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Review

Biomarkers That Predict Crohn's Disease Outcomes

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Abstract

Crohn's disease (CD), a chronic inflammatory condition of the digestive tract, poses significant challenges in terms of disease prognosis and treatment selection. Biomarkers have the potential to predict CD outcomes and guide clinical decision-making. This review aims to summarize the current literature on promising biomarkers associated with CD outcomes and their potential clinical implications. The identification of reliable biomarkers for CD outcomes is of paramount importance in tailoring treatment strategies, monitoring disease activity, and predicting the risk of complications. Clinical prognostic factors traditionally used to assess disease severity, and the likelihood of complications have limitations in accuracy and predictive value. Thus, there is a need for more precise biomarkers, particularly in newly diagnosed and treatment-naive patients. Pharmacogenomic markers, such as TPMT and NUDT15 polymorphisms, have been utilized to identify patients at risk of adverse events with thiopurine therapy. Several biomarkers, including HLA haplotypes, oncostatin M expression, and transcriptomic profiles, have shown associations with response to anti-TNF therapy. Confocal laser endomicroscopy and single-cell analyses hold promise in predicting treatment response to specific therapies. The identification of biomarkers associated with post-operative recurrence in CD is crucial, as it could lead to changes in management algorithms. Several promising microbiome signatures and proteomic profiles have been identified. In conclusion, biomarkers have the potential to revolutionize the management of CD by providing valuable prognostic information and guiding treatment decisions. However, further research and validation are necessary to establish their clinical utility and integration into routine practice.

Key words: biomarkers; Crohn's disease; prediction; precision medicine.

Introduction

Crohn's disease (CD), one of the main forms of inflammatory bowel disease (IBD), is a chronic condition characterized by inflammation and damage to any part of the digestive tract, which can result in a range of symptoms, including abdominal pain, diarrhoea, fatigue, weight loss, and extraintestinal manifestations.[1] These symptoms can have a significant impact on the quality of life of affected individuals, leading to decreased productivity, social isolation, and psychological distress.[2] Moreover, CD is associated with an increased risk of complications such as strictures, fistulas, and abscesses, which can lead to further symptoms and may require surgical intervention in a significant number of patients.[3] Conversely, many patients with CD have an indolent disease course.

Biomarkers are essential tools in medicine, providing information on biological functions and processes in the human body. Commonly used body fluids or tissues for biomarker analysis include blood (serum or plasma), intestinal tissue, urine, stool, saliva, and breath.[4] Biomarkers can be genetic (SNPs), genomic (RNA), microbial, proteins, or metabolites. An ideal biomarker should be accurate, simple, easy to measure, minimally invasive, cheap, rapid, and reproducible.

Given the progressive nature of CD, there has been an increasing interest in biomarker discovery and translation into clinical practice in recent years.[5] The identification of reliable biomarkers for CD outcomes has important clinical implications, as they can help physicians to tailor treatment strategies to individual patients, monitor disease activity, and predict the risk of complications.

While there has been a sheer increase in available treatment options for CD in recent years, predicting disease outcomes and appropriate drug positioning can still be challenging. In this article, we will review the available literature on promising biomarkers that predict CD outcomes (Table 1). We will examine the evidence for the use of biomarkers in predicting disease course, response to treatment, and post-operative recurrence (POR).

Biomarkers of disease prognosis and risk of complications

Clinicians have long relied on their own judgment, based on clinical prognostic factors, to assess the risk of aggressive disease and potential complications in patients with CD. Several factors have been associated with worse disease outcomes in these patients, including smoking, perianal disease, upper gastrointestinal involvement, ileum-predominant disease, endoscopic severity in index assessment, and requirement for steroids at diagnosis.[6–8] However, despite their widespread use, these clinical prognostic factors have limitations in accuracy and predictive value.[9] Therefore, reliable biomarkers are needed to predict patient outcomes, especially in newly diagnosed, treatment-naive patients.

Table 1. Promising biomarkers to predict Crohn's disease outcomes.

Biomarkers of disease prognosis
IBD-Character Consortium protein panel (ITGAV, EpCAM, IL-18, SLAMF7, and IL-8)
Endoscopic Healing Index (EHI) protein panel
RISK Cohort model (combined clinical, transcriptional, and antimicrobial serology data)
CD4+ T-cell-specific miRNA profiles
PredictSURE IBD
Radiomics
Biomarkers of treatment selection
Oncostatin-M
GIMATS module
TREM-1
HLA-DQA1*05 haplotype
Confocal laser endomicroscopy
Biomarkers of disease recurrence after surgery
Microbial signatures (e.g., *Faecalibacterium prausnitzii*)
CXCL9 and CXCL11

Proteomics for disease prognostication

C-reactive protein (CRP) is a well-established marker for estimating inflammation and disease activity in CD.[10] A Norwegian population-based study from the IBSEN cohort showed that persistently elevated CRP concentrations one year after diagnosis could predict progression to abdominal surgery in patients with CD.[11] Also, for individuals achieving clinical remission who exhibit sustained elevation CRP levels, a negative correlation exists with long-term outcomes, including frequency of hospitalizations and intestinal resections.[12,13] However, it is crucial to acknowledge that CRP functions as a measure of existing inflammation, and the correlations identified stem from the notion that untreated and ongoing inflammation results in heightened complications in contrast to when the disease is in biochemical remission.

Faecal calprotectin (FCP) is another commonly used marker to assess disease activity in IBD, given its higher sensitivity compared to CRP.[14,15] It is a validated marker for disease activity and has been reported to be useful in predicting relapse.[16–18] In a prospective Spanish study involving patients with CD in remission on therapy, the measurement of FCP every three months revealed that if FCP remains below 130 mg/g at any time, it allows for the accurate prediction of achieving remission over the subsequent four months with a negative predictive value of 100 percent.[19] The CALM trial demonstrated that normalizing FCP levels, in combination with other parameters, are associated with mucosal healing in CD.[20] Moreover, a retrospective cohort study found that higher levels of FCP at index visit were associated with subsequent progression in Montreal behaviour, hospitalization, and intestinal resection.[21]

A prospective study from the IBD-Character Consortium assessed the utility of serum proteomics in defining prognosis in an inception cohort of IBD patients. They identified five proteins (ITGAV, EpCAM, IL-18, SLAMF7, and IL-8) that could identify high-risk IBD patients, defined as the need for biologic therapy or surgery.[22] However, this panel performed better in UC than in CD, and further independent prospective validation of these findings is warranted.[23,24]

The endoscopic healing index (EHI), a blood panel of 13 proteins, has undergone validation for its ability to forecast endoscopic remission in patients with CD.[25] This highlights the prospective practicality of employing more extensive protein panels in clinical settings, although it remains to be determined the utility of the EHI in predicting disease progression.

Several studies have investigated the association between disease course, aggressive phenotypes (i.e., stricturing and fistulizing behaviour), and various serologic markers reflecting immune responses to the gut microbiome and autoantigens.[26,27] These markers include perinuclear antineutrophil antibody (pANCA), anti-*Saccharomyces cerevisiae* antibody (ASCA), antibody to *Escherichia coli* outermembrane porin C (OmpC), and antibody to flagellin (CBir1).[28] In the RISK cohort, a large prospective study that recruited newly diagnosed, treatment-naive paediatric patients with IBD, and it was observed that patients that were positive for two or more antimicrobial antigens had a faster progression to complicated disease.[29] Another autoantibody, granulocyte-macrophage colony-stimulating factor (GM-CSF), has also been associated with disease course.[30] High expression of GM-CSF autoantibodies has been linked to stricturing and penetrating behaviour in CD.[26,31,32] The rise of antimicrobial antibodies before disease onset has been demonstrated in the PREDICTS study, which examined pre-diagnosis serum samples from US Army personnel. However, because disease duration is closely linked to complications, it remains uncertain to what extent these antibodies provide insights into the disease course or rather reflect disease duration.

Genetics for disease prognostication

Over the past decades, significant advances have been made to understand the genetic basis of IBD, with over 240 susceptibility loci identified to date.[33] Based on that success, efforts have been made to link identified susceptibility polymorphisms with disease outcomes, allowing their use as prognostic biomarkers. In that regard, genetic variants in NOD2, the most prominent genetic risk factor for CD, were associated with a shorter time to surgery and increased risk of POR, and they have been included in risk models of complications in CD.[34–37] However, it has been shown that NOD2 variants are primarily linked to ileal CD, and the previously observed association between NOD2 and a higher risk of complications was actually influenced by disease location.[38,39] Once this confounding effect was considered, no association was found between NOD2 and disease course.[40]

A genome-wide association study (GWAS) of two CD cohorts found four genome-wide significant loci (FOXO3, XACT, GFBP1, major histocompatibility complex from HLA-B to HLA-DR genes) to be associated with poor disease prognosis.[41,42] Interestingly, none of these loci showed an association with disease susceptibility, which suggest that genetic contribution to prognosis differs from disease onset.[41] Notwithstanding, given the small effect sizes of these variants, it is unlikely that they become clinically useful on their own. Moreover, another GWAS study from three large CD cohorts failed to identify any SNPs that reached genome-wide significance associated with disease progression.[43]

Transcriptomics for disease prognostication

In the RISK study, transcriptomic analysis of ileal biopsies found an extracellular matrix tissue signature to be associated with the future onset of stricturing behaviour in CD.[29]

This data was used to create a model that combined clinical, transcriptional, and antimicrobial serology data, which was found to be superior in predicting stricturing complications within thirty-six months to a model that only contained clinical phenotyping data. This prediction model requires further validation in independent cohorts.[29]

A recent study identified novel CD4 T-cell-specific miRNA profiles that differentiated IBD from controls.[44] Moreover, the top differentially expressed miRNA, miR-1307-3p, was able to predict disease progression in IBD, defined as treatment escalation, particularly in CD (HR 2.81; $P = 6.50 \times 10–4$). Although these markers have translational potential given that they can be measured with RT-quantitative polymerase chain reaction (qPCR) in whole blood, further validation is also required.[44]

One of the most promising biomarkers for disease progression to date is a whole blood 17-gene expression qPCR-based classifier designed to identify subgroups of patients with IBD at high risk for future aggressive disease (PredictSURE IBD). Previously, a gene expression signature in peripheral blood CD8 T cells from patients with active treatment naïve IBD and other IMIDs were found to predict two phenotypically distinct subgroups with different prognoses based on the frequency of flares and requirement of treatment escalation. Interestingly, this gene signature was found to be related to T-cell exhaustion, giving mechanistic insight into disease aggressiveness. To become useful clinically, the whole blood qPCR assay was developed to classify the two subgroups of patients with IBD previously identified by the CD8 T-cell signature, as this assay does not require cell separation. The assay was independently validated using prospectively collected samples from multiple centres in the United Kingdom. Importantly, this assay is currently being tested in the biomarker-stratified PROFILE trial to define its utility in enabling personalized medicine and improving clinical outcomes.[45,46]

Radiomics for disease prognostication

Advances in medical imaging have enabled the exploration of imaging-based biomarkers for prognostication.[47] Radiographic findings at the time of diagnosis can be valuable in determining prognosis by identifying bowel damage. For instance, Fiorino et al. found that bowel damage, as assessed by cross-sectional imaging using the Lémann index at diagnosis, was independently associated with future risk of intestinal resection and CD-related hospitalization.[48] In addition, ultrasound-based indices have been developed to assess bowel damage and disease activity, demonstrating their association with poorer disease outcomes in CD.[49–51] However, it is important to note that current imaging markers for established bowel damage or disease activity do not directly serve as true biomarkers for disease prognosis but rather indicate longer disease duration or uncontrolled inflammation. The emerging field of radiomics, which involves analyzing the distribution and texture of signals in computed tomography and magnetic resonance images through mathematical connections among adjacent pixel intensities, holds promising potential for novel research avenues in CD.[47,52]

Biomarkers of treatment selection

In recent years, the management of CD has witnessed remarkable advancements with the advent of targeted biologics and small-molecule drugs. However, despite these therapeutic options, the heterogeneous nature of CD poses a significant challenge in achieving optimal treatment outcomes. The variable response to interventions and the diverse safety profiles observed among patients underscores the need for reliable biomarkers to guide treatment selection and positioning. Biomarkers offer the potential to identify subsets of patients who are more likely to respond favourably to specific therapies, enabling clinicians to make informed decisions and enhance personalized medicine.

Genomics for treatment selection

Pharmacogenomics has been used to identify subjects at a higher risk of adverse events. The detection of thiopurine methyltransferase (TPMT) polymorphisms has been used to detect patients starting thiopurines at risk of severe haematopoietic toxicity. TPMT measurement before initiating thiopurine therapy is currently recommended, as specific alleles warrant dose adjustment or avoidance of these medications.[53] Likewise, mutations in nudix hydrolase 15 (NUDT15) have been associated with thiopurine-induced leucopoenia in Asian and European populations.[54–57] Indeed, it is estimated that susceptibility alleles in TPMT and NUDT15 account for approximately half of the cases of thiopurine-induced myelotoxicity.[56]. Polymorphisms in the human leukocyte antigen (HLA) have been associated with pancreatitis induced by thiopurine therapy and 5-ASA-induced nephrotoxicity,[58,59] although detection of these risk alleles has not been widely incorporated in clinical practice.

Several efforts have been made to discover biomarkers associated with response to biologics, especially anti-TNF therapy. The prospective PANTS study identified that carriers of the HLA-DQA1*05 haplotype had an approximately two-fold higher risk of anti-drug antibodies against anti-TNF agents.[60,61] Interestingly, this risk variant was not associated with immunogenicity in two cohorts undergoing proactive drug monitoring and dose optimization,[62,63] which might indicate that HLA-DQA1*05 carriers might still use anti-TNF agents in combination therapy or with early dose optimization.

Transcriptomics for treatment selection

Expression of higher levels of oncostatin M (OSM), a member of the interleukin (IL)-6 family, has been linked to anti-TNF refractoriness.[64,65] This finding has been validated across multiple cohorts and could be associated with inflammation in a TNF-independent manner.

Transcriptomic expression in the gut mucosal biopsies and peripheral blood of TREM-1 (Triggering Receptor Expressed in Myeloid Cells-1) has been associated with anti-TNF primary non-response.[66–68] However, there have been discordant results regarding the direction of the association, indicating that further validation is needed before being applicable for translation into clinical practice.

Disease heterogeneity has been implicated in differential response rates,[69] and single-cell analyses might help disentangle the underlying cellular heterogeneity involved in this process. Single-cell sequencing of ileal biopsies allowed the identification of a cellular module, denominated GIMATS, in a subset of patients with ileal CD. Its presence at diagnosis was associated with failure to achieve steroid-free remission with anti-TNF therapy.[70] The GIMAT refers to a unique cellular module with IgG plasma cells, inflammatory mononuclear phagocytes, activated T cells, and stromal cells and is driven

by a unique mononuclear phagocyte-dependent cytokine network.

To date, there are fewer studies on biomarkers that can predict a positive response to vedolizumab or ustekinumab compared to anti-TNF therapy. A small study that analyzed colonic samples of 31 patients with IBD found that the differential expression of four genes (RGS13, DCHS2, MAATS1, and PIWIL1) could predict endoscopic remission with vedolizumab. Interestingly, the same genes were not associated with response to anti-TNF therapy.[71] Although these findings underwent a preliminary validation, independent validation in external cohorts is warranted. Conversely, a small study from Japan showed that differentially higher mucosal expression of IL-23A is associated with response to ustekinumab in patients with IBD.[72]

Confocal laser endomicroscopy for treatment selection

Confocal laser endomicroscopy can be used to predict response to anti-TNF and vedolizumab therapies, which involves applying fluorescent antibodies that target either TNF-α or α4β7 integrin directly to the inflamed mucosa.[73,74] This allows for detecting and measuring membrane-bound TNF-α or α4β7-positive mucosal cells, which can be used to predict response to the respective therapies. These findings require further independent validation but provide a biologically plausible marker for treatment response.[75]

Biomarkers of disease recurrence after surgery

The identification of biomarkers associated with POR in CD is crucial, as it could lead to changes in management algorithms. For instance, identifying factors that predict a very low risk of POR could make surgery more attractive to patients, even in the early stages of the disease before complications arise, as this could enable patients to remain medication-free in the long term. Moreover, identifying biomarkers that can predict POR can aid clinicians in monitoring patients more closely and intervening early, which could prevent further disease progression and improve patient outcomes. Third, by understanding the molecular mechanisms underlying CD POR, biomarkers can guide the development of new drugs that target these mechanisms, potentially decreasing the need for further surgeries.

Microbial signatures of POR

Since the classical studies involving fecal diversion,[76,77] the microbiome has been implicated in CD POR pathogenesis, which is also supported by the effect of antibiotics as prophylactic agents.[78,79] Consequently, microbial signatures associated with POR that could potentially be used as biomarkers have been sought. A reduced abundance of *Faecalibacterium prausnitzii* in the ileal mucosa-associated microbiome has been previously associated with a higher rate of POR in patients with CD undergoing ileocolonic resection.[80] In the large, prospective, multi-centre REMIND cohort, ileal mucosa-associated microbiota at surgery was assessed as a predictor of endoscopic POR at first post-operative colonoscopy. In the random forest model, the three most informative taxa were *Streptococcus*, *Ruminococcus gnavus*, and Gammaproteobacteria.[81] In another prospective, multi-centre cohort study from NIDDK Genetics Consortium, the ileal mucosa-associated microbiome at first post-operative colonoscopy of patients without endoscopic POR was associated with later progression to endoscopic POR (Rutgeerts score ≥i2). A greater abundance of *Clostrium sensu stricto 1* and lower levels of *Faecalibacterium* were associated with endoscopic POR, independent of age, sex, and anti-TNF use after surgery.[82]

Other signatures of POR

Certain other features in the surgical specimen after ileocolonic resection might help predict future CD POR. A study analyzed the T-cell repertoire in a subset of the REMIND cohort. Patients with an increased proportion of T-cell clonal expansions at the time of surgery were associated with smoking status and an increased risk of endoscopic POR.[83] Also, abnormal Paneth cell phenotypes in the ileal resection specimen were found to be associated with a shorter time to CD POR.[84]

Proteomic analyses are another source of potential biomarkers that predict CD POR. A study on patients who underwent ileocecal resection found that an FCP concentration exceeding 100 μg/g was associated with endoscopic recurrence, with a 91 percent negative predictive value. This suggests that colonoscopy may not be necessary if FCP levels are normal in the post-operative setting.[85]

A recent study discovered protein biomarkers that were linked to endoscopic POR. CXCL9 showed the strongest signal. CXCL9 and CXCL11 were both associated with Rutgeerts score progression in patients who were on anti-TNF agents, which suggests a predominant role of the CXCR3 axis in the context of anti-TNF therapy.[86] The study also showed that incorporating the newly identified candidate biomarker proteins improved the ability to identify endoscopic POR compared to CRP alone. By interrogating single-cell data, the study also found that the innate immune system plays a prominent role in CD POR.[86]

Conclusions and future directions

Finding useful biomarkers that accomplish a successful translation to the clinic for the management of CD has proven to be a daunting challenge.[40] Many studies have relied on retrospective associations between the supposed biomarker and the outcome of interest. Ideally, samples should be taken before the outcome occurs, which usually requires costly and time-consuming prospective cohorts. A potential alternative for biomarker discovery involves data repurposing with the optimization of previously collected biospecimens. Promising methods involve spatial multi-omics, which allows for the analysis of archived longitudinal formalin-fixed paraffin-embedded biopsy samples taken as routine clinical care at different timepoints, such as disease diagnosis and before initiating therapies.[87–89] These methods preserve the spatial relationships within tissues and provide a better capture of all cell types, ensuring that all cells are present in ratios that reflect *in vivo* biology. Additionally, gene signatures derived from bulk or single-cell RNA sequencing for treatment response and non-response can be applied to existing tissue samples. Another source of biomarker discovery involves the collaboration between academia and industry, using publicly available datasets and clinical trial samples. There have been successful examples of this type of collaboration, such as the discovery of TREM1 and OSM.

A critical step for any potential biomarker is the need for validation in independent cohorts, a pitfall for most available candidate biomarkers.[9,40] Moreover, validation across

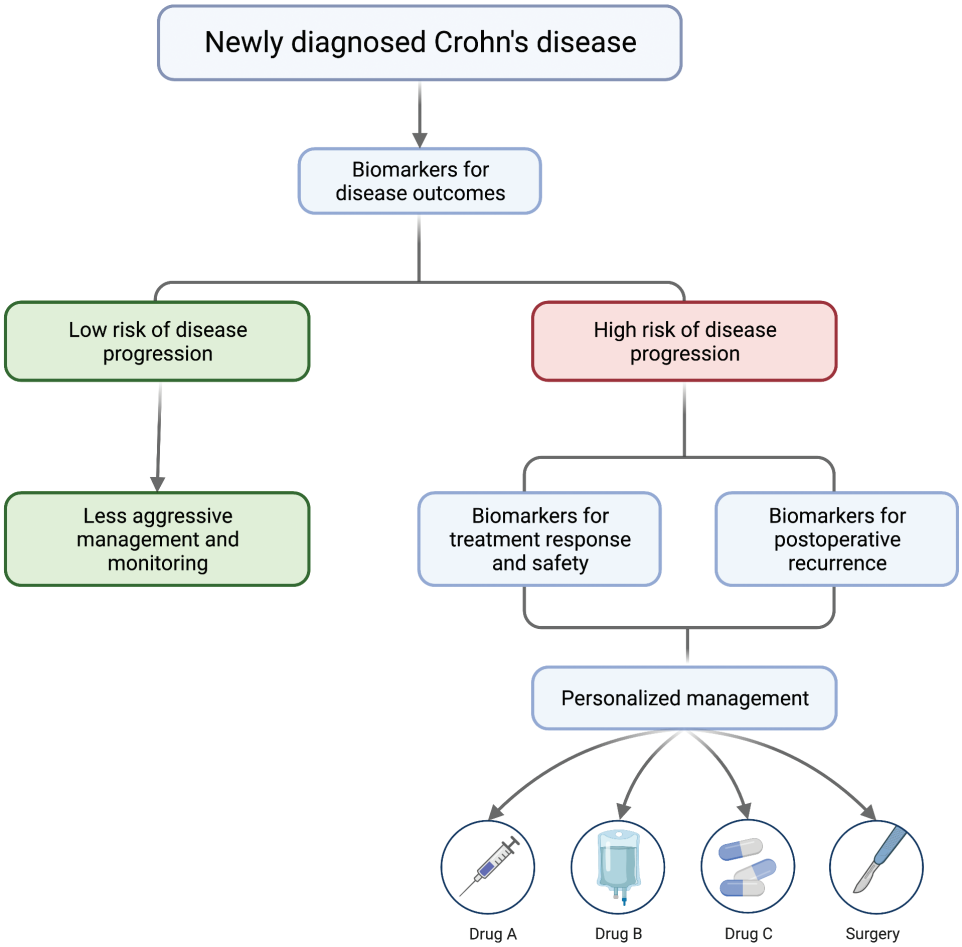

Figure 1. Potential positioning of biomarkers in Crohn's disease management. Created with BioRender.com.

different populations should be considered, as it is reasonable to assume that distinctive biological pathways determine disease outcomes and response to therapies caused by differences in genetics and environmental exposures, leading to differential performance of biomarkers across populations.

Pathophysiological heterogeneity is the major cause of the difficult-to-predict disease CD course and the limited success of novel drugs. Several new compounds with unique mechanisms of action have been approved for use in treating IBD or are in the final stages of development. As more therapeutic options become available, the demand for biomarkers that can pinpoint the most effective treatment for each patient will increase. In recent years, this has been identified by the pharmaceutical industry, and hence, biomarker discovery has been incorporated as a goal in modern clinical trials.

Reliable biomarkers that predict disease prognosis, treatment response, and POR could transform the management of CD (Fig. 1). In the context of a growing prevalence of IBD worldwide, resource allocation is paramount.[90] First, these biomarkers could discriminate which patients will have an indolent course versus those with a higher risk of disease complications, indicating who will benefit the most from treatment interventions and intense disease monitoring. Second, by having markers of POR recurrence after intestinal resection, some patients would benefit from surgical management upfront and maintained medication-free if found to be low risk. Third, treatment response and safety biomarkers are eagerly awaited, especially with an expanding therapeutic armamentarium. Indeed, further work in biomarker research is needed to transform personalized medicine in IBD from hype to reality.

Conflict of interest statement

Pablo A. Olivera declares no conflicts of interest. Mark S. Silverberg has received grants from AbbVie, Prometheus, Janssen, Takeda, and Pfizer; consulting fees from AbbVie, Amgen, Gilead, Janssen, Merck, Pfizer, and Takeda; honoraria from AbbVie, Amgen, Gilead, Janssen, Merck, Society for Continuing Professional Health Education (Canada), Takeda, and Pfizer; advisory board participation of AbbVie, Janssen, Pfizer, and Takeda.

Data Availability

No datasets were generated or analyzed during the current study.

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