnormal CRP concentrations, Falvey and colleagues demonstrated that any CRP above the ULN was associated with a higher risk of endoscopic Crohn's disease activity.^[38] This is reflected in the STRIDE-II recommendations which specifies that CRP should be normalised to values below the ULN.^[4]

Faecal calprotectin

Faecal calprotectin has proven useful in predicting disease progression in asymptomatic Crohn's disease, reflecting its utility as a non-invasive biomarker capable of facilitating like-for-like longitudinal comparison of luminal Crohn's disease activity.^[39-41] There is also good evidence that calprotectin levels correlate with small bowel and colonic Crohn's disease, although the correlation between faecal calprotectin and endoscopy has proven more robust in colonic Crohn's disease ($r = 0.73$ to 0.88) compared with isolated ileal Crohn's disease ($r = 0.437$).^[42, 43]

Faecal calprotectin has also been well described as a surrogate marker for endoscopic lesions in Crohn's disease. In fact, strong correlations have been documented between faecal calprotectin, endoscopic disease activity, and ulcer depth.^[44, 45] [46-48] D'Haens and colleagues reported that faecal calprotectin values below 250ug/g predicted endoscopic healing (CDEIS ≤ 3) with a ¹⁴sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 94.1%, 62.2%, 48.5%, and 96.6%, respectively.^[44] Conversely, faecal calprotectin values above 250 ug/g were indicative of large ulcers on ileo-colonoscopy with a sensitivity, specificity, PPV and NPV of 60.4%, 79.5%, 78.4%, and 62.0%, respectively. Similarly, targeting faecal calprotectin threshold below 250 μ g/g within 12 mo of Crohn's disease diagnosis has been associated with a reduced risk of composite disease progression, and clinical remission with a sensitivity and

specificity of 90% and 76%, respectively.^[49, 50] While faecal calprotectin cut-offs below 250ug/g may improve clinical sensitivity for disease remission, higher cut-offs increase specificity for active disease. In light of this, an optimal cut-off for faecal calprotectin has yet to be defined – with the STRIDE-II guidelines designating values of 100-250ug/g to reflect normalisation of faecal calprotectin.

While several studies have suggested a cut-off value of 250ug/g to distinguish between active and inactive Crohn's disease, studies have also advocated for lower thresholds depending on the target outcome.^[40, 50-52] The CALM study showcased the clinical utility of incorporating calprotectin thresholds *greater* than 250g/L to designate active Crohn's disease worthy of adalimumab escalation to achieve higher rates of endoscopic healing at 1 year as part of a T2T approach. ^[28] Conversely, a study by Noh and colleagues documented that a faecal calprotectin cut-off of 81.1mg/kg was useful in predicting deep healing reflective of combined endoscopic and radiologic remission in anti-TNF treated patients with Crohn's disease.^[52] Thus, faecal calprotectin has the potential to be used to achieve treatment targets reflective of deep remission if lower treatment target cut-offs are designated.

Combined biomarker remission

The CALM study demonstrated that the combination of biomarker remission (faecal calprotectin and CRP) and symptom driven tight disease control was associated with higher 12-month endoscopic healing and fewer hospitalisations (13.2 *vs* 28.0 events/100 patient-years; $p = 0.02$) than standard symptom based management alone in early Crohn's disease (adjusted risk difference 16.1%, 95%CI 3.9-28.3; $p = 0.01$).^[28] Moreover follow-up out to 3 years (range: 0.05, 6.26 years) suggested that achieving tight disease targets such as endoscopic remission, with or without associated clinical remission (i.e. deep remission), were associated with significantly reduced rates of adverse disease sequelae after adjusting for age, disease duration, prior stricture or surgery, and intervention group. These findings support STRIDE recommendations of deep

remission as the target of choice, with CALM also providing clinical justification to support treatment intensification to facilitate biomarker normalisation to achieve these targets.

C. ENDOSCOPIC TARGETS

KEY POINTS

- > *Endoscopic healing remains the designated long-term treatment target per STRIDE-II*
- > Short to Medium term (0-6 mo) : *endoscopic response; >50% reduction in SES-CD or CDEIS*
- > **Long term (> 6 mo) : *endoscopic remission; SES-CD ≤ 2 or CDEIS < 3, without ulcers***

Favourable associations between endoscopic healing and long-term disease related complications, flares, and surgeries in both Crohn's disease and ulcerative colitis, support the pursuit of endoscopic healing as a long-term treatment target.^[4, 53, 54] With this in mind, the STRIDE guidelines recommend that endoscopic assessment be undertaken 6-9 mo after initiation of medical therapy. However endoscopic healing may not always be achievable within this timeframe. This was addressed in the STRIDE-II guidelines which acknowledged that endoscopic response may suffice as a short-term target following initiation of a new therapy.^[4] However, a lack of consistency in the definitions of endoscopic response and remission in Crohn's disease, led the STRIDE-II panel to develop definitions to align with their proposed endoscopic endpoints.^[4] Endoscopic response was defined as > 50% decrease in the simple endoscopic score (SES-CD) or endoscopic index of severity (CDEIS), while endoscopic remission was defined as an SES-CD ≤ 2 or CDEIS < 3 without any ulcers, including aphthous ulcers.^[4]

Endoscopic response

Preliminary data suggests that early endoscopic assessment within 6 mo of biologic initiation may be associated with fewer disease-related complications (adjusted Hazard Ratio (aHR) 0.35, $p < 0.01$) and a reduction in 24-month risk of disease-related complications (aHR 0.87, $P = 0.02$) including corticosteroid use, emergency presentations, hospitalization, and surgery.^[55] Moreover, the benefit of early endoscopy in Crohn's disease was suggested to be greatest when performed within 4 mo of biologic initiation, with early endoscopic assessment also associated with an increased likelihood of changing biologic (aHR 1.15, $P < 0.01$).^[55] Interpreted together, these findings may reflect that the benefits of early endoscopic assessment may relate to proactive disease monitoring capable of facilitating early treatment optimisation and discontinuation of futile therapy. Nevertheless, further studies are required to clarify the generalisability of these findings given that unmeasured confounders may have accounted for, and influenced which patients underwent early endoscopic assessment, which was the minority (12.8% 2,279/17,807) in this studied cohort.^[55]

Endoscopic healing

Endoscopic healing in Crohn's disease is generally defined as the absence of ulceration of bowel mucosa.^[56] Recalibrating towards this treatment target in Crohn's disease has been driven by studies indicating that achieving endoscopic healing may be associated with more favourable long-term outcomes.^[57-60] A systematic review with meta-analysis of 673 Crohn's disease patients across 12 studies, 7 of which included anti-TNF therapies, highlighted the long-term benefits of medically induced endoscopic healing, with more than two-thirds (69%) of patients who achieved endoscopic healing within the first 6-months maintaining long-term clinical remission.^[61] Early documented endoscopic healing was also associated with high rates (94%) of long-term endoscopic healing relative to comparatively low rates (18%) amongst those with active disease at their first endoscopic re-assessment. In addition to favourable associations with long-term clinical symptoms, endoscopic healing has also been associated with lower rates of Crohn's related surgery and hospitalisation. ^[58, 61, 62] Baert *et al* also demonstrated that

endoscopic² healing in patients with early-stage Crohn's disease was associated with significantly higher steroid-free remission rates at 4 years, further emphasising the long-term benefits of achieving this treatment target.^[59] Schnitzler *et al* showed that endoscopic healing induced by maintenance infliximab therapy was associated with improved long-term disease outcomes, most notably, lower rates of abdominal surgery.^[58] Ananthakrishnan and colleagues also demonstrated, through the use of a decision analysis model, that striving for endoscopic healing as an endpoint was a cost-effective strategy in Crohn's disease patients initiating infliximab.^[60] Taken together, these studies suggest that striving to achieve endoscopic healing in the era of biologics is achievable, worthwhile and cost-effective.

Mirroring STRIDE recommendations,¹ the concept of "deep remission", reflective of both clinical and endoscopic remission, has emerged as the ultimate treatment target.¹² The was reflected by the EXTend the Safety and Efficacy of Adalimumab Through ENDoscopic Healing [EXTEND] trial which documented lower rates of hospitalisation and disease related surgery across Crohn's disease patients who demonstrated deep remission at 12 mo.^[63]

Limitations associated with endoscopic healing

One of the drawbacks associated with targeting endoscopic healing is its reliance on ileo-colonoscopy which is invasive, resource intensive, and does not allow for mucosal assessment of small bowel segments proximal to the terminal ileum. Similarly, endoscopic evaluation may be limited by the presence of Crohn's disease associated strictures which can lead to under-estimation of disease activity in up to 50% of patients.^[64] Hence STRIDE-II guidelines specify that¹⁰ cross-sectional imaging techniques such as magnetic resonance enterography (MRE), computed tomography enterography (CTE), and intestinal ultrasound (IUS), can be employed to monitor small bowel segments not readily accessible by ileo-colonoscopy.^[4]

The STRIDE-II guidelines also recommend that endoscopic assessment be undertaken 6-9 mo following initiation of any therapy.^[4] However, repeated ileo-colonoscopy over this timeframe to assess both short-term endoscopic response and longer-time endoscopic healing is unlikely to be favoured by patients and healthcare payers alike, particularly in light of emerging data to support the use of non-invasive endoscopic surrogates.^[4] These challenges highlights the need for accurate non-invasive disease monitoring strategies that are deemed acceptable by patients, considered cost-effective by healthcare payers, and deemed clinically useful and comparable to ileo-colonoscopy by clinicians. The use of non-invasive biomarkers such as faecal calprotectin in conjunction with cross sectional imaging techniques, particularly IUS, hold great promise in this regard.

T2T IN CLINICAL TRIALS

KEY POINTS

- > The CALM and STARDUST trials evaluated the efficacy of a T2T guided approach in achieving endoscopic endpoints in patients with Crohn's disease treated with adalimumab and ustekinumab, respectively
- > On the basis of these studies, we have yet to identify which patients and disease characteristics are likely to benefit most from a T2T approach.

To-date, two randomised clinical trials, namely CALM and STARDUST, have evaluated the efficacy of a T2T guided approach to therapeutic decision-making focused on achieving endoscopic endpoints, relative to symptom directed treatment adjustments alone, in patients with Crohn's disease treated with adalimumab and ustekinumab, respectively.

The clinical efficacy of therapeutic decision-making based on tight disease control, that is based on pre-defined clinical and inflammatory biomarker targets, *vs* standard clinical disease activity alone, was evaluated by the CALM study as part of a multi-

centre international randomised trial of Crohn's disease patients treated with adalimumab.^[28] The CALM study concluded that a clinical approach favouring tight disease control led to improved clinical and endoscopic outcomes compared to a symptom-driven management approach alone. Despite using an aggressive top-down approach across a Crohn's disease cohort with a relatively uncomplicated disease of short duration, only 46% of patients in the CALM study achieved ¹⁷ the primary endpoint of mucosal healing with absence of deep ulcers at 48 wk.^[28] More recently, the multicentre, randomised STARDUST trial evaluated the efficacy of a T2T approach in Crohn's disease patients treated with ¹⁶ ustekinumab, relative to a clinically driven dose-adjustment strategy, in achieving endoscopic response at week 48 (SES-CD score $\geq 50\%$ decrease from baseline).^[65] The T2T strategy involved using week 16 endoscopy to inform ustekinumab dosing decisions, following which further dosing adjustments were made on the basis of regular clinical and biomarker assessments over the ensuing 32 wk. Week 48 endoscopic response, which was the primary endpoint, was not significantly different between both groups (38 v 30%, 0.087). Notably, the T2T cohort in the STARDUST trial had very low rates of endoscopic remission (11%) and mucosal healing (14%), with comparable clinical and biomarker outcomes between T2T and clinically-directed treatment groups.

It is, however, important to acknowledge differences in patient, disease, and treatment characteristics between the Crohn's disease populations of the CALM and STARDUST trials. Patients recruited to CALM tended to have early Crohn's disease and be naïve to immunosuppressive therapies. The study also applied different criteria for treatment step-up, and used different endoscopic endpoints to those used in the STARDUST trial. By comparison, patients recruited to STARDUST typically had a longer duration of Crohn's disease and were more likely to have failed advanced medical therapies; potentially reflective of a more treatment refractory cohort. While these differences should caution direct comparison between both studies, they do highlight several important themes. First, the need to identify which patients stand to benefit most from a

T2T approach, such as those with a complex Crohn's disease phenotype and/or high inflammatory burden. Second, whether a T2T strategy may be more effective when enacted in Crohn's disease patients with a shorter duration of disease, and minimal or no prior exposure to advanced immunosuppressive therapies.

EMERGING TREATMENT TARGETS

On the basis of current evidence, treatment targets such as transmural healing and histologic remission have not yet been endorsed by the STRIDE-II guidelines. Similarly, treatment targets in complex Crohn's disease phenotypes such as stricturing Crohn's disease have yet to be defined. Nevertheless, these endpoints may represent future treatment targets and this section will briefly explore the current and emerging literature on these topics.

A. TRANSMURAL HEALING

KEY POINTS

- > Transmural healing was not endorsed as a treatment target by STRIDE-II
- > Evidence based consensus definitions of transmural response and healing are required before transmural endpoints can be integrated into clinical trials and subsequent clinical practice

Crohn's disease is a transmural disease process; highlighting potential limitations associated with simply using ileo-colonoscopy to assess disease activity, including response to therapy, at a mucosal level.^[66] This is supported by data from several studies indicating that transmural healing is associated with favourable disease-related outcomes in patients with Crohn's disease. In fact, Castiglione and colleagues compared long-term outcomes following transmural healing and endoscopic healing, reporting that transmural healing was superior to endoscopic healing in predicting steroid-free clinical remission ($P = 0.01$), clinical relapse at 1 year ($P = 0.03$), hospitalisation rate at 1

year ($P = 0.004$), surgery at 1 year ($P = 0.009$), and need for therapeutic dose escalation ($P = 0.005$) in patients with Crohn's disease.^[67]

A recent systematic review identified 17 studies that evaluated transmural healing in Crohn's disease using any of MRE, CTE, or bowel sonography, reporting that transmural healing was achieved in 14.0 to 42.4% of patients.^[68] Moreover, good correlation between transmural healing and endoscopic healing across these studies highlighted the potential of using radiologic assessments in lieu of ileo-colonoscopy in select cases. This was also acknowledged by the STRIDE-II guidelines wherein imaging was recognised to play a complementary role in the assessment of small bowel Crohn's disease, specifically in patients whose disease may not easily and repeatedly be assessed *via* ileo-colonoscopy.^[1] Despite the documented utility of using cross sectional imaging to identify therapy related response and remission, the clinical application and uptake of this strategy has been hampered by significant heterogeneity in the definitions of transmural healing across published studies thus far.^[68] On this basis, the IOIBD Delphi group recommended imaging targets be considered adjuvant treatment targets until validated consensus evidence based definitions of transmural response and transmural healing are established.^[1]

Examining the utility of IUS in T2T

IUS represents a safe, non-invasive, inexpensive and clinically useful method of evaluating transmural Crohn's disease activity.^[69, 70] These qualities are particularly valuable in the context of a T2T approach that requires frequent assessments of Crohn's disease activity, with IUS capable of being repeated at short-intervals to evaluate treatment response in a manner that is acceptable to patients and healthcare payers alike. ^[69, 71] Similarly, IUS also offers unique advantages over endoscopy and MRI for the assessment of Crohn's disease activity in pregnant and paediatric IBD populations.^[72-74] It is also favoured by patients, exemplified by a recent study in which 98/121 (81%) IBD patients who had an IUS ranked it as their preferred modality to

monitor disease activity.^[71] These attributes support positioning IUS ahead of endoscopy and other cross-sectional imaging modalities such as CT and MRI in several clinical scenarios, including early assessments of treatment response.

The STRIDE-II guidelines define short, intermediate, and long-term treatment targets, with IUS capable of being repeated at all of these timepoints. In addition to serial disease monitoring, IUS also has the potential to facilitate early assessments of response to newly initiated therapies, and/or immediately prior to treatment changes.^[70] This was exemplified by the IUS-sub study of the STARDUST trial which demonstrated that sonographic response to ustekinumab in patients with Crohn's disease could be detected as early as week-4.^[75] Similarly, de Voogd *et al* reported that a reduction in bowel wall thickness as early as 4-8 wk following initiation of anti-TNF therapy predicted future endoscopic response and remission.^[76] This highlights the potential of using early sonographic assessment to differentiate between responders and non-responders in a manner capable of facilitating early therapeutic optimisation, and discontinuation of ineffective therapy. Hence serial IUS assessments at early, intermediate and later timepoints following initiation or changes to therapy may hold merit, and thus be incorporated into existing T2T monitoring algorithms.

Imaging features of intestinal inflammation such as bowel wall thickness, hyperaemia, and mesenteric inflammatory changes, all of which represent important parameters in the evaluation of transmural disease activity in Crohn's disease, can also be evaluated by IUS.⁶⁶⁻⁶⁸ Meta-analyses have also documented that IUS has comparable sensitivity and specificity to MRE and CT in the diagnosis and identification of Crohn's disease related complications.^[77, 78] In light of this, the joint ⁷European Society of Gastrointestinal and Abdominal Radiology (ESGAR) and European Crohn's and Colitis Organisation (ECCO) committees endorsed IUS as a suitable diagnostic and monitoring tool in Crohn's disease.^[79] The METRIC Study also reported that both MRE and IUS have high sensitivity for detecting small bowel Crohn's disease, concluding that both

investigations represent suitable first line investigations, and alternatives to ileo-colonoscopy in the diagnosis and monitoring of Crohn's disease.^[80] It is, however, important to acknowledge that uniform reporting of IUS disease activity represents a key issue to be addressed before sonographic response and transmural endpoints can be routinely used as surrogate endpoints in clinical trials. This is exemplified by a lack of validated and consensus IUS disease activity scores, with a recent systematic review documenting the use of 21 ultrasound indices in 26 studies.^[81] To-date, bowel wall thickness represents the most studied and reliable measure of sonographic disease activity and has been shown to correlate well with future clinical and objective outcomes. ^[75, 76, 82, 83]

B. HISTOLOGIC HEALING

KEY POINTS

- > Histologic healing was not endorsed by STRIDE-II as a treatment target in Crohn's disease
- > Further studies are required to clarify the clinical significance of histologic disease activity in the setting of endoscopic remission in Crohn's disease

Despite achieving endoscopic remission, patients with Crohn's disease may have evidence of persisting histologic inflammation. In contrast to ulcerative colitis wherein persistent histologic activity has been shown to predict subsequent relapse, the significance of histologic activity in determining outcomes in Crohn's disease remains less clear. A recent systematic review and meta-analysis identified only one study that reported adequate data to evaluate the value of histologic ileocolonic activity on future relapse in Crohn's disease, finding that histologic activity did not predict future relapse in the setting of endoscopic healing.^[84, 85] In light of this, the authors concluded that there was no discernible association between histologic activity and relapse in Crohn's disease; acknowledging that further data is needed. Hence, despite the questionable benefit of histologic activity in a patchy transmural disease, additional high-quality

studies are required to more definitively evaluate the incremental value, if any, that histologic activity may add in the setting of endoscopic healing in patients with Crohn's disease.

C. STRICTURING CROHN'S DISEASE

KEY POINTS

- > Treatment targets specific to Crohn's disease associated strictures remain to be defined; hence STRIDE-II does not provide specific guidance on the management of strictures
- > To-date only one clinical trial, the STRIDENT study, has applied the principles of T2T to stricturing Crohn's disease

Up to 50% of patients with Crohn's disease develop clinically significant strictures over long-term follow-up, with stricturing complications representing one of the most frequent indications for Crohn's disease related surgery.^[2, 86] The advent of biologic therapies capable of effectively treating bowel inflammation, a known precursor to the development of Crohn's disease related strictures, has been associated with a decrease in the frequency of surgical resections over the past two decades.^[87, 88] This was exemplified by findings of a recent systematic review which documented that up to 50% of patients treated with anti-TNF therapy avoided surgery over 4 years of follow-up.^[89]

In view of the inflammatory nature of Crohn's disease strictures, applying a T2T approach focused on treating stricture associated inflammation using anti-TNF therapy was recently investigated by the STRIDENT study.^[90] This study remains the first and only randomised controlled study of both drug therapy and treatment strategy, using a T2T approach, in patients with Crohn's disease complicated by symptomatic de novo or anastomotic strictures.^[90] In this single-centre open-label study, Schulberg and colleagues compared the efficacy of standard adalimumab monotherapy ($n = 25$), with

combination high-dose adalimumab and thiopurine co-therapy ($n = 52$) dose intensified on the basis of a T2T approach. The study's primary endpoint, a decrease in the 14-day obstructive symptom score at 12 mo by one or more points from baseline, was achieved in 41/52 (79%) and 16/25 (64%) of the high-dose and standard adalimumab dosing groups (OR 2.10 [95%CI 0.73–6.01]; $P = 0.17$), respectively.^[90] Notably, the combination of intensive immunosuppression with adalimumab-thiopurine co-therapy and T2T dosing adjustments on the basis of objective non-invasive measures of inflammation, was associated with fewer episodes of treatment failure, more favourable structural stricture characteristics, and less stricture-related inflammation; however these differences were not significantly different from standard adalimumab monotherapy. The STRIDENT study did, however, unequivocally demonstrate the efficacy of anti-TNF therapy for the treatment of Crohn's disease strictures, with the authors postulating that the efficacy of anti-TNF therapy, irrespective of the dose applied, may have reduced anticipated advantages associated with the combination of intensive dosing and a T2T approach.

Despite the findings of the STRIDENT study, a lack of agreement regarding the definition of a stricture, an absence of validated stricture-specific PROMs, and ambiguity surrounding clinical, radiologic and endoscopic definitions of response, reflect why stricture specific targets have not been included in current iteration of STRIDE recommendations. Nevertheless, an expert interdisciplinary panel of gastroenterologists and radiologists recently met with the objective of standardising the assessment of Crohn's disease strictures and defining clinically consequential treatment targets.^[91] Hence a validated suite of treatment targets specific to Crohn's disease strictures that are capable of being used in clinical practice are eagerly awaited.

INTEGRATING T2T INTO CLINICAL PRACTICE

To date, much of the focus has been on adopting STRIDE II recommendations, with comparatively less focus on the systems and processes required to support their

integration into routine clinical practice. Significant gaps between STRIDE-II recommendations and real-world clinical practice emphasise the need to define a standardised, easily reproducible and cost-effective model of care that embodies the principles of T2T in Crohn's disease. This represents an important first-step in reducing variability in care which has frequently been identified as a barrier to high-quality IBD care.^[92] Moreover, the cost and resource implications of executing a T2T approach, particularly in low resource healthcare settings, represents a potential obstacle to real-world uptake; highlighting the need to ensure that a T2T approach is not simply the domain of well-resourced healthcare settings. Despite the perceived benefits of a T2T approach, physician familiarity with the concept is also likely to influence its real-world application. These challenges highlight the need to devise strategies that promote uptake of a T2T approach in real-world clinical practice. This will be the focus of the section below.

A. DEFINING A SUITABLE MODEL OF CARE

KEY POINTS

- > The complex care needs of patients with Crohn's disease highlights the need for a bespoke model of care that includes systems and processes capable of supporting a T2T approach.
- > The optimal model of care remains yet to be defined, and should thus be the focus of future research.

Several models of IBD care have been proposed, including participatory, integrated, and values-based healthcare (VBHC) models. A participatory model of care encourages active collaboration and communication between the patient and their treating team of doctors, nurses, and allied health practitioners.^[92] The integration of e-health decision support tools that encourage patients to participate in their IBD care may be useful in this context.^[93] An integrated model of IBD care actively involves the patient in aspects of service development, encompasses an action plan for patient follow-up that includes

care-co-ordination, and prioritise strategies that optimise biopsychosocial wellbeing.^[94] This approach has been shown to reduce rates of hospitalisation (48 to 30%) and healthcare costs in an Australian IBD setting.^[95]

More recently, the concept of VBHC has been described. This model focuses on delivering cost-effective, patient focused IBD care based on quantification and continuous measurements of health-value.^[96] A pilot study that aimed to study the impact that a VBHC approach had on healthcare utilisation, demonstrated that a VBHC approach was able to reduce the need for endoscopies (10%), surgeries (25%), hospitalisations (28%), emergency presentations (37%), radiological studies (25-86%), and thereby favourably influence healthcare associated costs (16%) in patients with IBD.^[97] Regueiro *et al* similarly described the concept of a Patient Centred Medical Home that prioritised open access scheduling, remote disease monitoring, and telemedicine, demonstrating this approach to be associated with reduced hospital presentations and improved quality of life in patients with IBD within the first year of operation.^[98] However, a Dutch study, which evaluated the efficacy of self-managed telemedicine system (myIBDcoach) in terms of health-care utilisation and patient-reported quality of care, found that despite reducing outpatient visits and hospitalisations relative to standard IBD care, this strategy did not impact the mean number of flares, need for surgery, or patient reported quality of care scores.^[99] Importantly, several aspects of a VBHC model, including those centred on care co-ordination and improving patient-reported quality of life metrics, remain central to enacting a T2T approach, highlighting the potential utility of this model of care in IBD.^[4] Nevertheless, the optimal model of care, in both low and high resource settings, remains yet to be defined; highlighting the need for further research to define appropriate models of care for patients with Crohn's disease in both of these settings.

B. MULTI DISCIPLINARY CARE CO-ORDINATION

KEY POINTS

- > A multi-disciplinary approach remains central to the management of Crohn's disease and implementing a T2T approach
- > Care co-ordination represents a crucial, yet potentially overlooked, aspect of executing a T2T approach

Fragmentation of care has long been associated with less favourable clinical outcomes, highlighting the importance of a co-ordinated multidisciplinary approach that values input from medical, surgical, nursing, and allied health members of the IBD team.^[100] Patients also perceive a multidisciplinary approach to improve their quality of life and contribute towards a positive patient-physician relationship, with recent data also indicating that IBD patients value access to multidisciplinary care.^[101, 102] In light of this, a multidisciplinary approach has fast become standard of care in Crohn's disease, and has been shown to be of particular value in the management of complex phenotypes such as stricturing and perianal Crohn's disease.^[103, 104] Moreover, a multidisciplinary approach to chronic diseases such as IBD has been shown to improve continuity and cost-effectiveness of care, health and quality of life of patients, and to help limit health care costs across both in- and outpatient care.^[105, 106]

In the context of a T2T approach, a multidisciplinary approach also requires that the patient and their treating IBD team identify, document, and agree upon treatment goals; highlighting that the patient represents an integral member of the multidisciplinary team (Figure 2). Moreover, STRIDE-II guidelines require frequent assessment of disease activity, even more so in the setting of active disease, highlighting the need to schedule and follow-up investigations in manner capable of supporting timely clinical decision making. Hence, co-ordination of care represents a crucial, yet potentially overlooked, aspect of executing a T2T approach as part of routine clinical practice. Studies have also highlighted the utility of virtual models of care as a vehicle to help co-ordinate care and support clinical decision-making in this context. A virtual perianal clinic, inclusive of surgeons, IBD specialists, and nursing staff, was demonstrated to facilitate more timely

biologic initiation and surgical intervention, that standard IBD care.^[107] Similarly a virtual biologic clinic, designed specifically to manage heterogeneity associated with the management of loss of response to anti-TNF therapy, was shown to more frequently achieve tight disease control reflective of a T2T approach compared to standard outpatient IBD care alone.^[108] These findings highlight the potential utility of integrating non-traditional strategies such as ‘virtual care’ into traditional models of IBD care.

C. COST AND RESOURCE UTILISATION

KEY POINTS

- > The cost and resource implications of implementing a T2T approach, particularly in resource poor settings, remain important
- > A hybrid approach that combines non-invasive disease monitoring with endoscopic assessments may be the most cost-effective T2T strategy

In addition to being clinically important, treatment endpoints such as endoscopic remission must also be cost-effective. A decision analytic model demonstrated that a strategy focused on achieving mucosal healing, that is targeting the absence of mucosal ulceration, rather than clinical remission, was more cost-effective in patients with Crohn’s disease initiating infliximab over 2 years.^[60] This was also corroborated by post hoc analysis of data from the CALM study which indicated that a T2T approach in Crohn’s disease was more cost-effective than standard care from a United Kingdom and Canadian healthcare payer perspective.^[109, 110]

Although the STRIDE guidelines advocate for endoscopic remission, the integration of more cost-effective non-invasive disease monitoring strategies such as faecal calprotectin have been proposed. This was exemplified by a microsimulation model which sought to evaluate the cost-effectiveness, over a 5-year horizon, of a biomarker *vs* endoscopy-driven approach to T2T disease monitoring in Crohn’s disease to optimise

quality adjusted life years (QALYs) at a pre-specified willingness to pay threshold.^[11] This study concluded that a hybrid model that prioritised upfront biomarker based monitoring on a 6-monthly basis, reserving endoscopic disease monitoring for cases where endoscopic remission was not achieved by 1 year, and returning to biomarker based monitoring once endoscopic remission was achieved, represented the most cost-effective approach. The emerging utility of non-invasive disease monitoring strategies such as point-of-care IUS also promise to make scheduled assessments of Crohn's disease more accessible and cost-effective than routine ileo-colonoscopy in the context of a T2T framework.

It is also important to acknowledge the potential challenges, often related to cost and resource limitations, associated with implementing a T2T approach in low resource healthcare settings, where practicality and cost-effectiveness are prioritised. This emphasises the need to integrate cost-effective non-invasive surrogates of endoscopic endpoints to ensure that the potential benefits of a T2T approach are not limited to patients managed in well-resourced IBD centres.

D. INTERVENTIONS TO INCREASE UPTAKE OF T2T

KEY POINTS

- > Significant gap between STRIDE II recommendations and their real-world application exist
- > Clinician familiarity with T2T principles may influence its real-world application
- > Quality improvement and collaborative learning interventions directed at clinicians have been shown to increase uptake and application of a T2T approach

Several factors, including clinician familiarity, patient acceptance, and access to healthcare resources, have contributed toward a significant gap between STRIDE II recommendations and clinical practice.^[5, 7] Bryant and colleagues highlighted the significance of clinician familiarity with T2T principles, finding that familiarity with the

concept was associated with the perception of it being relevant to clinical practice (OR 5.5, 95%CI 1.5 – 20.4, $P = 0.01$).^[5] The patient perspective was evaluated by Selinger and colleagues who reported that only two-thirds of IBD patients appraised a T2T approach targeting endoscopic endpoints to be acceptable, illuminating potential gaps between patient perceptions and STRIDE II recommendations.^[7] Finally, the need to undertake frequent investigations, including ileo-colonoscopy is resource intensive and inconvenient to patients, potentially impacting the execution of a T2T approach outside of well-resourced IBD centres.

This highlights the need for interventions to support the implementation, and improve uptake, of a T2T approach.⁸ The Treat to target in RA: Collaboration To Improve adOption and adhereNce (TRACTION) cluster randomised trial sought to increase uptake of a T2T approach in rheumatoid arthritis through the use of a group-based learning collaborative focused on training and educating clinicians on how to apply a T2T approach in clinical practice.^[112] This intervention was able to increase the mean T2T implementation score from 11% to 57% compared to only 25% in the control group ($p < 0.004$). Moreover, increased uptake of a T2T approach following the group-based learning collaborative intervention was not associated with a disproportionate increase in resource use, or adverse events. A similar intervention, using a 12-month breakthrough series collaborative, sought to improve the implementation of T2T amongst IBD clinicians, using monthly report cards, webinars, an active listserv and two learning sessions.^[113] This quality improvement initiative led to a clinically significant increase in rates of 'intention to T2T' from 23% to 49% over 12 mo. Importantly, this initiative was also associated with increased rates of both steroid-free clinical and endoscopic remission.

CURRENT PRACTICE, EMERGING CONCEPTS AND FUTURE DIRECTIONS

The STRIDE-II guidelines specify short, intermediate, and long-term treatment goals (Figure 3), and document specific treatment targets to be achieved at each of these

timepoints. Scheduled appraisal of Crohn's disease activity against pre-defined treatment targets at these timepoints remains central to enacting a T2T approach. It is, however, also important that the timing of these assessments parallel therapy-specific time to response, to ensure that the results of these investigations can be reliably used to inform clinical decision-making. Although frequent endoscopic evaluation is recommended in the pursuit of endoscopic treatment targets, this approach is quite resource intensive; emphasising the need for comparable non-invasive assessments such as faecal calprotectin and IUS, which can be more easily, inexpensively, and acceptably repeated at multiple timepoints. Moreover, a hybrid approach that prioritises non-invasive biomarkers to undertake background disease monitoring, reserving more frequent endoscopic assessments for high-risk patients or those who do not achieve endoscopic endpoints within 12 mo, may hold promise, but requires real-world validation.^[111]

Although the CALM study, highlighted the utility of a T2T strategy in maintaining tight disease control to achieve improved clinical and endoscopic outcomes in patients with early Crohn's disease treated with adalimumab, the STARDUST trial did not demonstrate a T2T approach to be superior to symptom guided care in achieving endoscopic response in ustekinumab treated patients.^[28, 65] While differences in patient, disease, and treatment characteristics make direct comparison between these two studies difficult, they highlight that we have yet to identify which patients and disease characteristics are likely to benefit most from a T2T approach. Moreover, outside of clinical trials, evidence of the real-world effectiveness of a T2T approach remains scarce, highlighting the need for pragmatic real-world studies that not only evaluate the clinical effectiveness of this strategy, but also provide practical guidance regarding how to implement the principles of T2T into real-world clinical practice.

Emerging treatment targets such as transmural healing have also demonstrated good correlation with endoscopic outcomes.^[68] However, in the absence of consensus

definitions of transmural response and healing, including a lack of well-designed studies comparing endoscopic and transmural outcomes, guidelines advise that transmural healing remain an adjuvant endpoint at the present time. Similarly, treatment strategies and targets specific to complex disease phenotypes such as stricturing, penetrating, and perianal Crohn's disease remain to be well-defined on the basis of current data, highlighting another area of unmet need.

CONCLUSION

In conclusion, a T2T approach provides clinicians and patients with clear treatment goals and objectives. This alone has been transformative, providing much needed clarity and direction to IBD care. However, despite the obvious promise of this approach, a lack of guidance to support its integration into real-world clinical practice has the potential to limit widespread uptake. This highlights the need to develop models of care, inclusive of systems and processes, that are capable of meeting the specific care needs of patients with Crohn's disease. These models must be cost-effective and easily reproducible in both high and lower resource healthcare settings. The utility of non-invasive and cost-effective disease monitoring strategies such as point-of-care IUS also warrant strong consideration in this context as they promise to make scheduled assessments of Crohn's disease more achievable than routine endoscopy or MRI. Patient 'buy in' to, and clinician familiarity with, the principles of T2T have also been shown to greatly influence uptake of a T2T approach, emphasising the need for interventions focused on engaging and educating both parties. Hence several challenges remain to be addressed before the promise of a T2T approach can be fully realised in the context of managing the complex care needs of patients with Crohn's disease.

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SIMILARITY INDEX

PRIMARY SOURCES

- 1

Sophie Geyl, Lucas Guillo, Valérie Laurent, Ferdinando D'Amico, Silvio Danese, Laurent Peyrin-Biroulet. "Transmural healing as a therapeutic goal in Crohn's disease: a systematic review", *The Lancet Gastroenterology & Hepatology*, 2021

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Crossref
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www.researchgate.net

52 words — 1%

Internet
- 3

Dan Turner, Amanda Ricciuto, Ayanna Lewis, Ferdinando D'Amico et al. "STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD", *Gastroenterology*, 2021

42 words — < 1%

Crossref
- 4

"Accepted: Biliary/Pancreas (Abstracts 1-108)", *The American Journal of Gastroenterology*, 2018

28 words — < 1%

Crossref
- 5

Siddharth Singh, Fernando S. Velayos, David T. Rubin. "Common Instances of Low-value Care in Inflammatory Bowel Diseases", *Clinical Gastroenterology and Hepatology*, 2023

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9	Yaara Zisman-Ilani, Kimberly D. Thompson, Lori S. Siegel, Todd Mackenzie et al. "Crohn's disease shared decision making intervention leads to more patients choosing combination therapy: a cluster randomised controlled trial", <i>Alimentary Pharmacology & Therapeutics</i> , 2022 Crossref	15 words — < 1%
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