

## Disease monitoring strategies in inflammatory bowel diseases: What do we mean by “tight control”?

Lorant Gonczi, Talat Bessissow, Peter Laszlo Lakatos

**ORCID number:** Lorant Gonczi (0000-0002-8819-6460); Talat Bessissow (0000-0003-2610-1910); Peter Laszlo Lakatos (0000-0002-3948-6488).

**Author contributions:** All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version; Bessissow T reviewed and language edited the submitted version of the manuscript.

**Conflict-of-interest statement:** Authors declare no conflict of interest.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Invited Manuscript

**Received:** September 8, 2019

**Peer-review started:** September 8, 2019

**First decision:** September 19, 2019

**Revised:** September 26, 2019

**Accepted:** October 30, 2019

**Lorant Gonczi, Peter Laszlo Lakatos,** First Department of Medicine, Semmelweis University, Budapest H-1083, Hungary

**Talat Bessissow, Peter Laszlo Lakatos,** Division of Gastroenterology, McGill University Health Centre, Montreal H3G 1A4, Quebec, Canada

**Corresponding author:** Peter Laszlo Lakatos, DSc, FRCP (C), MD, Full Professor, Staff Physician, Division of Gastroenterology, McGill University Health Centre, 1650 Cedar Avenue, Montreal H3G 1A4, Quebec, Canada. [peter.lakatos@mcgill.ca](mailto:peter.lakatos@mcgill.ca)

**Telephone:** +1-514-9341934

**Fax:** +1-514-9344452

### Abstract

In recent years, there has been a critical change in treatment paradigms in inflammatory bowel diseases (IBD) triggered by the arrival of new effective treatments aiming to prevent disease progression, bowel damage and disability. The insufficiency of symptomatic disease control and the well-known discordance between symptoms and objective measures of disease activity lead to the need of reviewing conventional treatment algorithms and developing new concepts of optimal therapeutic strategy. The treat-to-target strategies, defined by the selecting therapeutic targets in inflammatory bowel disease consensus recommendation, move away from only symptomatic disease control and support targeting composite therapeutic endpoints (clinical and endoscopic remission) and timely assessment. Emerging data suggest that early therapy using a treat-to-target approach and an algorithmic therapy escalation using regular disease monitoring by clinical and biochemical markers (fecal calprotectin and C-reactive protein) leads to improved outcomes. This review aims to present the emerging strategies and supporting evidence in the current therapeutic paradigm of IBD including the concepts of “early intervention”, “treat-to-target” and “tight control” strategies. We also discuss the real-world experience and applicability of these new strategies and give an overview on the future perspectives and areas in need of further research and potential improvement regarding treatment targets and (“tight”) disease monitoring strategies.

**Key words:** Crohn’s disease; Ulcerative colitis; Treat-to-target; Tight control; Monitoring; Biomarker

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

**Article in press:** October 30, 2019  
**Published online:** November 7, 2019

**P-Reviewer:** Sipos F, Triantafyllou K, Tsuchiya K, Wenzl HH

**S-Editor:** Tang JZ

**L-Editor:** A

**E-Editor:** Ma YJ



**Core tip:** Inflammatory bowel diseases are chronic, progressive, immune-mediated disorders leading to disability and cumulative intestinal damage. There has been a major change in treatment paradigms favouring an early introduction of highly effective therapies, applying a treat-to-target approach to target composite clinical and endoscopic therapeutic endpoints and using close monitoring of objective markers of inflammation (with clinical, endoscopic and biomarker assessment) to direct therapeutic decisions until these goals are reached. Although several data support the benefit of ‘treat-to-target’ and ‘tight control’ strategies so far, these approaches require further validation assessing long-term outcomes and more precise definition of therapeutic targets (for both endoscopic and biomarker monitoring).

**Citation:** Gonczy L, Bessissow T, Lakatos PL. Disease monitoring strategies in inflammatory bowel diseases: What do we mean by ‘tight control’? *World J Gastroenterol* 2019; 25(41): 6172-6189

**URL:** <https://www.wjgnet.com/1007-9327/full/v25/i41/6172.htm>

**DOI:** <https://dx.doi.org/10.3748/wjg.v25.i41.6172>

## INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic immune-mediated inflammatory disorders that primarily affect the gastrointestinal tract and if uncontrolled, lead to disabling conditions that impact severely on the patient’s physical health and quality of life. The incidence and prevalence of IBD is increasing worldwide, putting significant burden on both individuals and the health care system<sup>[1]</sup>. The past two decades have brought substantial advances in the pharmacological management of IBD by the introduction of immunosuppressive agents, biologics and lately small molecules. Numerous new drugs with different mechanisms of action have emerged, however determining the specific role of each drug in the therapeutic armamentarium of IBD has become challenging. In addition to the burst of novel therapeutic options, probably the second most important result of the past years is the observation that most therapeutic approaches driven only by symptomatic control of disease activity probably failed to change the natural course of the disease<sup>[2-5]</sup>.

The availability of new, effective therapies with biologics and the insufficiency of symptomatic disease control inherently lead to the need of reviewing conventional treatment algorithms and developing new concepts of optimal therapeutic strategy. This review aims to present the emerging trends and evidence in the current therapeutic paradigm of IBD including ‘early intervention’, ‘treating to target’ and ‘tight control’ as three pillars of a modern, individualized therapeutic approach in IBD management.

## THE EVOLUTION OF TREATMENT STRATEGIES—EARLY INTERVENTION AND RISK STRATIFICATION

The treatment approach and the positioning of available therapies in the management of IBD has evolved significantly. It has now been widely acknowledged that IBD is a progressive disease and in the absence of timely and effective treatment causes cumulative structural damage and disability to the gastrointestinal tract alongside the disease course, especially in Crohn’s disease (CD)<sup>[6-8]</sup>. The Lémann score is the first disability index for CD providing comprehensive assessment of structural bowel damage (strictures, abscesses, fistulas, and surgical requirements)<sup>[7]</sup>. In ulcerative colitis (UC), there is less evidence whether ongoing inflammation necessarily leads to permanent bowel damage, however data suggests that UC also present a progressive nature in about one-fifth of patients (proctitis or left-sided colitis progressing to extensive colitis over time)<sup>[3,9]</sup>. This recognition led to the revision of conventional ‘step-up’ treatment approaches based on the idea that the introduction of more efficacious therapies early in the disease course can potentially modify the disease trajectory.

TOP-DOWN<sup>[10]</sup> was the first trial to assess and compare different treatment algorithms in IBD. In this landmark study, treatment-naïve CD patients were randomly assigned to ‘top-down’ strategy [start with a combination of biological

therapy and immunosuppressant-early combined immunosuppression (ECI)] compared with the standard “step-up” management (start with steroids and step up to immunosuppressant and biologics if necessary). Authors found that ECI was more effective than conventional management for achieving corticosteroid-free remission at week 52 (61.5 *vs* 42.2%;  $P = 0.0278$ ). A subsequent trial proving the superiority of combined immunosuppression in biologic naïve CD patients was the SONIC<sup>[11]</sup> trial. Results showed a clear benefit for ECI in terms of corticosteroid-free clinical remission at week 26. The REACT<sup>[12]</sup> study was designed to validate the efficacy, safety and generalizability of the top-down algorithm-based therapy in community GI practices. In this study, 1982 patients with CD were randomized to receive either ECI or conventional “step-up” therapy. The composite endpoint of hospitalization, surgery and serious disease related complications was lower in patients treated with ECI strategy at 24 mo (27.7 and 35.1%,  $P < 0.001$ ). However, the primary outcome, the proportion of patients in corticosteroid-free remission at 12 mo, was not superior (66% *vs* 61.9%;  $P = 0.52$ ). A notable limitation to the REACT study is that although the trial is supposed to investigate the effects of “early” introduction of combined immunosuppression, a large proportion of patients had longstanding disease or prior respective surgery, and had been treated with biologics and/or immunosuppressants. The very recent CALM<sup>[13]</sup> trial also verified the benefits of early introduction and quick escalation of immunosuppressive and biologic therapies when meeting treatment failure criteria (either clinical or biomarker). Despite certain limitations and methodological differences, the above results suggest that highly effective therapy initiated early in the course can potentially lead to better outcomes without a significant increase in drug-related risk (concept of “window of opportunity”).

It is important to recognize that a significant proportion of IBD patients have mild disease course. Population-based data suggests that 40% of patients with CD have a clinically indolent disease, and approximately half of the patients with CD will present non-complicated (B1) disease behavior 10 years after diagnosis<sup>[8]</sup>. In both CD and UC, potentially indolent disease must be distinguished from severe disease, assuring the opportunity of early intensive therapy for the latter one, while those with indolent disease might benefit from a slower escalation of therapeutic steps, avoiding potential overtreatment. With the introduction of multiple new therapies, the identification of populations with high risk of severe disease course gained a growing interest. Predictive factors have been identified in population-based cohorts for CD, including younger age at disease onset, smoking, extensive small bowel disease, perianal disease, deep ulceration on endoscopy, prior surgery, corticosteroid use at diagnosis, and extra-intestinal manifestations<sup>[14,15]</sup>. In the case of UC, patients with pancolitis, deep ulcers on endoscopy and non-smoking status are at higher risk for colectomy<sup>[16]</sup>. Prediction models for assessing the probability of advanced disease 5 and 10 years after diagnosis have been developed in both CD and UC, however external validation of these prediction tools are still warranted<sup>[16-18]</sup>.

## THE CONCEPT OF TREAT-TO-TARGET

The concept of “treat-to-target” has been studied and applied thoroughly in chronic diseases, such as diabetes or rheumatoid arthritis for several years and resulted in improved outcomes. For IBD patients, this concept originated from the observation that current symptom oriented therapeutic strategies failed to alter the natural progression of IBD according to the results of many population-based studies, even though immunosuppressives and biologicals have been introduced<sup>[2-5,19-21]</sup>. This could at least partly be the results of the frequent and widely acknowledged discordance between symptoms and objective measures of disease activity, especially in CD. In a post-hoc analysis of the SONIC trial, half of the patients who were in clinical remission had evidence of residual disease activity, based on endoscopic assessment or C-reactive protein (CRP) measurement, whereas other patients with endoscopic and CRP normalization still had persistent clinical symptoms<sup>[22]</sup>. In the case of UC, symptoms usually correlate better with endoscopic activity compared to CD, although a significant proportion of patients in clinical remission still have endoscopic activity and the normalization of stool frequency does not always follow endoscopic healing<sup>[23]</sup>. Switching the therapeutic endpoints from clinical remission to endoscopic healing has been increasingly supported by post-hoc analyses of pivotal clinical trials. Achieving mucosal healing was shown to predict long-term steroid free remission and better outcomes in terms of surgical and hospitalization requirements<sup>[10,24-27]</sup>.

The treat-to-target concept in IBD was developed by the selecting therapeutic targets in inflammatory bowel disease (STRIDE) committee, a group of international IBD experts established by the International Organization for the Study of

Inflammatory Bowel Diseases in 2015. The treat-to-target implies the identification of a predefined goal in the context of the patient's individual needs to be achieved by the therapy, followed by regular monitoring and treatment optimization if needed, until this goal is achieved. The definition of recommended treatment targets were performed based on an evidence-based expert consensus process<sup>[28]</sup>.

In CD, the treat-to-target recommendations are composite endpoints of clinical (defined as resolution of abdominal pain and altered bowel habit) and endoscopic remission (defined as resolution of ulceration). For patients who could not be adequately assessed by ileocolonoscopy, resolution of inflammation based on cross-sectional imaging is the desired target. The primary target recommendations for UC also consist of clinical (defined as resolution of rectal bleeding and normalisation of bowel habit) and endoscopic endpoints (defined as resolution of friability and ulceration at flexible sigmoidoscopy or colonoscopy). Biochemical targets [CRP or fecal calprotectin (FCAL)] and histopathology were not recommended as adjunctive endpoints. The use of biomarkers (CRP and FCAL) are recommended in both CD and UC for disease monitoring, and persistent failure of normalization should prompt further endoscopic or radiologic evaluation, regardless of symptoms. Imaging modalities are considered having a complementary role to endoscopy in CD, and they are not recommended for disease assessment in UC<sup>[28]</sup>.

---

## INSTRUMENTS OF TIGHT CONTROL IN DISEASE MONITORING

---

At the time of the development of STRIDE, supporting evidence for target recommendations were available only from retrospective studies and post-hoc analyses of randomized clinical trials. Emerging prospective and clinical trial data with long-term outcomes of the application of the treat-to-target concept have been published, which will help further understanding of the treat-to-target approach and adjusting and optimizing the various targets in everyday clinical practice. The importance of timely assessment of disease activity has been clearly emphasized in the STRIDE creating the concept of "tight" disease control. The CALM<sup>[13]</sup> trial was the first randomized study to show that tight disease monitoring using objective markers of inflammation and timely escalation of therapy in patients with early CD leads to better clinical and endoscopic outcomes compared to symptom-driven management alone. Objective measurement of inflammatory activity requires invasive and costly procedures, such as ileocolonoscopy or cross-sectional imaging. Levels of CRP and FCAL are among the most widely investigated non-invasive markers of inflammation in IBD. In recent years, the most significant adjustment to the STRIDE recommendations is the increasing role of biomarkers (CRP and FCAL) in treatment decisions based on the supporting results of the CALM trial. In the following sections we aim to give a detailed description and review of current evidence on each therapeutic target and their role in a "tight control" disease management (see [Table 1](#)).

### **Clinical targets**

Although resolution of symptoms alone is not a sufficient therapeutic endpoint, it is still necessary to properly monitor and treat symptoms of the disease. Multiple clinical scoring systems have been developed in clinical practice; the Crohn's Disease Activity Index (CDAI) and Harvey Bradshaw Index (HBI) being the most widely used in CD, and the partial Mayo score (pMayo) and the Simple Clinical Colitis Activity Index in UC<sup>[29-32]</sup>.

The CDAI, HBI or pMayo scores are composite clinical scores, meaning that they include laboratory features, disease characteristics or the general assessment of the physician. As the STRIDE recommendation outlined the resolution of clinical symptoms as a separate therapeutic target, it is logical to develop independent clinical measures that reliably assess symptoms coming directly from a patient. A "patient reported outcome" (PRO) is a report from the patient's perspective about the status of their symptoms and perceived response to therapy. According to the FDA guidance, creating a PRO must involve generation of items based on qualitative patient interviews and thorough testing for responsiveness and internal consistency<sup>[33]</sup>. Although composite clinical scores such as the CDAI and HBI indices include patient-reported severity of symptoms, their development was not conducted in accordance with these stringent requirements. In the absence of a well-characterized PRO items for IBD, the STRIDE program recommends the use of a two-item interim PRO that should be resolution of abdominal pain and normalization of bowel habit for CD, and in the case of UC, resolution of rectal bleeding and normalization of bowel habit. Assessment of clinical targets should be tailored to the patient's individual needs,

**Table 1 Selected studies supporting the use of clinical, biochemical, endoscopic, histological and combined targets since the publication of selecting therapeutic targets in inflammatory bowel disease consensus**

Study	Study type	Treatment targets evaluated	Patient population	Compared patient groups	Outcomes
Colombel <i>et al</i> <sup>[13]</sup> (CALM)	Randomized clinical trial	Combined clinical and biomarker	CD- 244 patients	Incremental therapy escalation based on "tight control" with biomarker (CRP and FCAL) and clinical assessment every 12 wk vs "clinical management" with only clinical assessment	Outcomes at 48 wk: Mucosal healing (CDEIS < 4 and no deep ulcerations), 45.9% vs 30.3%; <i>P</i> = 0.010 steroid free remission, 59.8% vs 39.3%; <i>P</i> < 0.001 deep remission (CDAI < 150, CDEIS < 4 and no deep ulcers), 36.9% vs 23.0%; <i>P</i> = 0.014 biological remission (FCAL < 250 µg/g, CRP < 5 mg/L, and CDEIS < 4), 29.5% vs 15.6; <i>P</i> = 0.006
Ungaro <i>et al</i> <sup>[55]</sup> (CALM - long term extension)	Randomized clinical trial	Endoscopy	CD - 122 patients	Endoscopic remission (CDEIS < 4 and no deep ulcerations) at 1 yr vs NOT Deep remission (CDAI < 150, CDEIS < 4 and no deep ulcers) at 1 yr vs NOT	Composite of major adverse outcomes reflecting CD progression: New internal fistula/abscess, stricture, perianal fistula/abscess, CD hospitalization, or CD surgery (median 3 yr follow-up after end of CALM): aHR = 0.44, 95%CI: 0.20-0.96, <i>P</i> = 0.038 aHR = 0.25, 95%CI: 0.09-0.72, <i>P</i> = 0.01
Shah <i>et al</i> <sup>[38]</sup>	Meta-analysis	Endoscopy	CD - 673 patients (12 studies included)	Achieving MH at first endoscopic assessment after therapy initiation vs NOT	Outcomes reported at ≥ 50 wk: Clinical remission [OR] 2.80, 95%CI: 1.91-4.10 maintenance of mucosal healing [OR] 14.30, 95%CI: 5.57-36.74 resective surgery [OR] 2.22, 95%CI: 0.86-5.69
Shah <i>et al</i> <sup>[39]</sup>	Meta-analysis	Endoscopy	UC - 2073 patients (13 studies included)	Achieving MH at first endoscopic assessment after therapy initiation vs NOT	Outcomes reported at ≥ 50 wk: clinical remission [OR] 4.50, 95%CI: 2.12-9.52 avoiding colectomy [OR] 4.15, 95%CI: 2.53-6.81 maintenance of mucosal healing [OR] 8.40, 95%CI: 3.13-22.53 long-term corticosteroid-free clinical remission [OR] 9.70, 95%CI: 0.94-99.67
Park <i>et al</i> <sup>[70]</sup>	Meta-analysis	Histology	UC - 13 studies included	Histological remission vs NO histological remission at baseline Histological remission vs NO histological remission at baseline among patients in combined clinical and endoscopic remission	Outcomes up to 12 mo follow-up: Clinical relapse/ exacerbation [RR] 0.48, 95%CI: 0.39-0.60 Clinical relapse/ exacerbation [RR] 0.81, 95%CI: 0.70-0.94
Bryant <i>et al</i> <sup>[68]</sup>	Prospective	Histology	UC - 91 patients	Histological remission vs NO histological remission at baseline	Outcomes reported over a median 72 mo follow-up: corticosteroid use [HR] 0.42, 95%CI: 0.2-0.9; <i>P</i> = 0.02 acute severe colitis requiring hospitalization [HR] 0.21, 95%CI: 0.1-0.7; <i>P</i> = 0.02



Lasson <i>et al</i> <sup>[93]</sup>	Prospective, Randomized	Biomarker	UC – 91 patients	Monthly FCAL measurement: Dose-escalation of 5-ASA in patients with FCAL > 300 µg/g <i>vs</i> NO intervention	18 mo follow-up: Fewer clinical relapses observed in intervention group, 28.6% <i>vs</i> 57.1%; <i>P</i> <0.05
Zhulina <i>et al</i> <sup>[52]</sup>	Prospective	Biomarker	CD – 49 patients; UC – 55 patients	First clinical relapse <i>vs</i> NO relapse in patients with clinical remission at baseline	2 yr of follow-up: Doubling of faecal calprotectin level between two consecutively samples 3 mo apart predicted relapse [HR] 2.01, 95%CI: 1.53-2.65
Sollelis <i>et al</i> <sup>[94]</sup>	Prospective	Combined clinical and biomarker	CD – 40 patients	Clinical and biomarker remission at 12 wk (CDAI < 150 and CRP ≤ 2.9 mg/L and FCAL < 300 µg/g) <i>vs</i> NOT	Predictive power for corticosteroid-free clinical remission at 52 wk: Sensitivity = 69.2% (42.0-87.4) specificity = 100.0% (84.9-100.0) PPV = 100.0% (100.0-100.0) NPV = 87.1% (75.3-98.9)

CD: Crohn's disease; UC: Ulcerative colitis; CRP: C-reactive protein; FCAL: Fecal calprotectin; CDAI: Crohn's Disease Activity Index; CDEIS: Crohn's Disease Endoscopic Index of Severity; 5-ASA: 5-aminosalicylic acid; RR: Relative risk; HR: Hazard ratio; OR: Odds ratio; CI: Confidence interval; NPV: Negative predictive value; PPV: Positive predictive value; aHR: Adjusted hazard ratio.

with a minimum of every 3 mo during active disease and every 6-12 mo after symptom resolution for both CD and UC<sup>[28]</sup> (see [Table 2](#)).

Since the STRIDE recommendations, newer PRO tools, including more clinical variables (abdominal pain and urgency for UC) in accordance with FDA guidance, have been developed, however their applicability in clinical trial design or everyday clinical practice still remain to be validated<sup>[34-36]</sup>. Various other PROs have already been used in clinical trials reporting depression, anxiety, disability and other quality of life parameters, however available data on these PROs in IBD are yet limited. The IBD disability index (IBD-DI), developed in accordance with the WHO International Classification of Functioning is a validated tool to measure disability, and shows good correlation with clinical disease activity<sup>[37]</sup>. Future studies will assess the role of IBD-DI as a potential clinical target.

### Endoscopic targets

Numerous recent studies support the STRIDE recommendation to target endoscopic healing, since several clinical trials (post-hoc analysis) and population-based studies have demonstrated that achieving mucosal healing is associated with improving outcomes, such as lower rates of hospitalizations, disease relapse, and lower surgery requirements<sup>[24-27]</sup>. In a systematic review and meta-analysis of 12 studies, endoscopic remission (or mucosal healing) on the first post-treatment endoscopy was associated with a higher rates of long-term clinical remission [pooled odds ratio (OR) = 2.80, 95%CI: 1.91-4.10], maintenance of mucosal healing (14.30, 95%CI: 5.57-36.74), and lower risk of surgery (2.22, 95%CI: 0.86-5.69) in patients with CD<sup>[38]</sup>. The same meta-analysis of 13 studies was performed for UC, resulting that mucosal healing on the first post-treatment endoscopy was associated with long-term (52 wk) clinical remission [OR = 4.50, 95%CI: 2.12-9.52], avoiding colectomy (4.15, 95%CI: 2.53-6.81), achieving long-term corticosteroid-free clinical remission (9.70, 95%CI: 0.94-99.67), and long-term mucosal healing (8.40, 95%CI: 3.13-22.53)<sup>[39]</sup>. The feasibility of applying a treat-to-target approach in regard to mucosal healing was studied by Bouguen *et al*<sup>[40]</sup>. Sixty-seven CD patients with endoscopic lesions underwent two to four subsequent endoscopies with a median follow-up of 76 wk. Factors associated with achieving mucosal healing were fewer than 26 wk between endoscopic procedures [hazard ratio (HR) = 2.21; 95%CI: 1.16-4.26; *P* = 0.016] and adjustment to medical therapy when mucosal healing was not observed (2.35; 95%CI: 1.2-4.94; *P* = 0.012), concluding that serial endoscopic procedures and treatment optimizations accordingly are feasible in clinical practice and high rates of MH can be achieved.

Although, the predictive value of early mucosal healing and the need for applying endoscopic targets as primary therapeutic endpoints is clear, the definition for optimal endoscopic targets is lacking. The STRIDE recommendations specify endoscopic targets as resolution of ulceration in CD and resolution of ulceration and friability in UC assessed at 6-9 mo and 3-6 mo after commencing therapy, respectively<sup>[28]</sup> ([Table 2](#)). The definition of mucosal healing is however highly

**Table 2 Intervals of clinical, biomarker, and endoscopic assessment in the treat-to-target and tight control framework**

	Active disease/at flare	Clinical remission
<b>Crohn's disease</b>		
Clinical evaluation (PRO, CDAI, HBI indices)	3 mo [STRIDE and CALM protocol] <sup>[28,13]</sup>	6-12 mo [STRIDE] <sup>[28]</sup> 3 mo [CALM protocol] <sup>[13]</sup>
Endoscopic evaluation	6-9 mo after therapy initiation [STRIDE] <sup>[28]</sup>	Based on screening recommendations in deep remission Prompted by clinical symptoms or (consecutive) biomarker positivity - FCAL <sup>[52,53]</sup>
Biomarker evaluation (CRP and FCAL)	3 mo (FCAL + CRP) [CALM protocol] <sup>[13,94]</sup> Approximately 12-14 wk after therapy initiation (CRP) <sup>[95,96]</sup> Approximately 14 wk after therapy initiation (FCAL) <sup>[94,97,98]</sup>	3 mo (FCAL + CRP) [CALM protocol] <sup>[13]</sup> (2)-3 mo (FCAL) <sup>[52,53]</sup> 3 mo (CRP) <sup>[99]</sup>
<b>Ulcerative colitis</b>		
Clinical evaluation (PRO, CDAI, HBI indices)	3 mo [STRIDE] <sup>[28]</sup>	6-12 mo [STRIDE] <sup>[28]</sup>
Endoscopic evaluation	3-6 mo after therapy initiation [STRIDE] <sup>[28]</sup>	Based on screening recommendations in deep remission Prompted by clinical symptoms or (consecutive) biomarker positivity - FCAL <sup>[52,53]</sup>
Biomarker evaluation (CRP and FCAL)	Approximately 10 wk after therapy initiation (FCAL) <sup>[100]</sup>	(2)-3 mo <sup>[51-53,101]</sup>

<sup>1</sup>Using C-reactive protein alone has only moderate predictive value in identifying relapse in patients with clinical remission. PRO: Patient reported outcome; CDAI: Crohn's Disease Activity Index; HBI: Harvey Bradshaw Index; CRP: C-reactive protein; FCAL: Fecal calprotectin; STRIDE: Selecting therapeutic targets in inflammatory bowel disease.

heterogenous, especially in CD. The most commonly accepted definition of endoscopic healing is the disappearance of all ulcerative lesions, however this definition does not allow for the interpretation of partial resolution of mucosal inflammation. A different solution would be the use of reproducible endoscopic activity scores capable of depicting precise degree of endoscopic activity and subsequent changes. Widely used endoscopic scores in CD are the Crohn's disease Endoscopic Index of Severity (CDEIS) and Simple Endoscopic Score for Crohn's disease (SES-CD), and Rutgeerts' score for post-surgical evaluation of endoscopic recurrence. In UC, the endoscopic Mayo score and the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) are most frequently used. However, the proper definition of "optimal" or "targeted" degree of endoscopic healing is lacking.

A post-hoc analysis of the SCONIC trial tried to identify an optimal definition for endoscopic healing/remission that would predict long term outcomes in CD. Mucosal healing (resolution of ulcers) and endoscopic response (defined as a decrease from baseline SES-CD or CDEIS by at least 50%) at week 26 showed the best performance in identifying those most likely to be in corticosteroid-free clinical remission at week 50, however AUC values were fairly modest in either case, moreover a higher decrease from baseline SES-CD or CDEIS scores did not show better predictive performance<sup>[41]</sup>. This further strengthens the fact that the desired degree of endoscopic healing to reach superior long-term outcomes or the absence of endoscopic improvement which should prompt therapy change is largely unknown. The same problem applies for clinical trial design where the absence of validated definitions of endoscopic healing leads to the arbitrary choice of endoscopic endpoints by investigators. Recently, the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) reviewed endoscopic scoring systems and achieved consensus on definitions of endoscopic remission and response in CD. Expert investigators chose a > 50% decrease in SES-CD or CDIES for the definition of endoscopic response, and an SES-CD 0-2 for the definition of endoscopic remission<sup>[42]</sup>. Of note, these recommendations are yet to be subjected to thorough validation and prospective testing before widely incorporated into clinical trial endpoints or everyday clinical practice.

Although endoscopic healing is a critical target in UC, the scoring systems and endoscopic criteria of healing also warrant revision. Generally, a Mayo 0 or 1 endoscopic score is considered to be endoscopic remission, however new data show that a score of 0 is associated with lower risk of clinical relapse compared with a score of 1<sup>[43,44]</sup>. Updates in the endoscopic Mayo score incorporating disease extent correlate well with clinical and endoscopic outcomes and may improve the applicability and accuracy of the most widely used scoring system<sup>[45]</sup>. The UCEIS is also accurate and responsive, and takes ulcer size and depth in consideration, parameters that are not captured by the endoscopic Mayo score, however the assessment of friability is excluded from the UCEIS<sup>[46]</sup>. Recently, the IOIBD suggested the use of UCEIS of 0 as the definition of endoscopic remission and a decrease in Mayo endoscopic score  $\geq 1$

grade or a decrease in UCEIS  $\geq 2$  points for the definition of endoscopic response in UC<sup>[47]</sup>.

### Biochemical targets

The most broadly used and thoroughly studied biomarkers are the serum CRP and FCAL. In general, elevated CRP levels in CD are associated with clinical disease activity and endoscopic inflammation<sup>[48]</sup>. Compelling results show that early normalization of CRP is associated with therapeutic response in CD and in patients having an elevated CRP concentration at baseline, changes in CRP may provide useful information in monitoring treatment response. However, CRP is not a specific marker of intestinal inflammation with an overall specificity of 0.49 (95%CI: 0.72–0.98) in CD, moreover, approximately 20% of patients do not present with an elevated CRP during disease flare<sup>[49]</sup>. Much less data support the applicability of CRP measurements in UC as many patients with UC do not have elevated CRP levels. However, serial measurements may be useful for assessment of treatment response in patients with severe colitis.

FCAL is a highly sensitive marker of endoscopic disease activity in both UC and CD<sup>[49]</sup>. However, identifying the optimal FCAL concentration cut-off values best predictive of disease activity is challenging. D'Haens *et al*<sup>[50]</sup> suggested a fecal calprotectin cut-off value of 250  $\mu\text{g/g}$ , as levels above this concentration predicted large ulcers in CD (sensitivity 60%, specificity 80%) and active mucosal disease (Mayo score  $> 0$ ) in UC (sensitivity 71%, specificity 100%). A recent study also demonstrated that during the regular monitoring of FCP levels, two consecutive FCAL measurements of  $> 300 \mu\text{g/g}$  with 1-mo interval were identified as the best predictor of disease flare (61.5% sensitivity and 100% specificity)<sup>[51]</sup>. Furthermore, two recent studies showed that patients had significantly higher FCAL levels as soon as 3 mo before disease flare<sup>[51,52]</sup>. Zhulina *et al*<sup>[52]</sup> reported that doubling of faecal calprotectin level between two consecutively collected samples 3 mo apart was associated with a 101% increased risk of relapse (HR = 2.01; 95%CI: 1.53–2.65;  $P < 0.001$ ). A systematic analysis of six studies has shown that increased levels of FCAL on at least two consecutive measurements were associated with a higher risk of relapse within 2–3 mo in asymptomatic patients<sup>[53]</sup>. In predicting relapse after surgery, evidence suggests that FCAL may be best utilized as a monitoring strategy for postoperative recurrence, with values  $< 100 \mu\text{g/mg}$  strongly suggesting no recurrent disease<sup>[54]</sup> (see [Table 2](#)).

Biochemical targets (CRP or FCAL) were not recommended by STRIDE as primary treat-to-target endpoints due to lack of sufficient evidence in support of their use at the time the guidance. However, their use is recommended in both CD and UC as adjunctive measure to monitor disease activity<sup>[28]</sup>. The use of biomarkers for disease monitoring has the advantage of being non-invasive and relatively inexpensive. The above results suggest that after identifying the appropriate cut-off levels, the combined measurement of these biomarkers (FCAL and CRP) could very much help disease monitoring and decision making about the optimal timing of endoscopy. Significant progress has been made since the STRIDE recommendations in this regard.

The most compelling evidence for the tailored use of biomarkers in tight disease monitoring derives from the CALM<sup>[13]</sup> study, seeking whether it is appropriate to intensify therapy in patients based on close monitoring of inflammatory biomarkers (CRP and/or FCAL). The CALM study is the first randomized trial to demonstrate that in patients with early CD, therapy based on biochemical targets in addition to clinical targets (tight control arm) is associated with higher endoscopic remission at 1 year compared with therapy based on clinical targets alone (clinical management arm). Treatment in both arms was escalated in a stepwise manner from no treatment to adalimumab induction, followed by adalimumab every other week, adalimumab every week, and lastly to both weekly adalimumab and daily azathioprine. Evaluations were performed at 12, 24, and 36 wk and escalation was based on meeting one of the following failure criteria; tight control group: faecal calprotectin  $\geq 250 \mu\text{g/g}$ , CRP  $\geq 5\text{mg/L}$ , CDAI  $\geq 150$  or prednisone use in the previous week; clinical management group: CDAI decrease of  $< 100$  points compared with baseline or CDAI  $\geq 200$ , or prednisone use in the previous week. For the tight control arm, even if patients were symptomatically well, treatment was escalated if biomarkers were raised. The primary outcome at 48 wk after randomisation was mucosal healing (CDEIS  $< 4$  and no deep ulcerations). A significantly higher proportion of patients achieved the primary endpoint (46% *vs* 30%; adjusted risk difference 16.1%, 95%CI: 3.9–28.3;  $P = 0.010$ ) when applying a tight control strategy, compared to symptom-driven clinical management. In addition, fewer CD-related hospitalizations occurred in the tight control arm (13.2 *vs* 28.0 events/100 patient-years;  $P = 0.021$ ). Subsequent follow-up data of the CALM study on 122 patients for 3 additional years revealed that endoscopic remission [adjusted hazard ratio = 0.44, 95%CI: 0.20–0.96] and combined endoscopic and clinical (deep) remission (0.25, 95%CI: 0.09–0.72) at 1 year were



associated with lower risk of adverse events such as new internal fistula/abscess, stricture, perianal fistula/abscess, hospitalization, or surgery in long-term follow-up<sup>[53]</sup>. These data further strengthen the STRIDE recommendations for targeting combined endoscopic and clinical remission and adds the importance of the timely assessment and aiming for normalization of biochemical markers.

Therapeutic drug monitoring (TDM) is an integral component of tight disease monitoring in IBD. Numerous studies have shown that optimal levels of anti-TNF agents are associated with clinical and endoscopic remission, and conversely, low drug levels are associated with reduced clinical efficacy, suboptimal control of inflammation, and higher risk of disease flares<sup>[56-58]</sup>. The most evidence support the role of drug Trough Level (TL) and anti-drug antibody (ADA) evaluations ideally in patients losing response to biologic therapy- *i.e.*, reactive TDM in the case of suspected loss of response (LOR)<sup>[59-61]</sup>. The use of reactive TDM is based on a widely known algorithmic approach, originally developed to assess treatment failure (LOR) in patients treated with anti-TNF agents (see [Table 3](#)). There are currently insufficient data to determine the exact role of TDM in other newer biologics, such as vedolizumab or ustekinumab.

Results of clinical trials investigating the benefit of proactive/routine drug monitoring have been however somewhat disappointing. In the TAXIT (Trough Level Adapted Infliximab Treatment) trial, no difference in the primary outcomes (clinical remission at 1 year) was observed between patients randomly assigned to a drug-monitoring group in which infliximab dosing was continuously adjusted, (drug levels within 3–7 µg/mL), or to a conventional therapy group, with infliximab dosing based on clinical symptoms alone (69% *vs* 66%;  $P = 0.686$ )<sup>[62]</sup>. The TAILORIX (Tailored treatment with infliximab for active CD) trial also studied CD patients receiving infliximab and subsequent dose-escalation guided by infliximab levels, biomarkers and clinical symptoms *vs* clinical symptoms alone. No significant difference was observed between the patient groups for the primary outcome of steroid-free clinical remission at 22 and 54 wk<sup>[63-65]</sup>. Although other single cohort or retrospective studies show potential benefits of proactive TDM<sup>[66]</sup>, based on the above trials it is questionable whether routine proactive monitoring of aTNF agents lead to improving outcomes, or TDM measurements can be reserved optimally for assessment of therapeutic failure. Observational studies also show that measuring drug and anti-drug antibody levels can guide decisions for anti-TNF withdrawal or restart after a drug holiday<sup>[67]</sup>. Further reviewing the available evidence on TDM is beyond the scope of this article.

### **Histologic targets**

Histologic remission, which means resolution of inflammation on microscopical/histological examination of the colonic mucosa, was not recommended as a target by the STRIDE recommendation due to lack of sufficient evidence. Lately, histological assessment in UC has an emerging role in clinical trials. Recent studies consistently suggest that achieving histologic remission may demonstrate better prognostic value in long-term outcomes (relapse-free survival, corticosteroid use, and hospitalization) than endoscopy<sup>[68,69]</sup>. In a meta-analysis of 15 studies, the risk of UC exacerbation was lower with histologic remission compared with patients with histological activity but in endoscopic and clinical remission [pooled OR = 0.81, 95% CI: 0.70–0.94]<sup>[70]</sup>. Several histologic scoring systems are available in UC, the Nancy index and the Robarts Histopathology Index (RHI) being properly validated and showing good correlation with endoscopic disease activity and biomarkers, however optimal endpoints in histologic healing are yet to be determined<sup>[71]</sup>. In the case of CD, there are very few data to support histologic remission as a treatment target. The lack of a validated histologic scoring systems to identify remission and the risk of sampling error due to the manifestation of CD (skip-lesions) limit the applicability of histologic assessment.

### **Imaging targets**

Several study demonstrated that cross-sectional imaging have superior diagnostic accuracy compared to ileocolonoscopy in extensive ileal, stricturing or penetrating CD, and have a higher impact on therapeutic decisions in appropriate patients<sup>[72]</sup>. The STRIDE consensus recommended resolution of lesions in cross-sectional imaging as not a universal target, although imaging modalities should have a complementary role in patients with CD who cannot be adequately assessed by colonoscopy. Further data in CD patients using imaging modalities to target resolution of inflammation have been reported since the publication of STRIDE. In a retrospective analysis, complete resolution of small bowel lesions on CTE or MRE was associated with a decrease in hospitalization [(HR), 0.28, 95% CI: 0.15–0.50] and surgery (0.34, 95% CI: 0.18–0.63) over a median of 9 years observed period<sup>[73]</sup>. Patients with transmural

**Table 3 Therapeutic drug monitoring-based algorithm for handling patients with treatment failure on biologic therapy<sup>[59-61]</sup>**

	Detectable anti-drug antibodies	Undetectable anti-drug antibodies
Sub-therapeutic anti-TNF drug levels	Change to different TNF-inhibitor.	Intensify the treatment regimen of the currently used TNF-inhibitor.
Therapeutic anti-TNF drug levels	(Repeat assessments of anti-TNF drug and anti-drug antibodies over time) Switch to another biological agent with a different mechanism of action.	Switch to another biological agent with a different mechanism of action.

TNF: Tumor necrosis factor.

healing on MRE presented lower rates of therapy escalation, hospital admission and surgery at 1 year in a prospective cohort<sup>[74]</sup>. In a retrospective study, fast-track MRI examinations coupled with clinical and biomarker activity assessment had a significant impact on patient management, leading to better patient stratification and earlier optimization of the therapy (medical or surgical)<sup>[75]</sup>. Abdominal ultrasound (US) is a safe and inexpensive diagnostic modality, and shows comparable overall diagnostic performance to MRI and CT modalities in ileal CD<sup>[72]</sup>. Recently, several US indices have been developed for assessing disease activity, however further validation of these tools and their impact in disease monitoring need more research<sup>[76]</sup>.

Cross-sectional imaging modalities are not recommended by the STRIDE in the evaluation of UC, considering that it is primarily a mucosal disease. However, the MaRIA MRI index or diffusion-weighted MRI modalities studied mainly in patients with CD, have high sensitivity in detecting mucosal lesions, thus could have potential applicability in UC<sup>[77]</sup>. The lack of invasiveness and radiation exposure makes MRI an attractive diagnostic tool, although further investigation is definitely warranted however to demonstrate long-term outcomes in MRI guided therapeutic strategies.

## TREATMENT DE-ESCALATION

As a result of the changing treatment paradigms, there has been an exponential increase in the exposure to immunosuppressive and biologic agents. Several long-term trials have shown that discontinuation of therapy is associated with high relapse rates, suggesting that cessation of biologics can be considered only in selected patients. It is important to recognize that tight control management strategies could also help identifying those patients through proper disease monitoring strategies and not only promote therapy escalation but de-escalation as well. The STORI (infliximab discontinuation in CD patients in stable Remission on combined therapy with Immunosuppressors) trial showed that the relapse rate within a 1 year of discontinuation was approximately 50%, however, patients having  $\leq 2$  risk factors, including male gender, elevated leukocytes, an elevated CRP level, elevated FC level, and decreased hemoglobin showed only a 15% risk of relapse<sup>[78]</sup>. Safety signals were not different between patient groups in the CALM<sup>[13]</sup> study despite a higher exposure to combined immunosuppression in the tight control arm, nevertheless, safety concerns regarding combined immunosuppression and the huge increase in drug related costs makes it necessary to develop appropriate de-escalation strategies for selected patients, and determine the exact role of biomarkers and endoscopy in this area as well.

## REAL-WORD EXPERIENCE WITH TREAT-TO-TARGET STRATEGIES

Although the treat-to-target and tight control strategies seem to achieve improved long-term outcomes in CD and UC, certain factors can limit the applicability and acceptance of these new paradigms in clinical practice. Although there are reports of these new strategies to be properly translated in clinical practice in several IBD centers, some studies propose significant gaps in the implementation of treat-to-target strategies<sup>[79,80]</sup>. The overall increase in doctor-patient visits, laboratory testing, and endoscopies could be "burdensome" for both patients and physicians and could potentially slow the uptake of treat-to-target strategies, especially in community gastroenterology services. In contrast to the STRIDE recommendations, which advocate for endoscopic evaluation after 3 mo of therapy start in active UC,

endoscopy was performed in only 47% of such patients within 3 mo, and in 68% within 6 mo in a recent Australian multicenter study of IBD outpatient services<sup>[80]</sup>. In the same study, a clinician survey was performed showing that 80% of respondents had heard of the “treat-to-target” concept, 61% were familiar with the recommendations, but only 64% considered it relevant to local clinical practice.

It is important for individual IBD centers to assess and measure local therapeutic strategies and processes, and evaluate whether they are in concordance with current expert recommendations and consensus Quality of Care standards<sup>[81,82]</sup>. A study by Reinglas *et al*<sup>[83]</sup> is one of the few reporting a detailed assessment of patient evaluation strategies, disease monitoring, treatment decisions, disease-related outcomes from a tertiary care IBD center in Canada. Results confirmed the application of objective patient re-evaluation and monitoring (ileocolonoscopy or colonoscopy was performed in 79% of all IBD patients within the past 2 years from a chosen time point), timely access to diagnostic procedures and accelerated treatment pathways. Another example for the application of tight control strategies is from Hungary, where a harmonized monitoring strategy is mandatory with serial clinical (CDAI and pMayo scores) and laboratory (CBC and CRP) assessments reported every 3 mo as requested by the Hungarian National Health Fund for patients receiving biologic therapies<sup>[84]</sup>.

A properly working platform for rapid patient access (in case of flare or other IBD related emergency situations) is equally important in the framework of “tight control” management. A special emphasis on providing rapid patient access could potentially help avoiding undesirable outcomes such as steroid dependency, frequent Emergency Department (ED) visits or emergency hospitalizations/surgeries. Several data show that inadequate ‘patient access’ to treating physician or healthcare services is frequently a source of dissatisfaction among patients<sup>[85]</sup>. Our group performed a detailed analysis of patient access, diagnostic procedures, resource utilization, and outcome parameters after the implementation of a new Rapid Access Clinic service at the McGill University Health Centre tertiary care IBD center. Patients presenting with flare had a fast-track clinical and biomarker evaluation (CRP and FCAL measured in 91% and 73%) within a median of 2 d. Patient evaluations by an IBD specialist instead of the ED services led to a more optimal resource utilization (fewer cross-sectional imaging and fewer hospitalizations) in the majority of cases<sup>[86]</sup>.

Targeting MH as treatment endpoint and the tight control strategies may result in a potential increase in healthcare costs because of the more frequent use of diagnostic procedures and services and more importantly the increased rate of therapy escalations (dose intensification of biologics). Whether these additional costs could be balanced by the reduction of other healthcare expenditures associated with the long-term remission could also have major influence on the real-world application of the treat-to-target strategies. A decision analysis model performed by Ananthakrishnan *et al*<sup>[87]</sup> using existing clinical trial data demonstrated that targeting MH was more effective at a 2 year endpoint (QALY 0.71) compared to convention clinical management strategies (QALY 0.69) with an incremental cost-effectiveness ratio (ICER) of \$ 47,278/QALY gained. A similar cost-effectiveness analysis of the CALM trial was also performed. At 48 wk, the tight control arm produced a total of £ 13296 in direct medical costs and a QALY of 0.684, while the same results were £ 12627 and 0.652 for the clinical management arm. The difference in costs (£ 669) divided by the difference in QALY (0.032) produced an ICER of £ 20913 per QALY gained which is within the acceptable range that is considered cost-effective (\$ 50–100000/QALY gained)<sup>[88,89]</sup>. Further investigations are however needed to determine the cost-effectiveness of treat-to-target strategies in reducing disease progression, taking into account proper de-escalation strategies as well.

---

## FUTURE PERSPECTIVES AND UNANSWERED QUESTIONS—EXPERT OPINION

---

In recent years, there has been a critical change in the treatment paradigms with the arrival of biologic agents. Many studies showed that the introduction of highly effective treatments in selected patients early in the disease course is crucial in achieving deep remission and avoiding disease complications. An important limitation to the landmark clinical trials evaluating the early use of biologics and immunosuppressives is that they only measured clinical outcomes as primary endpoints and endoscopic data are usually available in a subgroup of patients, except for the CALM study. In this regard, the CURE<sup>[90]</sup> study is currently underway and is evaluating the impact of early adalimumab therapy on the disease course in CD, including mucosal healing. Personalization of the therapeutic strategy by proper early patient stratification have an increasingly important role in selecting patients who

benefit from early aggressive therapy.

The other pillar of achieving sustained deep remission is a stringent patient follow-up and timely re-evaluation. The current focus on objective parameters as treatment targets is an important step towards that direction, as proposed by the STRIDE guidance. Since the STRIDE recommendations have been published, an increasing amount of clinical data emerged on the use of various targets and subsequent long-term outcomes, thus the re-evaluation of the recommendations and targets (*e.g.*, the role of biomarkers) is warranted.

Recent long-term follow-up data of the CALM study show that endoscopic and deep remission at 1 year prevents disease progression in early CD<sup>[55]</sup>, however further clinical trials are needed to demonstrate the long-term superiority of treating to endoscopic remission. The REACT2 trial (Enhanced Algorithm for Crohn's Treatment Incorporating Early Combination Therapy trial) assesses the exact role of endoscopy in the tight control concept by comparing an enhanced treat-to-target strategy featuring early use and rapid escalation of combined antimetabolite/adalimumab therapy based on timely endoscopic evaluations with a traditional step-care algorithm with symptom driven treatment escalation (ClinicalTrials.gov: NCT01698307)<sup>[91]</sup>. In addition, a unified definition of endoscopic response/remission tailored to the everyday clinical practice is missing, especially in CD.

The evidence is clearly increasing on the role of biomarkers, supported by the positive results of the CALM study. Biomarkers emerge as treatment targets as they can guide treatment escalations, leading to superior endoscopic and clinical outcomes, which is the foundation of the tight control concept. However, more evidence is needed to determine the optimal role and cut-offs of biomarkers in monitoring disease control. Using directly the "therapeutic failure" from the CALM study solely based on biomarker positivity to prompt therapy escalation in certain cases would potentially be overly stringent in everyday clinical practice, leading to frequent overtreatment. Long term cost-efficacy has to be established as well. Further data is needed to evaluate the role of different biomarkers, especially used as composite (biomarker and endoscopic) "treatment failure" criteria.

Other elements of the treat-to-target and tight control strategies, such as the adequate intervals of patient monitoring also need clarification. Although the STRIDE specifies recommendations for timing of clinical and endoscopic evaluations, data on optimal biomarker follow-up intervals are partly conflictive. Moreover, patients in different clinical scenarios—active disease, clinical remission or at relapse, mild(er) or complex complicated disease—may require different disease monitoring strategy and intervals. Biomarker evaluations were performed every 12 wk in the CALM, and other studies reported that FCAL may predict clinical flare as soon as approximately 3 mo before symptoms occur. These data may suggest an optimal interval of approximately 3 mo for biomarker monitoring in patients with clinically controlled disease, however detailed recommendations for patient monitoring intervals—including clinical, biochemical and endoscopic evaluation as well— is urgently needed (see Table 2).

Although there has been a significant increase and earlier exposure to immunosuppressive and biologic agents in IBD recently, population-based data on long-term outcomes show somewhat controversial results and prompt caution when translating clinical trial results into clinical practice. The Epi-IBD<sup>[5]</sup> cohort is a prospective population-based inception cohort of unselected CD patients from 29 European centres. Although significant geographic differences were observed in medication timing and exposures (in Western Europe 33% of patients received biological therapy and 66% immunomodulators; in Eastern Europe 14% and 54%, respectively,  $P < 0.01$ ), the course of disease—including rates of patients undergoing surgery, developing stricturing or penetrating disease phenotype or being hospitalized— did not differ between in Western and Eastern Europe. Similar results are being reported from two very recent administrative database analyses from Canada. Data from Murthy *et al*<sup>[92]</sup> showed that the introduction of anti-TNF therapy failed to modify the trend of IBD-related hospitalizations and surgeries in both CD and UC between 1995 and 2012. This suggests that disease monitoring in real life practice is suboptimal and in the future, using new, algorithm-based therapeutic strategies as standard of care may translate into improved outcomes as observed in pivotal clinical trials<sup>[12,28]</sup>.

---

## CONCLUSION

---

Data favoring the treat-to-target strategies and tight patient control still continue to accumulate and results from ongoing trials will further clarify its long-term



implications. Early and effective treatment with optimal patient stratification and monitoring using treat-to-target and tight control concepts is emerging as superior therapeutic strategy. The use of biologic agents should be optimized with timely monitoring, appropriate treatment escalation and de-escalation strategies are both warranted in selected patients. Finally, improving patient-physician communication and patient access to IBD specific healthcare services to receive proper evaluation in urgent IBD related situations is vital in the framework of tight control management. These approaches however require further validation with more precise definition of therapeutic targets (endoscopic, biomarker) in prospective studies of newly diagnosed patients with assessment of long-term outcomes.

## REFERENCES

- 1 Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, Panaccione R, Ghosh S, Wu JCY, Chan FKL, Sung JY, Kaplan GG. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2018; **390**: 2769-2778 [PMID: 29050646 DOI: 10.1016/S0140-6736(17)32448-0]
- 2 Peyrin-Biroulet L, Loftus EV, Colombel JF, Sandborn WJ. Long-term complications, extraintestinal manifestations, and mortality in adult Crohn's disease in population-based cohorts. *Inflamm Bowel Dis* 2011; **17**: 471-478 [PMID: 20725943 DOI: 10.1002/ibd.21417]
- 3 Torres J, Billioud V, Sachar DB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis as a progressive disease: the forgotten evidence. *Inflamm Bowel Dis* 2012; **18**: 1356-1363 [PMID: 22162423 DOI: 10.1002/ibd.22839]
- 4 Bouguen G, Peyrin-Biroulet L. Surgery for adult Crohn's disease: what is the actual risk? *Gut* 2011; **60**: 1178-1181 [PMID: 21610273 DOI: 10.1136/gut.2010.234617]
- 5 Burisch J, Kiudelis G, Kupcinskas L, Kievit HAL, Andersen KW, Andersen V, Salupere R, Pedersen N, Kjeldsen J, D'Inca R, Valpiani D, Schwartz D, Odes S, Olsen J, Nielsen KR, Vegh Z, Lakatos PL, Toca A, Turcan S, Katsanos KH, Christodoulou DK, Fumery M, Gower-Rousseau C, Chetcuti Zammit S, Ellul P, Eriksson C, Halfvarson J, Magro FJ, Duricova D, Bortlik M, Fernandez A, Hernández V, Myers S, Sebastian S, Oksanen P, Collin P, Goldis A, Misra R, Arebi N, Kaimakliotis IP, Nikuina I, Belousova E, Brinar M, Cukovic-Cavka S, Langholz E, Munkholm P; Epi-IBD group. Natural disease course of Crohn's disease during the first 5 years after diagnosis in a European population-based inception cohort: an Epi-IBD study. *Gut* 2018 [PMID: 29363534 DOI: 10.1136/gutjnl-2017-315568]
- 6 Peyrin-Biroulet L, Cieza A, Sandborn WJ, Coenen M, Chowers Y, Hibi T, Kostanjsek N, Stucki G, Colombel JF; International Programme to Develop New Indexes for Crohn's Disease (IPNIC) group. Development of the first disability index for inflammatory bowel disease based on the international classification of functioning, disability and health. *Gut* 2012; **61**: 241-247 [PMID: 21646246 DOI: 10.1136/gutjnl-2011-300049]
- 7 Pariente B, Mary JY, Danese S, Chowers Y, De Cruz P, D'Haens G, Loftus EV, Louis E, Panés J, Schölmerich J, Schreiber S, Vecchi M, Branche J, Bruining D, Fiorino G, Herzog M, Kamm MA, Klein A, Lewin M, Meunier P, Ordas I, Strauch U, Tontini GE, Zagdanski AM, Bonifacio C, Rimola J, Nachury M, Leroy C, Sandborn W, Colombel JF, Cosnes J. Development of the Lémann index to assess digestive tract damage in patients with Crohn's disease. *Gastroenterology* 2015; **148**: 52-63.e3 [PMID: 25241327 DOI: 10.1053/j.gastro.2014.09.015]
- 8 Solberg IC, Vatn MH, Høie O, Stray N, Sauar J, Jahnsen J, Moum B, Lygren I; IBSEN Study Group. Clinical course in Crohn's disease: results of a Norwegian population-based ten-year follow-up study. *Clin Gastroenterol Hepatol* 2007; **5**: 1430-1438 [PMID: 18054751 DOI: 10.1016/j.cgh.2007.09.002]
- 9 Solberg IC, Lygren I, Jahnsen J, Aadland E, Høie O, Cvancarova M, Bernklev T, Henriksen M, Sauar J, Vatn MH, Moum B; IBSEN Study Group. Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort (IBSEN Study). *Scand J Gastroenterol* 2009; **44**: 431-440 [PMID: 19101844 DOI: 10.1080/00365520802600961]
- 10 D'Haens G, Baert F, van Assche G, Caenepeel P, Vergauwe P, Tuynman H, De Vos M, van Deventer S, Stitt L, Donner A, Vermeire S, Van De Mierop FJ, Coche JR, van der Woude J, Ochsenkühn T, van Bodegraven AA, Van Hooft PP, Lambrecht GL, Mana F, Rutgeerts P, Feagan BG, Hommes D; Belgian Inflammatory Bowel Disease Research Group; North-Holland Gut Club. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet* 2008; **371**: 660-667 [PMID: 18295023 DOI: 10.1016/S0140-6736(08)60304-9]
- 11 Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens G, Diamond RH, Broussard DL, Tang KL, van der Woude CJ, Rutgeerts P; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010; **362**: 1383-1395 [PMID: 20393175 DOI: 10.1056/NEJMoa0904492]
- 12 Khanna R, Bressler B, Levesque BG, Zou G, Stitt LW, Greenberg GR, Panaccione R, Bitton A, Paré P, Vermeire S, D'Haens G, MacIntosh D, Sandborn WJ, Donner A, Vandervoort MK, Morris JC, Feagan BG; REACT Study Investigators. Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomised controlled trial. *Lancet* 2015; **386**: 1825-1834 [PMID: 26342731 DOI: 10.1016/S0140-6736(15)00068-9]
- 13 Colombel JF, Panaccione R, Bossuyt P, Lukas M, Baert F, Vaňásek T, Danalioglu A, Novacek G, Armuzzi A, Hébuterne X, Travis S, Danese S, Reinisch W, Sandborn WJ, Rutgeerts P, Hommes D, Schreiber S, Neimark E, Huang B, Zhou Q, Mendez P, Petersson J, Wallace K, Robinson AM, Thakkar RB, D'Haens G. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. *Lancet* 2018; **390**: 2779-2789 [PMID: 29096949 DOI: 10.1016/S0140-6736(17)32641-7]
- 14 Beaugier L, Seksik P, Nion-Larmurier I, Gendre JP, Cosnes J. Predictors of Crohn's disease. *Gastroenterology* 2006; **130**: 650-656 [PMID: 16530505 DOI: 10.1053/j.gastro.2005.12.019]
- 15 Lakatos PL, Czeglédi Z, Szamosi T, Banai J, David G, Zsigmond F, Pandur T, Erdelyi Z, Gemela O, Papp J, Lakatos L. Perianal disease, small bowel disease, smoking, prior steroid or early azathioprine/biological



- therapy are predictors of disease behavior change in patients with Crohn's disease. *World J Gastroenterol* 2009; **15**: 3504-3510 [PMID: 19630105 DOI: 10.3748/wjg.15.3504]
- 16 **Solberg IC**, Høivik ML, Cvancarova M, Moun B; IBSEN Study Group. Risk matrix model for prediction of colectomy in a population-based study of ulcerative colitis patients (the IBSEN study). *Scand J Gastroenterol* 2015; **50**: 1456-1462 [PMID: 26139389 DOI: 10.3109/00365521.2015.1064991]
- 17 **Solberg IC**, Cvancarova M, Vatn MH, Moun B; IBSEN Study Group. Risk matrix for prediction of advanced disease in a population-based study of patients with Crohn's Disease (the IBSEN Study). *Inflamm Bowel Dis* 2014; **20**: 60-68 [PMID: 24280875 DOI: 10.1097/01.MIB.0000436956.78220.67]
- 18 **Guizzetti L**, Zou G, Khanna R, Dulai PS, Sandborn WJ, Jairath V, Feagan BG. Development of Clinical Prediction Models for Surgery and Complications in Crohn's Disease. *J Crohns Colitis* 2018; **12**: 167-177 [PMID: 29028958 DOI: 10.1093/ecco-jcc/jjx130]
- 19 **Allen PB**, Peyrin-Biroulet L. Moving towards disease modification in inflammatory bowel disease therapy. *Curr Opin Gastroenterol* 2013; **29**: 397-404 [PMID: 23695427 DOI: 10.1097/MOG.0b013e3283622914]
- 20 **Sandborn WJ**, Hanauer S, Van Assche G, Panés J, Wilson S, Petersson J, Panaccione R. Treating beyond symptoms with a view to improving patient outcomes in inflammatory bowel diseases. *J Crohns Colitis* 2014; **8**: 927-935 [PMID: 24713173 DOI: 10.1016/j.crohns.2014.02.021]
- 21 **Magro F**, Rodrigues A, Vieira AI, Portela F, Cremers I, Cotter J, Correia L, Duarte MA, Tavares ML, Lago P, Ministro P, Peixe P, Lopes S, Garcia EB. Review of the disease course among adult ulcerative colitis population-based longitudinal cohorts. *Inflamm Bowel Dis* 2012; **18**: 573-583 [PMID: 21793126 DOI: 10.1002/ibd.21815]
- 22 **Peyrin-Biroulet L**, Reinisch W, Colombel JF, Mantzaris GJ, Kornbluth A, Diamond R, Rutgeerts P, Tang LK, Cornillie FJ, Sandborn WJ. Clinical disease activity, C-reactive protein normalisation and mucosal healing in Crohn's disease in the SONIC trial. *Gut* 2014; **63**: 88-95 [PMID: 23974954 DOI: 10.1136/gutjnl-2013-304984]
- 23 **Jharap B**, Sandborn WJ, Reinisch W, D'Haens G, Robinson AM, Wang W, Huang B, Lazar A, Thakkar RB, Colombel JF. Randomised clinical study: discrepancies between patient-reported outcomes and endoscopic appearance in moderate to severe ulcerative colitis. *Aliment Pharmacol Ther* 2015; **42**: 1082-1092 [PMID: 26381802 DOI: 10.1111/apt.13387]
- 24 **Baert F**, Moortgat L, Van Assche G, Caenepeel P, Vergauwe P, De Vos M, Stokkers P, Hommes D, Rutgeerts P, Vermeire S, D'Haens G; Belgian Inflammatory Bowel Disease Research Group; North-Holland Gut Club. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. *Gastroenterology* 2010; **138**: 463-468 [PMID: 19818785 DOI: 10.1053/j.gastro.2009.09.056]
- 25 **Colombel JF**, Rutgeerts P, Reinisch W, Esser D, Wang Y, Lang Y, Marano CW, Strauss R, Oddens BJ, Feagan BG, Hanauer SB, Lichtenstein GR, Present D, Sands BE, Sandborn WJ. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. *Gastroenterology* 2011; **141**: 1194-1201 [PMID: 21723220 DOI: 10.1053/j.gastro.2011.06.054]
- 26 **Colombel JF**, Rutgeerts PJ, Sandborn WJ, Yang M, Camez A, Pollack PF, Thakkar RB, Robinson AM, Chen N, Mulani PM, Chao J. Adalimumab induces deep remission in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2014; **12**: 414-22.e5 [PMID: 23856361 DOI: 10.1016/j.cgh.2013.06.019]
- 27 **Froslie KF**, Jahnsen J, Moun BA, Vatn MH; IBSEN Group. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. *Gastroenterology* 2007; **133**: 412-422 [PMID: 17681162 DOI: 10.1053/j.gastro.2007.05.051]
- 28 **Peyrin-Biroulet L**, Sandborn W, Sands BE, Reinisch W, Bemelman W, Bryant RV, D'Haens G, Dotan I, Dubinsky M, Feagan B, Fiorino G, Geary R, Krishnareddy S, Lakatos PL, Loftus EV, Marteau P, Munkholm P, Murdoch TB, Ordás I, Panaccione R, Riddell RH, Ruel J, Rubin DT, Samaan M, Siegel CA, Silverberg MS, Stoker J, Schreiber S, Travis S, Van Assche G, Danese S, Panes J, Bouguen G, O'Donnell S, Pariente B, Winer S, Hanauer S, Colombel JF. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. *Am J Gastroenterol* 2015; **110**: 1324-1338 [PMID: 26303131 DOI: 10.1038/ajg.2015.233]
- 29 **Best WR**, Beckett JM, Singleton JW. Rederived values of the eight coefficients of the Crohn's Disease Activity Index (CDAI). *Gastroenterology* 1979; **77**: 843-846 [PMID: 467941 DOI: 10.1016/0016-5085(79)90384-6]
- 30 **Harvey RF**, Bradshaw JM. A simple index of Crohn's-disease activity. *Lancet* 1980; **1**: 514 [PMID: 6102236 DOI: 10.1016/s0140-6736(80)92767-1]
- 31 **Walmsley RS**, Ayres RC, Pounder RE, Allan RN. A simple clinical colitis activity index. *Gut* 1998; **43**: 29-32 [PMID: 9771402 DOI: 10.1136/gut.43.1.29]
- 32 **Rutgeerts P**, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005; **353**: 2462-2476 [PMID: 16339095 DOI: 10.1056/NEJMoa050516]
- 33 **FDA Guidance for Industry**. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Cited 27 August 2019. Available from: <http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf>
- 34 **de Jong MJ**, Roosen D, Degens JHRJ, van den Heuvel TRA, Romberg-Camps M, Hameeteman W, Bodelier AGL, Romanko I, Lukas M, Winkens B, Markus T, Masclee AAM, van Tubergen A, Jonkers DMAE, Pierik MJ. Development and Validation of a Patient-reported Score to Screen for Mucosal Inflammation in Inflammatory Bowel Disease. *J Crohns Colitis* 2019; **13**: 555-563 [PMID: 30476099 DOI: 10.1093/ecco-jcc/jjy196]
- 35 **Higgins PDR**, Harding G, Leidy NK, DeBusk K, Patrick DL, Viswanathan HN, Fitzgerald K, Donelson SM, Cyrille M, Ortmeier BG, Wilson H, Revicki DA, Globe G. Development and validation of the Crohn's disease patient-reported outcomes signs and symptoms (CD-PRO/SS) diary. *J Patient Rep Outcomes* 2017; **2**: 24 [PMID: 29770803 DOI: 10.1186/s41687-018-0044-7]
- 36 **Higgins PDR**, Harding G, Revicki DA, Globe G, Patrick DL, Fitzgerald K, Viswanathan H, Donelson SM, Ortmeier BG, Chen WH, Leidy NK, DeBusk K. Development and validation of the Ulcerative Colitis patient-reported outcomes signs and symptoms (UC-pro/SS) diary. *J Patient Rep Outcomes* 2017; **2**: 26 [PMID: 29888745 DOI: 10.1186/s41687-018-0049-2]
- 37 **Gower-Rousseau C**, Sarter H, Savoye G, Tavernier N, Fumery M, Sandborn WJ, Feagan BG, Duhamel A, Guillon-Dellac N, Colombel JF, Peyrin-Biroulet L; International Programme to Develop New Indexes for Crohn's Disease (IPNIC) group; International Programme to Develop New Indexes for Crohn's Disease

- (IPNIC) group. Validation of the Inflammatory Bowel Disease Disability Index in a population-based cohort. *Gut* 2017; **66**: 588-596 [PMID: 26646934 DOI: 10.1136/gutjnl-2015-310151]
- 38 **Shah SC**, Colombel JF, Sands BE, Narula N. Systematic review with meta-analysis: mucosal healing is associated with improved long-term outcomes in Crohn's disease. *Aliment Pharmacol Ther* 2016; **43**: 317-333 [PMID: 26607562 DOI: 10.1111/apt.13475]
- 39 **Shah SC**, Colombel JF, Sands BE, Narula N. Mucosal Healing Is Associated With Improved Long-term Outcomes of Patients With Ulcerative Colitis: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2016; **14**: 1245-1255.e8 [PMID: 26829025 DOI: 10.1016/j.cgh.2016.01.015]
- 40 **Bouguen G**, Levesque BG, Pola S, Evans E, Sandborn WJ. Endoscopic assessment and treating to target increase the likelihood of mucosal healing in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2014; **12**: 978-985 [PMID: 24246770 DOI: 10.1016/j.cgh.2013.11.005]
- 41 **Ferrante M**, Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens GR, van der Woude CJ, Danese S, Diamond RH, Oortwijn AF, Tang KL, Miller M, Cornillie F, Rutgeerts PJ; International Organization for the Study of Inflammatory Bowel Diseases. Validation of endoscopic activity scores in patients with Crohn's disease based on a post hoc analysis of data from SONIC. *Gastroenterology* 2013; **145**: 978-986.e5 [PMID: 23954314 DOI: 10.1053/j.gastro.2013.08.010]
- 42 **Vuitton L**, Marteau P, Sandborn WJ, Levesque BG, Feagan B, Vermeire S, Danese S, D'Haens G, Lowenberg M, Khanna R, Fiorino G, Travis S, Mary JY, Peyrin-Biroulet L. IOIBD technical review on endoscopic indices for Crohn's disease clinical trials. *Gut* 2016; **65**: 1447-1455 [PMID: 26353983 DOI: 10.1136/gutjnl-2015-309903]
- 43 **Barreiro-de Acosta M**, Vallejo N, de la Iglesia D, Uribarri L, Bastón I, Ferreira-Iglesias R, Lorenzo A, Domínguez-Muñoz JE. Evaluation of the Risk of Relapse in Ulcerative Colitis According to the Degree of Mucosal Healing (Mayo 0 vs 1): A Longitudinal Cohort Study. *J Crohns Colitis* 2016; **10**: 13-19 [PMID: 26351390 DOI: 10.1093/ecco-jcc/jjv158]
- 44 **Boal Carvalho P**, Dias de Castro F, Rosa B, Moreira MJ, Cotter J. Mucosal Healing in Ulcerative Colitis--When Zero is Better. *J Crohns Colitis* 2016; **10**: 20-25 [PMID: 26438714 DOI: 10.1093/ecco-jcc/jjv180]
- 45 **Lobatón T**, Bessisow T, De Hertogh G, Lemmens B, Maedler C, Van Assche G, Vermeire S, Bisschops R, Rutgeerts P, Bitton A, Afif W, Marcus V, Ferrante M. The Modified Mayo Endoscopic Score (MMES): A New Index for the Assessment of Extension and Severity of Endoscopic Activity in Ulcerative Colitis Patients. *J Crohns Colitis* 2015; **9**: 846-852 [PMID: 26116558 DOI: 10.1093/ecco-jcc/jjv111]
- 46 **Ikeya K**, Hanai H, Sugimoto K, Osawa S, Kawasaki S, Iida T, Maruyama Y, Watanabe F. The Ulcerative Colitis Endoscopic Index of Severity More Accurately Reflects Clinical Outcomes and Long-term Prognosis than the Mayo Endoscopic Score. *J Crohns Colitis* 2016; **10**: 286-295 [PMID: 26581895 DOI: 10.1093/ecco-jcc/jjv210]
- 47 **Vuitton L**, Peyrin-Biroulet L, Colombel JF, Pariente B, Pineton de Chambrun G, Walsh AJ, Panes J, Travis SP, Mary JY, Marteau P. Defining endoscopic response and remission in ulcerative colitis clinical trials: an international consensus. *Aliment Pharmacol Ther* 2017; **45**: 801-813 [PMID: 28112419 DOI: 10.1111/apt.13948]
- 48 **Solem CA**, Loftus EV, Tremaine WJ, Harmsen WS, Zinsmeister AR, Sandborn WJ. Correlation of C-reactive protein with clinical, endoscopic, histologic, and radiographic activity in inflammatory bowel disease. *Inflamm Bowel Dis* 2005; **11**: 707-712 [PMID: 16043984 DOI: 10.1097/01.mib.0000173271.18319.53]
- 49 **Mosli MH**, Zou G, Garg SK, Feagan SG, MacDonald JK, Chande N, Sandborn WJ, Feagan BG. C-Reactive Protein, Fecal Calprotectin, and Stool Lactoferrin for Detection of Endoscopic Activity in Symptomatic Inflammatory Bowel Disease Patients: A Systematic Review and Meta-Analysis. *Am J Gastroenterol* 2015; **110**: 802-819 [PMID: 25964225 DOI: 10.1038/ajg.2015.120]
- 50 **D'Haens G**, Ferrante M, Vermeire S, Baert F, Noman M, Moortgat L, Geens P, Iwens D, Aerden I, Van Assche G, Van Olmen G, Rutgeerts P. Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease. *Inflamm Bowel Dis* 2012; **18**: 2218-2224 [PMID: 22344983 DOI: 10.1002/ibd.22917]
- 51 **De Vos M**, Louis EJ, Jahnsen J, Vandervoort JG, Noman M, Dewit O, D'haens GR, Franchimont D, Baert FJ, Torp RA, Henriksen M, Potvin PM, Van Hootegem PP, Hindryckx PM, Moreels TG, Collard A, Karlens LN, Kittang E, Lambrecht G, Grimstad T, Koch J, Lygren I, Coche JC, Mana F, Van Gossom A, Belaiche J, Cool MR, Fontaine F, Maisin JM, Muls V, Neuville B, Staessen DA, Van Assche GA, de Lange T, Solberg IC, Vander Cruyssen BJ, Vermeire SA. Consecutive fecal calprotectin measurements to predict relapse in patients with ulcerative colitis receiving infliximab maintenance therapy. *Inflamm Bowel Dis* 2013; **19**: 2111-2117 [PMID: 23883959 DOI: 10.1097/MIB.0b013e31829b2a37]
- 52 **Zhulina Y**, Cao Y, Amcoff K, Carlson M, Tysk C, Halfvarson J. The prognostic significance of faecal calprotectin in patients with inactive inflammatory bowel disease. *Aliment Pharmacol Ther* 2016; **44**: 495-504 [PMID: 27402063 DOI: 10.1111/apt.13731]
- 53 **Heida A**, Park KT, van Rheenen PF. Clinical Utility of Fecal Calprotectin Monitoring in Asymptomatic Patients with Inflammatory Bowel Disease: A Systematic Review and Practical Guide. *Inflamm Bowel Dis* 2017; **23**: 894-902 [PMID: 28511198 DOI: 10.1097/MIB.0000000000001082]
- 54 **Wright EK**, Kamm MA, De Cruz P, Hamilton AL, Ritchie KJ, Krejany EO, Leach S, Gorelik A, Liew D, Prideaux L, Lawrence IC, Andrews JM, Bampton PA, Jakobovits SL, Florin TH, Gibson PR, Debinski H, Macrae FA, Samuel D, Kronborg I, Radford-Smith G, Selby W, Johnston MJ, Woods R, Elliott PR, Bell SJ, Brown SJ, Connell WR, Day AS, Desmond PV, Geary RB. Measurement of fecal calprotectin improves monitoring and detection of recurrence of Crohn's disease after surgery. *Gastroenterology* 2015; **148**: 938-947.e1 [PMID: 25620670 DOI: 10.1053/j.gastro.2015.01.026]
- 55 **Ungaro RC**, Yzet C, Bossuyt P, Baert FJ, Vanasek T, D'Haens GR, Joustra VW, Panaccione R, Novacek G, Armuzzi A, Golovchenko O, Olga P, Goldis A, Travis SP, Hebuterne X, Ferrante M, Rogler G, Fumery M, Danese S, Ryzewska G, Pariente B, Hertervig E, Stanciu C, Grimaud J, Diculescu M, Peyrin-Biroulet L, Laharie D, Wright JP, Gomollon F, Gubonina I, Schreiber S, Motoya S, Hellström PM, Halfvarson J, Colombel JF. Sa1812 Endoscopic and deep remission at 1 year prevents disease progression in early Crohn's disease: long-term data from CALM. *Gastroenterology* 2019; **6** Suppl 1: S411 [DOI: 10.1016/S0016-5085(19)37879-5]
- 56 **Cornillie F**, Hanauer SB, Diamond RH, Wang J, Tang KL, Xu Z, Rutgeerts P, Vermeire S. Postinduction serum infliximab trough level and decrease of C-reactive protein level are associated with durable sustained response to infliximab: a retrospective analysis of the ACCENT I trial. *Gut* 2014; **63**: 1721-1727 [PMID: 24474383 DOI: 10.1136/gutjnl-2012-304094]

- 57 **Bortlik M**, Duricova D, Malickova K, Machkova N, Bouzkova E, Hrdlicka L, Komarek A, Lukas M. Infliximab trough levels may predict sustained response to infliximab in patients with Crohn's disease. *J Crohns Colitis* 2013; **7**: 736-743 [PMID: [23200919](#) DOI: [10.1016/j.crohns.2012.10.019](#)]
- 58 **Mazor Y**, Almog R, Kopylov U, Ben Hur D, Blatt A, Dahan A, Waterman M, Ben-Horin S, Chowers Y. Adalimumab drug and antibody levels as predictors of clinical and laboratory response in patients with Crohn's disease. *Aliment Pharmacol Ther* 2014; **40**: 620-628 [PMID: [25039584](#) DOI: [10.1111/apt.12869](#)]
- 59 **Affif W**, Loftus EV, Faubion WA, Kane SV, Bruining DH, Hanson KA, Sandborn WJ. Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. *Am J Gastroenterol* 2010; **105**: 1133-1139 [PMID: [20145610](#) DOI: [10.1038/ajg.2010.9](#)]
- 60 **Roblin X**, Rinaudo M, Del Tedesco E, Phelip JM, Genin C, Peyrin-Biroulet L, Paul S. Development of an algorithm incorporating pharmacokinetics of adalimumab in inflammatory bowel diseases. *Am J Gastroenterol* 2014; **109**: 1250-1256 [PMID: [24913041](#) DOI: [10.1038/ajg.2014.146](#)]
- 61 **Papamichael K**, Cheifetz AS. Use of anti-TNF drug levels to optimise patient management. *Frontline Gastroenterol* 2016; **7**: 289-300 [PMID: [28839870](#) DOI: [10.1136/flgastro-2016-100685](#)]
- 62 **Vande Castele N**, Ferrante M, Van Assche G, Ballet V, Comperolle G, Van Steen K, Simoens S, Rutgeerts P, Gils A, Vermeire S. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. *Gastroenterology* 2015; **148**: 1320-9.e3 [PMID: [25724455](#) DOI: [10.1053/j.gastro.2015.02.031](#)]
- 63 **D'Haens G**, Vermeire S, Lambrecht G, Baert F, Bossuyt P, Pariente B, Buisson A, Bouhnik Y, Filippi J, Vander Woude J, Van Hooft P, Moreau J, Louis E, Franchimont D, De Vos M, Mana F, Peyrin-Biroulet L, Brixi H, Allez M, Caenepeel P, Aubourg A, Oldenburg B, Pierik M, Gils A, Chevret S, Laharie D; GETAID. Increasing Infliximab Dose Based on Symptoms, Biomarkers, and Serum Drug Concentrations Does Not Increase Clinical, Endoscopic, and Corticosteroid-Free Remission in Patients With Active Luminal Crohn's Disease. *Gastroenterology* 2018; **154**: 1343-1351.e1 [PMID: [29317275](#) DOI: [10.1053/j.gastro.2018.01.004](#)]
- 64 **Papamichael K**, Juncadella A, Wong D, Rakowsky S, Sattler LA, Campbell JP, Vaughn BP, Cheifetz AS. Proactive Therapeutic Drug Monitoring of Adalimumab Is Associated With Better Long-term Outcomes Compared With Standard of Care in Patients With Inflammatory Bowel Disease. *J Crohns Colitis* 2019; **13**: 976-981 [PMID: [30689771](#) DOI: [10.1093/ecco-jcc/jjz018](#)]
- 65 **Papamichael K**, Chachu KA, Vajravelu RK, Vaughn BP, Ni J, Osterman MT, Cheifetz AS. Improved Long-term Outcomes of Patients With Inflammatory Bowel Disease Receiving Proactive Compared With Reactive Monitoring of Serum Concentrations of Infliximab. *Clin Gastroenterol Hepatol* 2017; **15**: 1580-1588.e3 [PMID: [28365486](#) DOI: [10.1016/j.cgh.2017.03.031](#)]
- 66 **Fernandes SR**, Bernardo S, Simões C, Correia L, Santos PM, Gonçalves AR, Valente A, Baldaia C, Tato Marinho R. DOP59 Proactive infliximab drug monitoring is superior to conventional management in inflammatory bowel disease. *J Crohns Colitis* 2019; **13** Suppl 1: S064-S065 [DOI: [10.1093/ecco-jcc/jjy222.093](#)]
- 67 **Papamichael K**, Vande Castele N, Gils A, Tops S, Hauenstein S, Singh S, Princen F, Van Assche G, Rutgeerts P, Vermeire S, Ferrante M. Long-term outcome of patients with Crohn's disease who discontinued infliximab therapy upon clinical remission. *Clin Gastroenterol Hepatol* 2015; **13**: 1103-1110 [PMID: [25478919](#) DOI: [10.1016/j.cgh.2014.11.026](#)]
- 68 **Bryant RV**, Burger DC, Delo J, Walsh AJ, Thomas S, von Herbay A, Buchel OC, White L, Brain O, Keshav S, Warren BF, Travis SP. Beyond endoscopic mucosal healing in UC: histological remission better predicts corticosteroid use and hospitalisation over 6 years of follow-up. *Gut* 2016; **65**: 408-414 [PMID: [25986946](#) DOI: [10.1136/gutjnl-2015-309598](#)]
- 69 **Christensen B**, Hanauer SB, Erlich J, Kassim O, Gibson PR, Turner JR, Hart J, Rubin DT. Histologic Normalization Occurs in Ulcerative Colitis and Is Associated With Improved Clinical Outcomes. *Clin Gastroenterol Hepatol* 2017; **15**: 1557-1564.e1 [PMID: [28238954](#) DOI: [10.1016/j.cgh.2017.02.016](#)]
- 70 **Park S**, Abdi T, Gentry M, Laine L. Histological Disease Activity as a Predictor of Clinical Relapse Among Patients With Ulcerative Colitis: Systematic Review and Meta-Analysis. *Am J Gastroenterol* 2016; **111**: 1692-1701 [PMID: [27725645](#) DOI: [10.1038/ajg.2016.418](#)]
- 71 **Magro F**, Lopes J, Borralho P, Lopes S, Coelho R, Cotter J, Castro FD, Sousa HT, Salgado M, Andrade P, Vieira AI, Figueiredo P, Caldeira P, Sousa A, Duarte MA, Avila F, Silva J, Moleiro J, Mendes S, Giestas S, Ministro P, Sousa P, Gonçalves R, Gonçalves B, Oliveira A, Rosa I, Rodrigues M, Chagas C, Dias CC, Afonso J, Geboes K, Carneiro F; Portuguese IBD Study Group (GEDII). Comparison of different histological indexes in the assessment of UC activity and their accuracy regarding endoscopic outcomes and faecal calprotectin levels. *Gut* 2019; **68**: 594-603 [PMID: [29437913](#) DOI: [10.1136/gutjnl-2017-315545](#)]
- 72 **Panés J**, Bouzas R, Chaparro M, García-Sánchez V, Gisbert JP, Martínez de Guereñu B, Mendoza JL, Paredes JM, Quiroga S, Ripollés T, Rimola J. Systematic review: the use of ultrasonography, computed tomography and magnetic resonance imaging for the diagnosis, assessment of activity and abdominal complications of Crohn's disease. *Aliment Pharmacol Ther* 2011; **34**: 125-145 [PMID: [21615440](#) DOI: [10.1111/j.1365-2036.2011.04710.x](#)]
- 73 **Deepak P**, Fletcher JG, Fidler JL, Barlow JM, Sheedy SP, Kolbe AB, Harmsen WS, Loftus EV, Hansel SL, Becker BD, Bruining DH. Radiological Response Is Associated With Better Long-Term Outcomes and Is a Potential Treatment Target in Patients With Small Bowel Crohn's Disease. *Am J Gastroenterol* 2016; **111**: 997-1006 [PMID: [27166131](#) DOI: [10.1038/ajg.2016.177](#)]
- 74 **Fernandes SR**, Rodrigues RV, Bernardo S, Cortez-Pinto J, Rosa I, da Silva JP, Gonçalves AR, Valente A, Baldaia C, Santos PM, Correia L, Venâncio J, Campos P, Pereira AD, Velosa J. Transmural Healing Is Associated With Improved Long-term Outcomes of Patients with Crohn's Disease. *Inflamm Bowel Dis* 2017; **23**: 1403-1409 [PMID: [28498158](#) DOI: [10.1097/MIB.0000000000001143](#)]
- 75 **Ilias A**, Lovasz BD, Gonczi L, Kurti Z, Vegh Z, Sumegi LD, Golovics PA, Rudas G, Lakatos PL. Optimizing Patient Management in Crohn's Disease in a Tertiary Referral Center: the Impact of Fast-Track MRI on Patient Management and Outcomes. *J Gastrointest Liver Dis* 2018; **27**: 391-397 [PMID: [30574621](#) DOI: [10.15403/jgld.2014.1121.274.oem](#)]
- 76 **Bots S**, Nylund K, Löwenberg M, Gecse K, Gilja OH, D'Haens G. Ultrasound for Assessing Disease Activity in IBD Patients: A Systematic Review of Activity Scores. *J Crohns Colitis* 2018; **12**: 920-929 [PMID: [29684200](#) DOI: [10.1093/ecco-jcc/jjy048](#)]
- 77 **Laurent V**, Naudé S, Vuitton L, Zallot C, Baumann C, Girard-Gavanier M, Peyrin-Biroulet L. Accuracy of Diffusion-weighted Magnetic Resonance Colonography in Assessing Mucosal Healing and the Treatment Response in Patients with Ulcerative Colitis. *J Crohns Colitis* 2017; **11**: 716-723 [PMID: [28365486](#) DOI: [10.1016/j.cgh.2017.03.031](#)]

- 27932450 DOI: [10.1093/ecco-jcc/jjw211](https://doi.org/10.1093/ecco-jcc/jjw211)]
- 78 **Louis E**, Mary JY, Vernier-Massouille G, Grimaud JC, Bouhnik Y, Laharie D, Dupas JL, Pillant H, Picon L, Veyrac M, Flamant M, Savoye G, Jian R, Devos M, Porcher R, Pintaud G, Piver E, Colombel JF, Lemann M; Groupe D'etudes Thérapeutiques Des Affections Inflammatoires Digestives. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. *Gastroenterology* 2012; **142**: 63-70.e5 [PMID: [21945953](https://pubmed.ncbi.nlm.nih.gov/21945953/) DOI: [10.1053/j.gastro.2011.09.034](https://doi.org/10.1053/j.gastro.2011.09.034)]
- 79 **Bryant RV**, Costello SP, Schoeman S, Sathananthan D, Knight E, Lau SY, Schoeman MN, Mountfield R, Tee D, Travis SPL, Andrews JM. Limited uptake of ulcerative colitis "treat-to-target" recommendations in real-world practice. *J Gastroenterol Hepatol* 2018; **33**: 599-607 [PMID: [28806471](https://pubmed.ncbi.nlm.nih.gov/28806471/) DOI: [10.1111/jgh.13923](https://doi.org/10.1111/jgh.13923)]
- 80 **Römkens TE**, Gijsbers K, Kievit W, Hoentjen F, Drenth JP. Treatment Targets in Inflammatory Bowel Disease: Current Status in Daily Practice. *J Gastrointestin Liver Dis* 2016; **25**: 465-471 [PMID: [27981302](https://pubmed.ncbi.nlm.nih.gov/27981302/) DOI: [10.15403/jgld.2014.1121.254.ken](https://doi.org/10.15403/jgld.2014.1121.254.ken)]
- 81 **Bitton A**, Vutcovici M, Lytvyak E, Kachan N, Bressler B, Jones J, Lakatos PL, Sewitch M, El-Matary W, Melmed G, Nguyen G; QI consensus group; Promoting Access and Care through Centers of Excellence-PACE program). Selection of Quality Indicators in IBD: Integrating Physician and Patient Perspectives. *Inflamm Bowel Dis* 2019; **25**: 403-409 [PMID: [30169582](https://pubmed.ncbi.nlm.nih.gov/30169582/) DOI: [10.1093/ibd/izy259](https://doi.org/10.1093/ibd/izy259)]
- 82 **Fiorino G**, Allocca M, Chaparro M, Coenen S, Fidalgo C, Younge L, Gisbert JP. 'Quality of Care' Standards in Inflammatory Bowel Disease: A Systematic Review. *J Crohns Colitis* 2019; **13**: 127-137 [PMID: [30423033](https://pubmed.ncbi.nlm.nih.gov/30423033/) DOI: [10.1093/ecco-jcc/jjy140](https://doi.org/10.1093/ecco-jcc/jjy140)]
- 83 **Reinglas J**, Restellini S, Gonczi L, Kurti Z, Verdon C, Nene S, Kohen R, Afif W, Bessissow T, Wild G, Seidman E, Bitton A, Lakatos PL. Harmonization of quality of care in an IBD center impacts disease outcomes: Importance of structure, process indicators and rapid access clinic. *Dig Liver Dis* 2019; **51**: 340-345 [PMID: [30591367](https://pubmed.ncbi.nlm.nih.gov/30591367/) DOI: [10.1016/j.dld.2018.11.013](https://doi.org/10.1016/j.dld.2018.11.013)]
- 84 **Gonczi L**, Gecece KB, Vegh Z, Kurti Z, Rutka M, Farkas K, Golovics PA, Lovasz BD, Banai J, Bene L, Gasztonyi B, Kristof T, Lakatos L, Miheller P, Nagy F, Palatka K, Papp M, Patai A, Salamon A, Szamosi T, Szepes Z, Toth GT, Vincze A, Szalay B, Molnar T, Lakatos PL. Long-term Efficacy, Safety, and Immunogenicity of Biosimilar Infliximab After One Year in a Prospective Nationwide Cohort. *Inflamm Bowel Dis* 2017; **23**: 1908-1915 [PMID: [28922253](https://pubmed.ncbi.nlm.nih.gov/28922253/) DOI: [10.1097/MIB.0000000000001237](https://doi.org/10.1097/MIB.0000000000001237)]
- 85 **Gonczi L**, Kurti Z, Verdon C, Reinglas J, Kohen R, Morin I, Chavez K, Bessissow T, Afif W, Wild G, Seidman E, Bitton A, Lakatos PL. Perceived Quality of Care is Associated with Disease Activity, Quality of Life, Work Productivity, and Gender, but not Disease Phenotype: A Prospective Study in a High-volume IBD Centre. *J Crohns Colitis* 2019; **13**: 1138-1147 [PMID: [30793162](https://pubmed.ncbi.nlm.nih.gov/30793162/) DOI: [10.1093/ecco-jcc/jjz035](https://doi.org/10.1093/ecco-jcc/jjz035)]
- 86 **Reinglas J**, Nene S, Gonczi L, Kurti Z, Restellini S, Kohen R, Afif W, Bessissow T, Wild G, Seidman E, Bitton A, Lakatos P. P452 Impact of implementing a rapid access clinic in a high-volume inflammatory bowel disease centre: accessibility, resource utilisation and outcomes. *J Crohns Colitis* 2019; **13** Suppl 1: S337-S337 [DOI: [10.1093/ecco-jcc/jjy222.576](https://doi.org/10.1093/ecco-jcc/jjy222.576)]
- 87 **Ananthakrishnan AN**, Korzenik JR, Hur C. Can mucosal healing be a cost-effective endpoint for biologic therapy in Crohn's disease? A decision analysis. *Inflamm Bowel Dis* 2013; **19**: 37-44 [PMID: [22416019](https://pubmed.ncbi.nlm.nih.gov/22416019/) DOI: [10.1002/ibd.22951](https://doi.org/10.1002/ibd.22951)]
- 88 **Panaccione R**, Colombel JF, Bossuyt P, Baert F, Vanasek T, Danalioglu A, Novacek G, Armuzzi A, Reinisch W, Johnson S, Buessing M, Neimark E, Petersson J, M Robinson A, Thakkar RB, Lee WJ, Skup M, D'Haens G. DOP065 Long-term costeffectiveness of tight control for Crohn's disease with adalimumab-based treatment: economic evaluation beyond 48 wk of CALM trial. *J Crohns Colitis* 2018; **12** Suppl 1: S074-S075 [DOI: [10.1093/ecco-jcc/jjx180.102](https://doi.org/10.1093/ecco-jcc/jjx180.102)]
- 89 **Hirth RA**, Chernew ME, Miller E, Fendrick AM, Weissert WG. Willingness to pay for a quality-adjusted life year: in search of a standard. *Med Decis Making* 2000; **20**: 332-342 [PMID: [10929856](https://pubmed.ncbi.nlm.nih.gov/10929856/) DOI: [10.1177/0272989X0002000310](https://doi.org/10.1177/0272989X0002000310)]
- 90 Changing the course of Crohn's Disease With an Early Use of Adalimumab (CURE). Cited: 7 September 2019 ClinicalTrials.gov Identifier: NCT03306446. Available from: <https://clinicaltrials.gov/ct2/show/record/NCT03306446>
- 91 Enhanced Algorithm for Crohn's Treatment Incorporating Early Combination Therapy (REACT2) Cited: 7 September 2019 ClinicalTrials.gov Identifier: NCT01698307. Available from: <https://clinicaltrials.gov/ct2/show/NCT01698307>
- 92 **Murthy SK**, Begum J, Benchimol EI, Bernstein CN, Kaplan GG, McCurdy JD, Singh H, Targownik L, Taljaard M. Introduction of anti-TNF therapy has not yielded expected declines in hospitalisation and intestinal resection rates in inflammatory bowel diseases: a population-based interrupted time series study. *Gut* 2019 [PMID: [31196874](https://pubmed.ncbi.nlm.nih.gov/31196874/) DOI: [10.1136/gutjnl-2019-318440](https://doi.org/10.1136/gutjnl-2019-318440)]
- 93 **Lasson A**, Öhman L, Stotzer PO, Isaksson S, Überbacher O, Ung KA, Strid H. Pharmacological intervention based on fecal calprotectin levels in patients with ulcerative colitis at high risk of a relapse: A prospective, randomized, controlled study. *United European Gastroenterol J* 2015; **3**: 72-79 [PMID: [25653861](https://pubmed.ncbi.nlm.nih.gov/25653861/) DOI: [10.1177/2050640614560785](https://doi.org/10.1177/2050640614560785)]
- 94 **Solleis E**, Quinard RM, Bouguen G, Goutte M, Goutorbe F, Bouvier D, Pereira B, Bommelaer G, Buisson A. Combined evaluation of biomarkers as predictor of maintained remission in Crohn's disease. *World J Gastroenterol* 2019; **25**: 2354-2364 [PMID: [31148906](https://pubmed.ncbi.nlm.nih.gov/31148906/) DOI: [10.3748/wjg.v25.i19.2354](https://doi.org/10.3748/wjg.v25.i19.2354)]
- 95 **Reinisch W**, Wang Y, Oddens BJ, Link R. C-reactive protein, an indicator for maintained response or remission to infliximab in patients with Crohn's disease: a post-hoc analysis from ACCENT I. *Aliment Pharmacol Ther* 2012; **35**: 568-576 [PMID: [22251435](https://pubmed.ncbi.nlm.nih.gov/22251435/) DOI: [10.1111/j.1365-2036.2011.04987.x](https://doi.org/10.1111/j.1365-2036.2011.04987.x)]
- 96 **Kiss LS**, Szamosi T, Molnar T, Miheller P, Lakatos L, Vincze A, Palatka K, Barta Z, Gasztonyi B, Salamon A, Horvath G, Tóth GT, Farkas K, Banai J, Tulassay Z, Nagy F, Szenes M, Veres G, Lovasz BD, Vegh Z, Golovics PA, Szathmari M, Papp M, Lakatos PL; Hungarian IBD Study Group. Early clinical remission and normalisation of CRP are the strongest predictors of efficacy, mucosal healing and dose escalation during the first year of adalimumab therapy in Crohn's disease. *Aliment Pharmacol Ther* 2011; **34**: 911-922 [PMID: [21883326](https://pubmed.ncbi.nlm.nih.gov/21883326/) DOI: [10.1111/j.1365-2036.2011.04827.x](https://doi.org/10.1111/j.1365-2036.2011.04827.x)]
- 97 **Molander P**, af Björkstén CG, Mustonen H, Haapamäki J, Vauhkonen M, Kolho KL, Färkkilä M, Sipponen T. Fecal calprotectin concentration predicts outcome in inflammatory bowel disease after induction therapy with TNF $\alpha$  blocking agents. *Inflamm Bowel Dis* 2012; **18**: 2011-2017 [PMID: [22223566](https://pubmed.ncbi.nlm.nih.gov/22223566/) DOI: [10.1002/ibd.22863](https://doi.org/10.1002/ibd.22863)]
- 98 **Sipponen T**, Björkstén CG, Färkkilä M, Nuutinen H, Savilahti E, Kolho KL. Faecal calprotectin and lactoferrin are reliable surrogate markers of endoscopic response during Crohn's disease treatment. *Scand J*



- Gastroenterol* 2010; **45**: 325-331 [PMID: 20034360 DOI: 10.3109/00365520903483650]
- 99 **Consigny Y**, Modigliani R, Colombel JF, Dupas JL, Lémann M, Mary JY; Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives (GETAID). A simple biological score for predicting low risk of short-term relapse in Crohn's disease. *Inflamm Bowel Dis* 2006; **12**: 551-557 [PMID: 16804391 DOI: 10.1097/01.ibd.0000225334.60990.5b]
- 100 **De Vos M**, Dewit O, D'Haens G, Baert F, Fontaine F, Vermeire S, Franchimont D, Moreels T, Staessen D, Terriere L, Vander Cruyssen B, Louis E, behalf of BIRD. Fast and sharp decrease in calprotectin predicts remission by infliximab in anti-TNF naïve patients with ulcerative colitis. *J Crohns Colitis* 2012; **6**: 557-562 [PMID: 22398050 DOI: 10.1016/j.crohns.2011.11.002]
- 101 **Jauregui-Amezaga A**, López-Cerón M, Aceituno M, Jimeno M, Rodríguez de Miguel C, Pinó-Donnay S, Zabalza M, Sans M, Ricart E, Ordás I, González-Suárez B, Cuatrecasas M, Llach J, Panés J, Pellise M. Accuracy of advanced endoscopy and fecal calprotectin for prediction of relapse in ulcerative colitis: a prospective study. *Inflamm Bowel Dis* 2014; **20**: 1187-1193 [PMID: 24874457 DOI: 10.1097/MIB.000000000000069]





Published By Baishideng Publishing Group Inc  
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA  
Telephone: +1-925-2238242  
E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
Help Desk: <http://www.f6publishing.com/helpdesk>  
<http://www.wjgnet.com>

