Title:

Challenges in IBD Research 2024: Precision Medicine

Authors:

Sana Syed, MD[# †]; Brigid Boland, MD[‡]; Lauren Bourke, PhD[§]; Lea A. Chen, MD[¶]; Laurie Churchill, PhD[††]; Angela Dobes, MPH[‡‡]; Adam Greene, PhD[†]; Caren Heller, MD[‡‡]; Christina Jayson, PhD[§§]; Benjamin Kostiuk, PhD[‡‡]; Alan Moss, MD[‡‡*]; Fedaa Najdawi, MD[§§]; Lori Plung#, John David Rioux, PhD[¶¶]; Michael Rosen, MD[||]; Joana Torres, MD[‡‡‡]; Hannah Wajdner, PhD[§§§]; Fatima Zulqarain, MD[†]; Jack Satsangi, MD[¶¶¶]

Affiliations:

[†] Department of Pediatrics, University of Virginia, Charlottesville, VA, USA

[‡] Department of Medicine, University of California, San Diego, La Jolla, CA, USA.

[§] AstraZeneca UK

[¶]New York University School of Medicine – Division of Gastroenterology, Department of Medicine

[††]Helmsley Charitable Trust

[‡‡] Crohn's & Colitis Foundation, New York, NY, USA

[§§]PathAI Diagnostics

[¶¶]Université de Montréal and the Montreal Heart Institute, Research Center, Montréal, Québec H1T 1C8, Canada.,

[||]Division of Pediatric Gastroenterology, Department of Pediatrics, Stanford University School of Medicine, Stanford, CA, United States

[‡‡‡]Division of Gastroenterology, Hospital Beatriz Ângelo, Loures 2674-514, Portugal

[§§§] GlaxoSmithKline

¶¶¶¶Translational Gastroenterology Unit, Nuffield Department of Medicine, Experimental Medicine Division, University of Oxford, John Radcliffe Hospital, Oxford, UK

Author Notes: # Patient representative for Crohn's & Colitis Foundation, New York, NY, USA

*Address correspondence to: Alan C. Moss, MD, 733 3rd Ave Suite 510, New York, NY 10017, USA (amoss@crohnscolitisfoundation.org)

Summary

Research gap #1:

There is a lack of validated biomarkers to understand the heterogeneity of disease development:

Priority actions for biomarkers:

- *pre-clinical disease.*
- *deep remission.*
- *disease phenotype and complications.*
- *tissue / function restoration .*
- *EIM and comorbidities.*

Research gap #2:

There is a lack of validated biomarkers that aid in therapeutic decision making.

Priority biomarkers :

- *phenotype / genotype based optimal treatments*
- *prediction of loss of response to a treatment*
- *prediction of disease stability after treatment de-escalation*

Research gap #3:

There is an unrealized value of biosamples and biosample-derived data due to the lack of generation and integration of multimodal data.

Priority research actions:

- *optimize archival data and samples*
- *novel technology for biomarkers discovery.*
- *integration of multimodal data in biomarker discovery.*

Research gap #4:

There is a lack of standardized and pragmatic processes for navigating regulation, thereby slowing down biomarkers from reaching the clinic.

Priority actions:

- *utilization of validation cohorts.*
- *standardized biomarker discovery during clinical development.*
- *practical, regulatory, and economic considerations.*
- *standardized protocols for sample and data collection*

* An optimal treatment is any diet, lifestyle, medication, or surgery that provides safe therapeutic efficacy in a manner that aligns with the patient's goals.

INTRODUCTION

Precision medicine is one of the five focus areas of Challenges in IBD Research 2024, which also includes environmental triggers, novel technologies, pragmatic clinical research, and preclinical human IBD mechanisms. Generating optimal patient-specific treatment regimens to restore health, activity and quality of life requires the synergized efforts of all five Challenges in IBD foci.

IBD is a highly complex chronic disease in which patients often present with varying clinical symptoms and individuals can respond differently to the same therapeutic interventions. Regular, life-long monitoring is required to optimize clinical outcomes and prevent complications of disease[1]. While the mechanisms of IBD have long been studied, there remains a significant gap in understanding the mechanisms driving disease progression and response to therapies in the individual patient. Thus, the overall focus of the Precision Medicine Workgroup is the identification of high priority knowledge gaps and research methodologies that are hindering the discovery of disease biomarkers and development of tools capable of stratifying patients into risk subgroups with the goal of informing the right intervention for the right patient at the right time. Precision medicine involves utilizing granular, patient-specific information at the level of the disease pathway through tools such as genetics, proteomics, metabolomics, and imaging. Advancing precision medicine by associating biomarkers to clinical traits and defining complex IBD endotypes (subtyping patients through molecular drivers of disease) will result in more targeted clinical and translational research, new avenues for drug development, and ultimately, improved clinical paradigms that provide individualized patient healthcare.

In 2019, the *Challenges in IBD Research Precision Medicine* identified four research gaps requiring attention: 1) Better stratification of patients at diagnosis to predict disease course and response to therapies, 2) Better monitoring for response to treatment, 3) Identification of technological improvements needed to advance precision medicine, and 4) Understanding the regulatory and economic aspects in bringing new precision medicine approaches to the clinic.

Reflection on the Advances since 2019

Significant progress has been made in advancing precision medicine over the past several years, albeit without current effect on daily clinical practice. Biomarker discovery in ulcerative colitis (UC) has been well categorized in a recent review article[2]. To this end, recent studies have successfully identified potential novel biomarkers that correlate with future onset and/or progression of disease complications and treatment response[3–29]. However, disease progression lacks a robust definition, making it difficult to generalize findings from these studies. Additional studies have investigated biomarkers that stratify patients with established IBD based on disease mechanisms and characteristics[11,22,30–47,47–52]. Significant steps have been taken to understand predictive biomarkers and mechanisms of response to various treatments, including anti-Tumor Necrosis Factor (TNF) agents (e.g., adalimumab, infliximab) and other biologics and small molecules (such as ustekinumab, tofacitinib, and vedolizumab)[48,53–87,87–107]. However, further progress is needed to fully realize precision medicine in routine care , especially in validating these candidate biomarkers.

The development and widespread access of technological advances since 2019 have also spurred remarkable innovations in IBD research[13,18,26,29,30,32,33,103–106,108–125]. Among these technologies, the increased access to cutting-edge single-cell RNA sequencing techniques and machine learning tools have revolutionized our understanding of disease pathogenesis and improved clinical classification of disease subtypes. Traditional RNA sequencing is done in bulk, pooling hundreds of thousands of cells together to understand the broad transcriptomic composition of a tissue. In contrast, single-cell RNA sequencing analyzes the transcriptome of thousands of individual cells[126], facilitating much more granular studies probing the cellular heterogeneity across IBD. The recent commercial availability of single-cell RNA sequencing platforms has been a significant boon to IBD research, allowing investigators to probe for cellular-level genetic markers indicating disease course or response to treatment[106,127–129]. Not only will the continued refinement and application of single-cell technologies improve our understanding of the cellular mechanisms of IBD, but it will also allow researchers to decode the transcriptomic heterogeneity found in large IBD datasets, characterize novel cell populations involved in IBD pathogenesis, discover novel targets for therapeutic intervention, and inform more personalized care by identifying genetic features relevant to an individual patient's disease course.

Machine learning has been another area of exponential growth in IBD research over the last five years. Machine learning attempts to mirror human problem solving by optimizing algorithms that reveal patterns within datasets. Over

the course of thousands of computational iterations, these algorithms can eventually "learn" the unique, complex genetic, visual, and/or biochemical features that indicate a given classification, including specific IBD subtypes. These techniques are particularly well-suited to identify patterns and extract features from images that are pertinent for disease classification[130]. Since 2019, machine learning techniques have supported new scientific discoveries and novel diagnostic tools that may soon be applied in a clinical setting[13,30,32,33,115–121,123–125,131]. As the quality of machine learning is heavily dependent upon the robustness of data that the models are trained on, it is critical that future machine learning tools are trained on large, unbiased datasets that accurately reflect the heterogeneity of patient characteristics. However, clinical knowledge must be incorporated into the review of any machine learning recommendations as machine learning can inadvertently introduce bias resulting in misleading conclusions. As with single-cell sequencing, future studies utilizing machine learning will require significant synergy with other Challenges in IBD foci, necessitating novel technological advancements in the approach and analyses as well as the establishment of pragmatic clinical research cohorts. Together, these cross-cutting studies will help deliver impactful precision medicine on a patient-specific level.

Limitations in the field

Despite the significant headway made in addressing the 2019 Challenges in IBD Research goals, several key limitations remain. First, few biomarker studies have focused on understanding molecular signatures at or preceding disease onset. This is largely due to the difficulty in identifying and recruiting cohorts of currently healthy subjects who will eventually be diagnosed with IBD. The second limitation has been the limited application of cross-cutting technologies to large, multi-omic datasets. Previous studies primarily focused on collecting and interpreting one specific data modality. Furthermore, contemporary biomarker studies are not often paired with broader patient clinical metadata, meaning the presence of a biomarker may have different functional relevance when contextualized with different clinical characteristics (e.g., disease activity). Thus, future studies must seek to establish large, multi-center studies to collect and probe diverse sets of multi-omic data across different patient states, both before and after diagnosis. An example of an initiative generating longitudinal multi-omic datasets is the Crohn's & Colitis Foundation IBD Plexus program.

Finally, the regulatory and economic barriers that impede the delivery of validated biomarkers to the clinic remain a key gap facing precision medicine in IBD. At-home, direct-to-consumer tests have been extremely valuable for improving the early diagnosis and management of various diseases, such as colorectal cancer[132]. However, only fecal calprotectin and c-reactive protein (CRP) have been approved by the FDA as biomarkers of IBD as of 2023[133,134]. A formalized validation process for molecular and imaging biomarkers must be developed to ensure the biomarker candidates are given the greatest chance of making an impact on our IBD patients.

There remains an urgent need for additional tests to predict IBD risk, to distinguish between IBD subtypes and to predict disease course and response to therapies. Bringing these diagnostics into the realm of public-private partnerships would better help patients and aid in defining molecular endotypes in IBD in an open and transparent way. Test accuracy and clinically feasible workflows will furthermore be especially important to the uptake of these tests and could significantly improve capabilities for pre-clinical screening of IBD, earlier intervention, and patient-specific care. As each future test platform will require similar validation and regulatory approval, developing a consistent set of guidelines for integrating precision medicine practices into biomarker assays would be extremely beneficial towards streamlining the production and authorization of translational biomarker assays and expediting the delivery of improved, personalized clinical tests directly to consumers.

Outstanding gaps

After reflecting upon where the field has advanced or is still in need of advancement from the 2019 Challenges in IBD Research Precision Medicine goals, we have identified four gaps, that when addressed will drive the next five years of IBD research in precision medicine:

1. There is a lack of validated biomarkers to *understand the heterogeneity of early disease development*.
2. There is a lack of validated biomarkers that *aid in clinical decision making*.
3. There is a recognized but unrealized value of biosamples and of biosample-derived data due to the lack of generation and integration of multimodal data.

4. There is a lack of standardized and pragmatic processes for navigating regulation, thereby slowing down biomarkers from reaching the clinic.

To enable precision interception of disease, we must both understand how pre-symptomatic molecular alterations can predict a variety of disease attributes and identify thoroughly validated biomarkers that map the entire disease journey. As such, there is a great need to bring newly discovered and yet-to-be discovered biomarkers into the clinic where they can directly impact patient lives. As biomarkers are unlikely to come in the form of a single analyte, we must harmonize all available data types and sources to find these complex sets of biomarkers. Finally, it is critical to ensure biomarkers are scientifically validated, economically feasible, and based on a patient centric understanding of the disease and disease progression. Together, innovative new research into these four gap areas will deliver meaningful improvements to IBD care by delivering individualized precision medicine that significantly improves health outcomes for all.

Gap #1 There is a lack of validated biomarkers to understand the heterogeneity of early disease development

Crohn's disease (CD) and UC are complex diseases. Patients often alternate between acute periods of inflammation and life debilitating symptoms and periods of remission, a state where there is no inflammation and symptoms are either completely absent or reduced [135,136]. Flares in disease activity can occur, even in the presence of appropriate medical therapy[137], and poorly controlled disease activity can result in, irreversible bowel damage and adverse outcomes, such as surgery, loss of response to medication, and poor bowel function [138,139]. Furthermore, the extent of intestinal disease often extends over time and complications of disease can develop, such as fibrosis or fistulas, making the disease even more difficult to treat[140]. Additionally, IBD can relate to other organs outside of the bowels in the form of extraintestinal manifestations or correlated diagnoses such as primary sclerosing cholangitis or colorectal cancer[141–143]. While some patients respond well to treatment (medical or surgical) and enter in long-standing remission, in which there are little to know symptoms or progression of disease, there are currently little data to predict who will have a more benign disease course and can be spared the potential risks of more potent therapy. As the induction of remission within 1 year of onset is critical to preventing relapse [144] better identification of disease stages and progression risks is critical to

selecting the appropriate level of therapy for each patient and minimizing unnecessary medication risks, costs, and complications of inadequately controlled disease.

Developing biomarkers to understand the mechanisms driving disease progression and phenotypic subtypes of IBD will furthermore create new opportunities for drug discovery[127]. While biomarkers that elucidate the current state of a patient provide value, the ideal biomarkers are prognostic and/or predictive. Beyond drug discovery, an ideal biomarker has many other uses, such as serving as a surrogate endpoint for clinical trials or as a tool to enrich clinical trial enrollment with the most relevant study subjects.

Clinical trials in IBD last for an insufficient time to properly capture the entire disease course; therefore, biomarkers associated with phenotypic changes and disease complication help to capture the full value of a drug[145]. Moreover, the optimal treatment sequence to sustain long-term remission and prevent disease progression is unknown. Furthermore, as the field embarks upon newer disease concepts like disease interception and restoration, it becomes necessary for the entire disease course of patients to be fully characterized with biomarkers to allow for novel interventions at the relevant clinical or pre-clinical (prior to symptom onset) timeframes.

Call to Action 1: Identify and validate biomarkers to identify pre-clinical disease.

The recognition of a pre-clinical phase of IBD is an important shift in how we frame reducing the burden of disease for future patients. Recent studies have shown that abnormal laboratory measures can pre-date IBD diagnosis by up to a decade[5,146–148]. However, the predictive power of these biomarkers varies in strength and is likely limited by cohort size, and tissue sampling[148].

To actualize disease interception, biomarkers that can identify a pre-clinical population are critical. It is important to validate existing biomarkers. To our knowledge, there are currently a number of cohorts addressing this issue and involved in identifying the pre-clinical phase: the PREDICTS study[149], the GEM study[147], the Danish Register of Laboratory Results for Research[148] and the Health's Nurse Study[150]. While each has made individual strides, cross validating one another's biomarkers, when possible, will increase their usability. In addition to this cross validation, combining the existing biomarkers in an integrated model could strengthen their predictive power. Furthermore, as underlying

mechanisms for other immune mediated inflammatory diseases (IMID) have indicated that there are shared mechanisms for disease initiation and activity, combining IBD specific biomarkers for the pre-clinical stage with those shared across multiple IMID indications could be a useful strategy in finding the best set of biomarkers.

Lastly, while first degree relative studies have focused primarily on siblings, there is growing evidence that there are potentially environmental factors from pregnancy and breastfeeding that could be identified as biomarkers to predict the development of disease[147,151].

As all candidate biomarkers for pre-clinical disease are strongly associated with established disease, newly diagnosed patients can be studied for biomarkers as a source of discovery. The pre-clinical cohorts can then be used to validate these markers and to determine how long before disease presentation they appear.

Overall, the past five years have been exceptionally fruitful for the identification of the pre-clinical phase[5,16,25,27,146,148]. As these cohorts continue to grow, new ones are developed, and new machine learning techniques become available, the field should be able to build upon this work. Examples of improved technology include the ability to screen one's response to antigens using TCR sequencing and autobody profiling[5,152–154].

The above will help identify a population who are at-risk for the development of IBD. Knowing the risk of an individual for developing IBD will enable targeted recommendations including increased monitoring for early diagnosis and lifestyle changes that could impact future disease development and outcomes. Furthermore, the ability to identify high CD-risk cohorts for clinical studies could increase our understanding of the disease pathogenesis and support the identification of novel therapeutic targets and drug development for the prevention and improved treatment of IBD. Without good pre-clinical biomarkers, interception is unlikely to be realized.

Call to Action 2: Identify and validate biomarkers to identify remission.

A strong biomarker of remission has several qualities including being non-invasive, stability in use across a diverse range of disease phenotypes, age, race, and sex. Additionally, biomarkers should help predict, identify, or prognosticate biological phenomena that are important to patients. Any biomarker that doesn't fit all these criteria may still be useful both in specific clinical situations or to help better understand disease.

The current landscape in IBD biomarkers is anchored by two approved indicators of inflammation, C-reactive protein (CRP) and fecal calprotectin[155]. While effective in distinguishing active disease from remission, their correlations with remission fall short of negating the necessity for endoscopy. Recent AGA guidelines while recommending their clinical usage, states that the evidence supporting biomarkers as alternatives to endoscopy in UC is, at best, very low to low[155]. In both Crohn's disease and ulcerative colitis, these may be used to guide treatment decisions, although many clinicians will use these in combination with, rather than in the place of, imaging and colonoscopy when changing, escalating, or de-escalating therapy.

The critical need arises for better non-invasive biomarkers, ones that guide therapeutic decision-making but also catalyze advancements in research. Discovery of such biomarkers can prove invaluable in scenarios where endoscopy results are unavailable, facilitating the identification of patients in or out of remission within patient registries and cohorts. Beyond their clinical applications, these biomarkers serve as crucial components in unraveling pathways leading to remission, potentially unlocking new drug targets.

Call to Action 3: Identify and validate biomarkers for disease phenotype and progression.

Disease progression in IBD exhibits significant variability, influenced by factors such as disease location, treatment history, genetics, phenotype, and likely many other unknown factors[11,17,136,144]. These variations have tangible impacts on patient quality of life, need for surgery, and the efficacy of prescribed medications. Biomarker discovery is essential for patient stratification, drug discovery, prognostication, and to serve as surrogate endpoints in clinical trials.

Research questions that demand attention include the identification of biomarkers for stratifying and predicting CD phenotypes (no complications, stricture, fistulizing disease, perianal disease) and biomarkers for the stratification and prediction of IBD disease location and location extension in UC.

Several biomarker initiatives have been formed to address the need in this area including the Foundation for the National Institutes of Health (FNIH) and the Stenosis Therapy and Anti-Fibrotic Research (STAR) Consortium on Fibrostenotic Crohn's Disease led by Cleveland Clinic, Mayo Clinic and Alimentiv, and the Perianal Crohn's Disease

Consortium led by the London North West University Healthcare NHS Trust. The success of these and other IBD biomarker initiatives will require the continued support and expansion of these studies by investigators and funders, and the rigorous validation of newly identified biomarkers.

Call to Action 4: Identify and validate biomarkers to identify restoration of health and well-being as a predominant aim of therapy

As patient's in endoscopic remission often experience symptoms, biomarkers are necessary to identify restoration: the state in which the gut is healed, reducing all disease burden from a patient [156–158]. This initiative not only aids in clinical differentiation but also delves into the mechanistic underpinnings of symptomatic remission.

Crucial research questions include collaboration with clinical researchers and patients to define restoration clinically, and stratifying patients based on drug-dependent versus drug-independent restoration. Projects exploring additional biomarkers associated with gut barrier function, gut pain, and comparative analyses of the restored gut, pre-clinical gut, and non-IBD gut serve as pivotal steps towards achieving this goal.

In conclusion, these calls to action underscore the necessity for a multifaceted approach to biomarker research in IBD. The anticipated outcomes encompass improved clinical differentiation and decision making, enhanced understanding of disease mechanisms, and the identification of novel therapeutic targets, collectively contributing to a more comprehensive and effective management of IBD.

Call to Action 5: Find and validate biomarkers for EIM and comorbidities.

Beyond inflammatory complications in the gut, IBD is linked to many extra-intestinal manifestations (EIMs) and associated comorbidities[141–143]. In many cases the morbidity and mortality of these complications are more significant than the core disease and therefore it is imperative to find and validate biomarkers that identify those at risk of, and progressing to, EIMs.

Certain extraintestinal manifestations persist beyond mucosal healing. In tandem, IBD patients frequently exhibit strongly correlated comorbidities such as colorectal cancer (CRC) and primary sclerosing cholangitis (PSC), presenting a pronounced unmet need in current clinical understanding[142,143].

The research questions that warrant attention encompass the discovery and validation of biomarkers, both novel and existing, with the predictive capacity for EIMs, CRC, PSC, and post-operative complications. Biomarkers will be key to understanding progression, prediction, prevention, and treatment. The anticipated outcomes aspire to contribute significantly to the holistic management of IBD, bridging the existing gaps in our understanding and paving the way for improved clinical strategies.

Gap #2 There is a lack of validated biomarkers that aid in therapeutic decision making.

The increase in therapeutic options gives more choice to clinicians when selecting the optimal therapy for their patients. Despite the range of choice, there are no consensus guidelines on how to choose the optimal treatment for the individual patient[137,159–162]. An optimal treatment may include a specific diet, lifestyle, medication, or surgery that provides safe therapeutic efficacy in a manner that aligns with the patient's goals. Once a therapy is chosen, additional questions arise[163]: when should the therapy be modified, increased, or de-escalated? When a treatment fails, which therapy has the best chance of succeeding next?

Hence, there is a gap in the ability of healthcare providers to make informed and effective decisions on treatment selection, modification, and sequencing. This can be addressed by finding biomarkers that correlate strongly with the success or failure of certain treatments, and by better understanding which patients will maintain durable remission or restoration after discontinuation of medication. In this section we outline the actionable steps to address these gaps, what outcomes would be achieved in the next 5 years and how they build towards achieving interception, remission, and restoration in IBD.

Call to Action 1: Identify and validate biomarkers to help identify the optimal treatments for the individual patient.

Many biomarkers and algorithms claim to predict response to drugs[54–56,114,155,164]. However, none are consistently used in the clinic. This is due in part to the quality of the biomarkers that have been presented and the other part is due to the complexity and lack clarity on how to bring these tools/biomarkers into the clinic. This section will focus on the lack of quality biomarkers from a scientific perspective.

When evaluating a biomarker for choosing an optimal treatment, there are many considerations. One consideration is to focus on biomarkers directly related to a specific mechanism of action. This can be done by avoiding biomarkers that simply describe disease severity and by running studies that directly compete two different drug classes side-by-side. Moreover, it is critical to understand how a patient's treatment journey might influence biologic processes and the success of later treatments. Finally, as the current treatment options do not alleviate all symptoms and complications, choosing the right treatment requires understanding the patient's goals.

The above will provide clinicians and patients with the biomarkers they need to collaborate on the appropriate treatment plan. The ideal chosen drug will be a drug that gets patients into restoration.

Call to Action 2: Identify and validate biomarkers for predicting the loss of response to a treatment or the need to modify the treatment.

Loss of response rates for IBD therapy can be nearly 50% depending on the study[165,166]. Many studies have shown that proper therapeutic drug monitoring can predict longer term success of the current medications, especially in certain populations[167,168]. However, trough levels of medication are not the sole reason for secondary non-response [169]. Recent studies have shown that molecular data, rather than clinical features, can predict secondary loss of response to anti-TNF biologics[163,170,171].

The ideal biomarkers for non-response must be easy to routinely measure and predate significant increase in disease activity. Additionally, biomarkers that indicate the need for an adjunct therapy, medication escalation, or the use of an entirely different therapy are critical. Improved foundational real-world data is critical to this endeavour. For example, having a strong database of PK/PD data that can serve as a benchmark for therapeutic drug monitoring across

various phenotypes and patient demographics would provide clinicians with strong tools to help treatment decisions for patients. However, specific biomarkers that predict loss of response will provide the most clinical utility.

The above will allow clinicians to monitor their patients' responses to a drug and potentially stratify their patients who will benefit most from therapeutic drug monitoring. Monitoring the patient's drug response will help guide patients from active disease to remission and finally restoration. High fidelity biomarkers should also be able to identify when patients are slipping from restoration to remission or remission to active disease.

Call to Action 3: Identify and validate biomarkers for predicting disease stability after treatment de-escalation

A consistent patient question and request revolves around reducing their medication dose and eventually terminating the need for medication. In fact, the patient provided definition of a cure for IBD includes no need for medication. This is an aspiring target for all clinicians and researchers. Studies show that significant numbers of patients remain in clinical remission after ceasing anti-TNF therapy, with one study demonstrating over 40% remain in remission for a 5-year follow-up period[172,173]. This invites an opportunity to better understand the heterogeneity of drug-induced remission to help predict which patients can de-escalate their medication.

As taking patients off a drug can lead to relapse, it is critical that these biomarkers are well validated across diverse populations. Types of biomarkers that could aid in this endeavour include biomarkers that predict disease stability after de-escalation of a drug; these might be dependent on therapeutic drug monitoring. Other biomarkers that have clinical value allow physicians to predict whether a patient will remain in restoration after termination of a drug. Finally, after termination of a therapy, routine monitoring is necessary to ensure that a patient has and will remain in this restored state.

The impact of these types of biomarkers will help guide discussions between doctors and patients about the relative risks and benefits of reducing medication dosage or going off advanced therapies altogether. Having biomarkers that carefully delineate whether a restored gut will be compromised after discontinuation is critical to shared decision making.

Gap #3 There is an unrealized value of biosamples and of biosample-derived data due to the lack of generation and integration of multimodal data.

The opportunity to access, generate, and glean insights from large and disparate data sources has never been greater. Advances in technology (both hardware and software) have made an impact in IBD and other diseases[126,174,175]. However, the potential impact on precision medicine in IBD is far from realized[176–178]. The best data collection, generation, and analytic capabilities and technologies are not enough to maximize value from data and samples. The data must be easily shared between teams with cross-functional expertise. Also, data must be collected to ensure interoperability with other data sources. Lastly, the best collected data cannot be used to its full value without broad and informed patient consent.

Recent technological improvements in proteomics, RNA-sequencing, and imaging have allowed scientists to explore biological phenomena at unprecedented detail. Such advancements have greatly increased the resolution by which we can generate and/or test hypotheses. This has also generated new data types that can be integrated into our more global understanding of disease.

Similarly, the technical capacity to process large datasets has improved such that we are no longer limited to smaller data sets or analyses of singular data types. Additionally, new statistical and bioinformatic approaches are ushering in a new era where we can exceed the human brain's ability for pattern recognition. This has encouraged scientists to set up larger cohorts of patients to create more data. These datasets represent a gold-mine of information for precision medicine strategies. Despite these incredible advances, it is imperative that we have a strong biological understanding of all biomarker panels and not simply blindly follow the outcome of a statistical algorithm.

Call to Action #1: Emphasize research that effectively uses archival data and samples in biomarker discovery.

When looking forward with technology, we must also look at the capabilities it gives us to improve and benefit from previously generated datasets and collected biosamples. For example, FFPE slides and blocks have been stored for decades and proteomics and spatial technologies have begun to leverage these samples[179,180]. Similarly, vision machine learning gives the ability to revisit these histology slides – whether to score them more quickly and with greater uniformity

or even to pick out insights invisible to the naked eye [181,182]. Many other sample types are banked for years, such as DNA, and blood.

To stay on the cutting edge of technology while ensuring reproducibility and a high standard of value, these activities will need to be collaborations among biotechnology companies, basic scientists, and clinicians. These efforts are not without limitation: archival samples might have degraded quality or be associated with incomplete or unverifiable clinical data. Additionally, it is important to highlight other barriers to working with these data, including that clinically collected samples are not always available for research purposes or not always collected at time of events important for research.

Incorporating historical datasets can increase statistical power in studies that focus on small populations, such as those who develop PSC or CRC. Some of these historical datasets are likely to come from clinical trials. Efforts should be made into the democratization of these data and biosamples. Resources like IBD Plexus, Vivli and Datavant are making large strides to helping with the accessibility of disparate data sources[17,183–186]. Reducing barriers and providing incentives for pharmaceutical companies to share their data is critical to fully realizing the potential of biomarker discovery. There are great strengths in increasing interoperability between the longitudinally and applicability of RWD sets and the depth and standardization of clinical trials.

The above research characteristics will ensure that we appropriately leverage historical learnings, data, and samples. This gives us the opportunity to properly validate former learnings and build on them as we look to create new cohorts in the future.

Call to Action #2: Emphasize research that uses state-of-the-art technologies in biomarkers discovery.

New biomarkers will likely require new technologies, both on the software and hardware side. Integrating existing and creating new tools is a critical success factor in ensuring that we are extracting the most value out of the existing samples and data. For example, bioinformatics tools like xCell and SQUID have helped oncology research extract single cell level insights from bulk RNA-seq data by deconvoluting data using benchmarked scRNA-seq datasets[187,188]. While these can also be applied to IBD samples, they likely will not always capture the correct cell types as they were generated

from different tissue for a different purpose. IBD specific bioinformatics tools would help scientists discover new biomarkers. Utilizing and creating state-of-the-art bioinformatics and machine learning tools to discover new biomarkers is critical. Bioinformatics and statistical tools should extend to RNA sequencing, proteomics, metabolomics, genomics, and to the microbiome.

Additionally, new sequencing platforms and imaging modalities need to be used to uncover new biomarkers that might get lost using cruder methodologies. This becomes particularly important as we further realize the importance of rare immune cell subtypes and new CD8+ cell populations in gut barrier function repair[189]. Once a discovery is made using a potentially expensive, invasive, or time-consuming technology, efforts should be made to find strong correlates with a more accessible biomarker that is easier to obtain.

Completing projects with the above technologies and resources will give scientists the data and tools to fully maximize the use of existing data and samples by digging deeper into the biology underlying disease.

Call to Action #3: Emphasize research that integrates multimodal data in biomarker discovery.

Most current biomarkers and biomarkers studies are singular in modality. For example, CRP is a single protein in the blood, fecal calprotectin is a single protein in the stool, and ulcers/erosions are visualized through endoscopy. To define more complex disease states like the pre-clinical and restoration stages of IBD, we will likely need to rely on information from several sources. Additionally, predictive biomarkers are likely to require information from different biochemical pathways.

These sources could include some combination of different 'omics from various tissues, one or more imaging modalities as well as patient characteristics, symptoms, and clinical outcomes. For example, an interception algorithm may include the presence of a first-degree relative with disease, presence of a specific immune reaction, a microbial shift in the gut, and a deficiency of a specific nutrient. Restoration will likely require a similar comprehensive evaluation of the patient.

To this end, research should be prioritized that develops tools to integrate genetic, transcriptomics, proteomic, microbiome, imaging, and clinical data together. Recent work has indicated that a systems biology approach can

differentiate patients who follow slight differences in biology[190]. Integrating these biological endotypes with clinical and patient reported outcomes is critical to define these endotypes into something meaningful for the patient. While tools are critically important, none of this can happen without infrastructure that allows for linkage of the multimodal datasets. Support of research infrastructure and large databases that have built out harmonization techniques to link multi-modal data such as IBD Plexus and UK Biobank is important and may facilitate integration.

Gap #4 There is a lack of standardized and pragmatic processes for navigating regulation, thereby slowing down biomarkers from reaching the clinic.

Despite dozens of biomarker candidates, fecal calprotectin and C-reactive protein are currently the only biomarkers that have received FDA approval for their use in diagnosing IBD[155]. This represents a major gap in reducing the burden of disease and addressing patient unmet need.

There are multiple obstacles to bringing any novel biomarker to clinical practice. This gap focuses on the non-scientific challenges. First and foremost, biomarker candidates must be developed then validated in large, diverse, and well characterized cohorts[164]. The validation process must be standardized and accessible to all researchers conducting biomarker studies through validation cohorts. Next, there are many practical, strategic, operational, access, and regulatory obstacles that must be addressed. Once defined, these considerations need to be integrated into every aspect of bringing a biomarker candidate into the clinic. It is unlikely that one group can overcome this gap on its own and therefore developing strategic partnerships with industry, regulatory bodies, payers, and clinical trialists to optimize biomarker approval for bedside use is critical. These key partnerships will allow for the prioritization of the development and subsequent approval of clinical tools to monitor symptoms and predict disease progression in an objective, practical, and patient-centric manner.

Research should be funded and conducted in accordance with the steps outlined to ensure high quality of biomarkers are clinic ready[164]. Briefly, after biomarker identification, an assay must be developed to measure biomarker concentrations. Next, the tests need to go through analytical validation where performance metrics such as reliability, precision, accuracy, and reproducibility are measured. After a strong test is in place, the test needs to be associated with

a clinically meaningful outcome. Finally, the utility must be evaluated – comparing the test to existing best practice and cost-effectiveness. While these steps are in some ways linear, all should be considered together for the most efficient development.

Call to action #1: Increase the utilization of validation cohorts.

Biomarker research is often siloed to the investigators and institutions conducting the study or clinical trial. Making validation cohorts accessible to researchers is the first step. The usage of the data must be clearly defined to ensure 1) reproducibility 2) a lack of bias in interpretation and 3) all aspects of the biomarker are properly validated. While institutes like C-path and the FNIH have been successful in other diseases areas to get biomarkers into the clinic, there is work outside of regulatory bodies needed to accelerate the candidate biomarkers earlier in development, these activities may be best targeted by a disease specific consortium[191,192]. IBD Plexus and the Character Consortium[193] are making major headway in these areas.

When developing cohorts, it is important to ensure that cohorts are diverse, fit for purpose and well-characterized clinically. When a researcher is undertaking a biomarker discovery project, there should already be a validation cohort in mind, such that the study is designed so that it can be effectively validated. This provides an opportunity to those running validation cohorts to play a leadership role in both defining and performing biomarker validation. This ensures the process is unbiased and uniformly applied.

Furthermore, funding agencies often do not support validation studies, and journals are turned off by the lack of novelty. This slows important validation work, which is often expensive and requires a strong mix of technical, biological, and clinical skillsets. Centralizing the utilization of validation cohorts is one solution to help ensure that the pipeline of biomarker candidates moves along.

Call to action #2: Emphasize standardized biomarker discovery across the entire clinical development spectrum.

To discover and validate biomarkers for the ambitious use described in this manuscript, biomarker discovery must be emphasized at all stages of drug development, from target identification through clinical trials. To fully realize precision medicine, every drug must have a companion diagnostic to predict its efficacy and safety[194–196].

Research and funding should prioritize biomarker identification during target identification. Once a target is identified, large transcriptomic and proteomic datasets should be leveraged to look for potential biomarkers that correlate strongly with the expression of the target. This ensures that precision medicine strategies are incorporated early in the process of drug development. This has many advantages to the asset and to the patient population, as the biomarker is already validated when it comes to patient enrichment for clinical trials.

Call to action #3: Define practical, regulatory, and economic considerations

Biomarkers are more than just science; they need to be a usable tool that a physician can deploy within the healthcare system to better understand a patient's disease. Ensuring practical and economic considerations are captured is important. There is a growing push to move disease monitoring out of the clinic, and into the home of the patient. This makes disease monitoring easier, faster, and gives the patients the flexibility to measure biomarkers right at the point of symptoms. For example, an inexpensive biomarker test that can be measured at home is likely to be the only way to test for disease interception on a large scale. Another example is measuring and identifying a flare. Obtaining patient samples right at flare initiation is more difficult to do in a hospital setting. When contemplating at home biomarker tests, it is critical to ensure that there is no sacrifice of quality and that at home biomarkers are held to the same standards as those used in the clinic.

Practical considerations must be contemplated at all stages of discovery, validation, and development including the time to test result, the invasiveness of the test, and the relationship between the biomarker and other existing tests. From a regulatory perspective, it is important to start building the Full Qualification Package for the FDA[197,198]. This includes fully understanding the context of use and developing solid methodologies including a statistical analysis plan. Finally, economic considerations must be considered. Conducting a health economic assessment will determine the full value of the biomarker to the patient as well as cost to payers.

Biomarker discovery and validation are scientifically complex and arduous, it is critical to ensure that all the non-scientific considerations are in place to not bring unnecessary delays after the scientific criteria are satisfied.

Call to action #4: Devise and use standardized protocols for sample and data collection and obtaining informed consent in clinical cohorts.

As our technology changes our ability to work with different sample types and larger datasets, we need to use that information to guide how biomarker research is conducted in cohorts. Our tools to allow use of larger datasets have allowed us to combine datasets together to increase the diversity beyond the original patients and increase statistical power. However, for this to be realized we need uniform datasets that can be easily integrated[199]. Cohorts need to be devised in a way that allows this to be done easily and reliably. This requires a lot of collaboration with clinical researchers. Additionally, as we look towards studying interception, we likely will need to tap into data and samples collected for the studying of other diseases and biological processes. Therefore, having standardized informed consent for the broad use of samples is critical. Finally, to combat batch effect of molecular data processing, it is critical that all researchers operate with standardized protocols for the collection, storage, and processing of samples. Consortium like Accelerated Medicine Partnerships (AMP) and other NIH resources represent a great framework for how to ensure that the data being collected and processed will benefit all researchers [200–202]. In addition, IBD Plexus selected central reference labs to enable standard use of technologies and protocols when generating molecular to not only mitigate against batch effects but ensure researchers using the data and samples trust that the derived biosample data is of highest value and is reusable[17,71].

Standardized clinical definitions and measurements strategies for the phenotyping of patients is critical to help compare biomarker discovery and validation efforts across different cohorts. Furthermore, the pre-analytical handling of any patient samples must be uniform as small changes can result in large batch effects in downstream analyses[164] These efforts would be aided with a unified biomarker readiness checklist with predefined standard operating protocols for sample collection, storage, and assay development.

Conclusion

Huge interest in precision medicine has developed in recent years, in parallel with technological advances, biobank development, and introduction of a choice of new therapies to the clinic. It is increasingly clear that a scientific basis for choice of therapy in each person with IBD is needed. In parallel, new therapeutic strategies have accelerated positive patient outcomes in several disease areas. There however, remain several gaps to achieving the goal of personalising care for each person with IBD. No biomarker has been introduced into routine use since the introduction of faecal calprotectin. The reasons for the slow progress to date are wide-ranging this is likely to reflect the complexity and heterogeneity of disease; as resources and technologies advance, there is real hope that the application of new and existing datasets with evolving analytic tools in large well-characterized cohorts will result in discovering and validating biomarkers to unmet patient needs.

References:

1. Fiocchi, C. Inflammatory bowel disease: Complexity and variability need integration. *Front Med Lausanne* **5**, (2018).
2. Nowak, J. K., Kalla, R. & Satsangi, J. Current and emerging biomarkers for ulcerative colitis. *Expert Rev. Mol. Diagn.* **23**, 1107–1119 (2023).
3. Vessby, J. *et al.* AGPAT1 as a Novel Colonic Biomarker for Discriminating Between Ulcerative Colitis With and Without Primary Sclerosing Cholangitis. *Clin. Transl. Gastroenterol.* **13**, e00486 (2022).
4. Kalla, R. *et al.* Analysis of Systemic Epigenetic Alterations in Inflammatory Bowel Disease: Defining Geographical, Genetic and Immune-Inflammatory influences on the Circulating Methylome. *J. Crohns Colitis* **17**, 170–184 (2023).
5. Livanos, A. E. *et al.* Anti-Integrin αvβ6 Autoantibodies Are a Novel Biomarker That Antedate Ulcerative Colitis. *Gastroenterology* **164**, 619–629 (2023).
6. Laass, M. W., Ziesmann, J., de Laffolie, J., Röber, N. & Conrad, K. Anti-Proteinase 3 Antibodies as a Biomarker for Ulcerative Colitis and Primary Sclerosing Cholangitis in Children. *J. Pediatr. Gastroenterol. Nutr.* **74**, 463 (2022).
7. Argmann, C. *et al.* Biopsy and blood-based molecular biomarker of inflammation in IBD. *Gut* **72**, 1271–1287 (2023).
8. Somineni, H. K. *et al.* Blood-Derived DNA Methylation Signatures of Crohn's Disease and Severity of Intestinal Inflammation. *Gastroenterology* **156**, 2254-2265.e3 (2019).
9. Jaenisch, S. E. *et al.* Circulating Dipeptidyl Peptidase Activity Is a Potential Biomarker for Inflammatory Bowel Disease. *Clin. Transl. Gastroenterol.* **13**, e00452 (2022).
10. Komosinska-Vassev, K., Kałużna, A., Jura-Półtorak, A., Derkacz, A. & Olczyk, K. Circulating Profile of ECM-Related Proteins as Diagnostic Markers in Inflammatory Bowel Diseases. *J. Clin. Med.* **11**, 5618 (2022).
11. Gettler, K. *et al.* Common and Rare Variant Prediction and Penetrance of IBD in a Large, Multi-ethnic, Health System-based Biobank Cohort. *Gastroenterology* **160**, 1546–1557 (2021).
12. Irwin, J. R. *et al.* Detectable laboratory abnormality is present up to 12 months prior to diagnosis in patients with Crohn's disease. *Dig Sci* **64**, 503–517 (2019).
13. Takenaka, K. *et al.* Development and Validation of a Deep Neural Network for Accurate Evaluation of Endoscopic Images From Patients With Ulcerative Colitis. *Gastroenterology* **158**, 2150–2157 (2020).

14. Raygoza Garay, J. A. *et al.* Gut microbiome composition is associated with future onset of Crohn's disease in healthy first-degree relatives. *Gastroenterology* **165**, 670–681 (2023).
15. Duryee, M. J. *et al.* Identification of Immunoglobulin G Autoantibody Against Malondialdehyde-Acetaldehyde Adducts as a Novel Serological Biomarker for Ulcerative Colitis. *Clin. Transl. Gastroenterol.* **13**, e00469 (2022).
16. Leibovitzh, H. *et al.* Immune response and barrier dysfunction-related proteomic signatures in preclinical phase of Crohn's disease highlight earliest events of pathogenesis. *Gut* **72**, 1462–1471 (2023).
17. Sazonovs, A. *et al.* Large-scale sequencing identifies multiple genes and rare variants associated with Crohn's disease susceptibility. *Nat Genet* **54**, 1275–1283 (2022).
18. Liñares-Blanco, J., Fernandez-Lozano, C., Seoane, J. A. & López-Campos, G. Machine Learning Based Microbiome Signature to Predict Inflammatory Bowel Disease Subtypes. *Front. Microbiol.* **13**, 872671 (2022).
19. Ungaro, R. C. *et al.* Machine learning identifies novel blood protein predictors of penetrating and stricturing complications in newly diagnosed paediatric Crohn's disease. *Aliment. Pharmacol. Ther.* **53**, 281–290 (2021).
20. Kraszewski, S., Szczurek, W., Szymczak, J., Reguła, M. & Neubauer, K. Machine Learning Prediction Model for Inflammatory Bowel Disease Based on Laboratory Markers. Working Model in a Discovery Cohort Study. *J. Clin. Med.* **10**, 4745 (2021).
21. Rydell, N., Ekoff, H., Hellström, P. M. & Movérare, R. Measurement of Serum IgG Anti-Integrin αvβ6 Autoantibodies Is a Promising Tool in the Diagnosis of Ulcerative Colitis. *J. Clin. Med.* **11**, 1881 (2022).
22. Şimşek-Onat, P. *et al.* Neutrophil-to-Lymphocyte Ratio: An Easy Marker for the Diagnosis and Monitoring of Inflammatory Bowel Disease in Children. *Dig. Dis. Sci.* **68**, 233–239 (2023).
23. Galipeau, H. J. *et al.* Novel Fecal Biomarkers That Precede Clinical Diagnosis of Ulcerative Colitis. *Gastroenterology* **160**, 1532–1545 (2021).
24. Watson, A., Forbes Satter, L., Reiland Sauceda, A., Kellermayer, R. & Karam, L. B. NOD2 polymorphisms may direct a Crohn disease phenotype in patients with very early-onset inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* **77**, 748–752 (2023).

25. Torres, J. *et al.* Serum Biomarkers Identify Patients Who Will Develop Inflammatory Bowel Diseases Up to 5 Years Before Diagnosis. *Gastroenterology* **159**, 96–104 (2020).

26. Kalla, R. *et al.* Serum proteomic profiling at diagnosis predicts clinical course, and need for intensification of treatment in inflammatory bowel disease. *J. Crohns Colitis* **15**, 699–708 (2021).

27. Bergemalm, D. *et al.* Systemic Inflammation in Preclinical Ulcerative Colitis. *Gastroenterology* **161**, 1526-1539.e9 (2021).

28. Pan, J., Li, J. & Gao, Y. The value of 7 peripheral blood serum ratios in diagnosis and prediction of disease activity of patients within inflammatory bowel disease individuals. *Front Med Lausanne* **10**, 1122005 (2023).

29. Kalla, R. *et al.* Whole blood profiling of T-cell-derived microRNA allows the development of prognostic models in inflammatory bowel disease. *J Crohns Colitis* **14**, 1724–1733 (2020).

30. Zand, A., Stokes, Z., Sharma, A., van Deen, W. K. & Hommes, D. Artificial Intelligence for Inflammatory Bowel Diseases (IBD); Accurately Predicting Adverse Outcomes Using Machine Learning. *Dig. Dis. Sci.* **67**, 4874–4885 (2022).

31. Mortensen, J. H. *et al.* A Specific Calprotectin Neo-epitope [CPa9-HNE] in Serum from Inflammatory Bowel Disease Patients Is Associated with Neutrophil Activity and Endoscopic Severity. *J. Crohns Colitis* **16**, 1447–1460 (2022).

32. Kiyokawa, H. *et al.* Deep Learning Analysis of Histologic Images from Intestinal Specimen Reveals Adipocyte Shrinkage and Mast Cell Infiltration to Predict Postoperative Crohn Disease. *Am. J. Pathol.* **192**, 904–916 (2022).

33. Ohara, J. *et al.* Deep learning-based automated quantification of goblet cell mucus using histological images as a predictor of clinical relapse of ulcerative colitis with endoscopic remission. *J. Gastroenterol.* **57**, 962–970 (2022).

34. Hashash, J. G. *et al.* Elevated serum globulin fraction as a biomarker of multiyear disease severity in inflammatory bowel disease. *Ann. Gastroenterol.* **35**, 609–617 (2022).

35. De Cruz, P. *et al.* Endoscopic prediction of Crohn's disease postoperative recurrence. *Inflamm Bowel Dis* **28**, 680–688 (2022).

36. Maeda, Y. *et al.* Evaluation in real-time use of artificial intelligence during colonoscopy to predict relapse of ulcerative colitis: a prospective study. *Gastrointest. Endosc.* **95**, 747-756.e2 (2022).

37. Globig, A.-M. *et al.* Exhaustion of CD39-Expressing CD8+ T Cells in Crohn's Disease Is Linked to Clinical Outcome. *Gastroenterology* **163**, 965-981.e31 (2022).

38. Swaminathan, A. *et al.* Faecal Myeloperoxidase as a Biomarker of Endoscopic Activity in Inflammatory Bowel Disease. *J. Crohns Colitis* **16**, 1862–1873 (2022).

39. Barry, R. *et al.* Faecal neutrophil elastase-antiprotease balance reflects colitis severity. *Mucosal Immunol.* **13**, 322–333 (2020).

40. Wang, J. *et al.* High circulating elafin levels are associated with Crohn's disease-associated intestinal strictures. *PLoS One* **15**, e0231796 (2020).

41. Domislovic, V. *et al.* Inflammatory biomarkers of extracellular matrix remodeling and disease activity in Crohn's disease and ulcerative colitis. *J Clin Med* **11**, 5907 (2022).

42. Yoshida, T. *et al.* Leucine-Rich Alpha-2 Glycoprotein in Monitoring Disease Activity and Intestinal Stenosis in Inflammatory Bowel Disease. *Tohoku J. Exp. Med.* **257**, 301–308 (2022).

43. Shimoyama, T., Yamamoto, T., Yoshiyama, S., Nishikawa, R. & Umegae, S. Leucine-Rich Alpha-2 Glycoprotein Is a Reliable Serum Biomarker for Evaluating Clinical and Endoscopic Disease Activity in Inflammatory Bowel Disease. *Inflamm. Bowel Dis.* **29**, 1399–1408 (2023).

44. Perez, K. *et al.* Meta-Analysis of IBD Gut Samples Gene Expression Identifies Specific Markers of Ileal and Colonic Diseases. *Inflamm. Bowel Dis.* **28**, 775–782 (2022).

45. Argmann, C. *et al.* Molecular Characterization of Limited Ulcerative Colitis Reveals Novel Biology and Predictors of Disease Extension. *Gastroenterology* **161**, 1953-1968.e15 (2021).

46. Anderson, A. *et al.* Monocytosis Is a Biomarker of Severity in Inflammatory Bowel Disease: Analysis of a 6-Year Prospective Natural History Registry. *Inflamm. Bowel Dis.* **28**, 70–78 (2022).

47. Szymanska, E. *et al.* New non-invasive biomarkers of intestinal inflammation and increased intestinal permeability in pediatric inflammatory bowel diseases and their correlation with fecal calprotectin: a pilot study. *Minerva Gastroenterol.* (2022) doi:10.23736/S2724-5985.22.03156-4.

48. Verstockt, S. *et al.* Oncostatin M Is a Biomarker of Diagnosis, Worse Disease Prognosis, and Therapeutic Nonresponse in Inflammatory Bowel Disease. *Inflamm. Bowel Dis.* **27**, 1564–1575 (2021).

49. Takenaka, K. *et al.* Serum Leucine-Rich α2 Glycoprotein: A Novel Biomarker for Transmural Inflammation in Crohn's Disease. *Am. J. Gastroenterol.* **118**, 1028–1035 (2023).

50. Zhang, Q., Gao, X., Wu, J. & Chen, M. The Correlation between Endotoxin, D-Lactate, and Diamine Oxidase with Endoscopic Activity in Inflammatory Bowel Disease. *Dis. Markers* **2022**, 9171436 (2022).

51. Boucher, G. *et al.* Serum Analyte Profiles Associated With Crohn's Disease and Disease Location. *Inflamm. Bowel Dis.* **28**, 9–20 (2022).

52. Ferru-Clément, R. *et al.* Serum Lipidomic Screen Identifies Key Metabolites, Pathways, and Disease Classifiers in Crohn's Disease. *Inflamm. Bowel Dis.* **29**, 1024–1037 (2023).

53. Feng, T. *et al.* Association of Infliximab Levels With Mucosal Healing Is Time-Dependent in Crohn's Disease: Higher Drug Exposure Is Required Postinduction Than During Maintenance Treatment. *Inflamm. Bowel Dis.* **25**, 1813–1821 (2019).

54. Rob, F. *et al.* Association between ustekinumab therapy and changes in specific anti-microbial response, serum biomarkers, and microbiota composition in patients with IBD: A pilot study. *PloS One* **17**, e0277576 (2022).

55. Pereira, M. S. *et al.* A [Glyco]biomarker that Predicts Failure to Standard Therapy in Ulcerative Colitis Patients. *J. Crohns Colitis* **13**, 39–49 (2019).

56. Pesole, P. L. *et al.* 90K/Mac-2 BP Is a New Predictive Biomarker of Response to Infliximab Therapy in IBD Patients. *Int. J. Mol. Sci.* **24**, 3955 (2023).

57. Gaujoux, R. *et al.* Cell-centred meta-analysis reveals baseline predictors of anti-TNFα non-response in biopsy and blood of patients with IBD. *Gut* **68**, 604–614 (2019).

58. Chaparro, M. *et al.* Correlation Between Anti-TNF Serum Levels and Endoscopic Inflammation in Inflammatory Bowel Disease Patients. *Dig. Dis. Sci.* **64**, 846–854 (2019).

59. Dubinsky, M. C. *et al.* Dashboard-Driven Accelerated Infliximab Induction Dosing Increases Infliximab Durability and Reduces Immunogenicity. *Inflamm. Bowel Dis.* **28**, 1375–1385 (2022).

60. Kosoy, R. *et al.* Deep Analysis of the Peripheral Immune System in IBD Reveals New Insight in Disease Subtyping and Response to Monotherapy or Combination Therapy. *Cell. Mol. Gastroenterol. Hepatol.* **12**, 599–632 (2021).

61. Park, S. K. *et al.* Development of a machine learning model to predict non-durable response to anti-TNF therapy in Crohn's disease using transcriptome imputed from genotypes. *J Med* **12**, 947 (2022).

62. Haglund, S., Söderman, J. & Almer, S. Differences in Whole-Blood Transcriptional Profiles in Inflammatory Bowel Disease Patients Responding to Vedolizumab Compared with Non-Responders. *Int. J. Mol. Sci.* **24**, 5820 (2023).

63. Pierre, N. *et al.* Discovery of biomarker candidates associated with the risk of short-term and mid/long-term relapse after infliximab withdrawal in Crohn's patients: a proteomics-based study. *Gut* **70**, 1450–1457 (2021).

64. Tournier, Q. *et al.* Early detection of anti-drug antibodies during initiation of anti-tumour necrosis factor therapy predicts treatment discontinuation in inflammatory bowel disease. *Aliment Pharmacol Ther* **53**, 1190–1200 (2021).

65. Strik, A. S. *et al.* Efficacy of dashboard driven dosing of infliximab in inflammatory bowel disease patients; a randomized controlled trial. *Scand. J. Gastroenterol.* **56**, 145–154 (2021).

66. Minar, P. *et al.* Elevated Pretreatment Plasma Oncostatin M Is Associated With Poor Biochemical Response to Infliximab. *Crohns Colitis 360* **1**, otz026 (2019).

67. Schmitt, H. *et al.* Expansion of IL-23 receptor bearing TNFR2+ T cells is associated with molecular resistance to anti-TNF therapy in Crohn's disease. *Gut* **68**, 814–828 (2019).

68. Verstockt, B. *et al.* Expression Levels of 4 Genes in Colon Tissue Might Be Used to Predict Which Patients Will Enter Endoscopic Remission After Vedolizumab Therapy for Inflammatory Bowel Diseases. *Clin. Gastroenterol. Hepatol. Off. Clin. Pract. J. Am. Gastroenterol. Assoc.* **18**, 1142-1151.e10 (2020).

69. Powell Doherty, R. D., Liao, H., Satsangi, J. J. & Ternette, N. Extended Analysis Identifies Drug-Specific Association of 2 Distinct HLA Class II Haplotypes for Development of Immunogenicity to Adalimumab and Infliximab. *Gastroenterology* **159**, 784–787 (2020).

70. Vatn, S. *et al.* Faecal microbiota signatures of IBD and their relation to diagnosis, disease phenotype, inflammation, treatment escalation and anti-TNF response in a European Multicentre Study (IBD-Character). *Scand. J. Gastroenterol.* **55**, 1146–1156 (2020).

71. Mehta, R. S. *et al.* Gut microbial metabolism of 5-ASA diminishes its clinical efficacy in inflammatory bowel disease. *Nat. Med.* **29**, 700–709 (2023).

72. Sasson, A. N. & Ananthakrishnan, A. N. High Anti-Infliximab Antibody Titers Do Not Impact Response to Subsequent Adalimumab Treatment in Inflammatory Bowel Diseases. *Dig. Dis. Sci.* **67**, 3124–3128 (2022).

73. Guo, A. *et al.* High oncostatin M predicts lack of clinical remission for patients with inflammatory bowel disease on tumor necrosis factor α antagonists. *Sci. Rep.* **12**, 1185 (2022).

74. El-Matary, W. *et al.* Higher postinduction infliximab serum trough levels are associated with healing of fistulizing perianal Crohn's disease in children. *Inflamm Bowel Dis* **25**, 150–155 (2019).

75. Sazonovs, A. *et al.* HLA-DQA1*05 carriage associated with development of anti-drug antibodies to infliximab and adalimumab in patients with Crohn's disease. *Gastroenterology* **158**, 189–199 (2020).

76. Friedrich, M. *et al.* IL-1-driven stromal–neutrophil interactions define a subset of patients with inflammatory bowel disease that does not respond to therapies. *Nat Med* **27**, 1970–1981 (2021).

77. Belarif, L. *et al.* IL-7 receptor influences anti-TNF responsiveness and T cell gut homing in inflammatory bowel disease. *J. Clin. Invest.* **129**, 1910–1925 (2019).

78. Kwon, Y., Kim, Y. Z., Choe, Y. H. & Kim, M. J. Increased monocyte abundance as a marker for relapse after discontinuation of biologics in inflammatory bowel disease with deep remission. *Front. Immunol.* **13**, 996875 (2022).

79. Kang, B. *et al.* Infliximab trough levels are associated with mucosal healing during maintenance treatment with infliximab in paediatric Crohn's disease. *J Crohns Colitis* **13**, 189–197 (2019).

80. Ye, C., Zhu, S., Gao, Y. & Huang, Y. Landscape of sialylation patterns identify biomarkers for diagnosis and prediction of response to anti-TNF therapy in crohn's disease. *Front Genet* **13**, (2022).

81. Blesl, A. *et al.* Limited long-term treatment persistence of first anti-TNF therapy in 538 patients with inflammatory bowel diseases: a 20-year real-world study. *Aliment Pharmacol Ther* **54**, 667–677 (2021).

82. Verstockt, B. *et al.* Longitudinal monitoring of STAT3 phosphorylation and histologic outcome of tofacitinib therapy in patients with ulcerative colitis. *Aliment. Pharmacol. Ther.* **56**, 282–291 (2022).

83. Mishra, N. *et al.* Longitudinal multi-omics analysis identifies early blood-based predictors of anti-TNF therapy response in inflammatory bowel disease. *Genome Med.* **14**, 110 (2022).

84. Verstockt, B. *et al.* Low TREM1 expression in whole blood predicts anti-TNF response in inflammatory bowel disease. *EBioMedicine* **40**, 733–742 (2019).

85. Aden, K. *et al.* Metabolic Functions of Gut Microbes Associate With Efficacy of Tumor Necrosis Factor Antagonists in Patients With Inflammatory Bowel Diseases. *Gastroenterology* **157**, 1279-1292.e11 (2019).

86. Prins, M. M. *et al.* Monocyte TREM-1 Levels Associate With Anti-TNF Responsiveness in IBD Through Autophagy and Fcγ-Receptor Signaling Pathways. *Front. Immunol.* **12**, 627535 (2021).

87. Gabriëls, R. Y. *et al.* Mucosal Eosinophil Abundance in Non-Inflamed Colonic Tissue Is Associated with Response to Vedolizumab Induction Therapy in Inflammatory Bowel Disease. *J. Clin. Med.* **11**, 4141 (2022).

88. Verstockt, B. *et al.* Mucosal IL13RA2 expression predicts nonresponse to anti-TNF therapy in Crohn's disease. *Aliment Pharmacol Ther* **49**, 572–581 (2019).

89. Zittan, E. *et al.* Post-Induction High Adalimumab Drug Levels Predict Biological Remission at Week 24 in Patients With Crohn's Disease. *Clin. Transl. Gastroenterol.* **12**, e00401 (2021).

90. Moore, H., Dolce, P., Devas, N., Baldassano, R. & Martinelli, M. Post-induction infliximab trough levels and disease activity in the clinical evolution of pediatric ulcerative colitis. *United Eur. Gastroenterol J* **8**, 425–435 (2020).

91. Wu, Z. & Bi, Y. Potential role of MALT1 as a candidate biomarker of disease surveillance and treatment response prediction in inflammatory bowel disease patients. *J. Clin. Lab. Anal.* **36**, e24130 (2022).

92. Kennedy, N. A. *et al.* Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. *Lancet Gastroenterol. Hepatol.* **4**, 341–353 (2019).

93. Assa, A. *et al.* Proactive monitoring of adalimumab trough concentration associated with increased clinical remission in children with Crohn's disease compared with reactive monitoring. *Gastroenterology* **157**, 985-996.e2 (2019).

94. Facciorusso, A. *et al.* Prognostic Role of Post-Induction Fecal Calprotectin Levels in Patients with Inflammatory Bowel Disease Treated with Biological Therapies. *Biomedicines* **10**, 2305 (2022).

95. Signore, A. *et al.* Radioimmune Imaging of α4β7 Integrin and TNFα for Diagnostic and Therapeutic Applications in Inflammatory Bowel Disease. *Pharmaceutics* **15**, 817 (2023).

96. Xiong, Y. *et al.* Real-world infliximab pharmacokinetic study informs an electronic health record-embedded dashboard to guide precision dosing in children with Crohn's disease. *Clin Pharmacol Ther* **109**, 1639–1647 (2021).

97. Shubhakar, A. *et al.* Serum N-Glycomic Biomarkers Predict Treatment Escalation in Inflammatory Bowel Disease. *J. Crohns Colitis* **17**, 919–932 (2023).

98. Bertani, L. *et al.* Serum oncostatin M at baseline predicts mucosal healing in Crohn's disease patients treated with infliximab. *Aliment. Pharmacol. Ther.* **52**, 284–291 (2020).

99. Abreu, M. T. *et al.* Transcriptional behavior of regulatory T cells predicts IBD patient responses to vedolizumab therapy. *Inflamm Bowel Dis* **28**, 1800–1812 (2022).

100. Haberman, Y. *et al.* Ulcerative colitis mucosal transcriptomes reveal mitochondriopathy and personalized mechanisms underlying disease severity and treatment response. *Nat Commun* **10**, 38 (2019).

101. Lin, S. *et al.* Understanding anti-TNF treatment failure: does serum triiodothyronine-to-thyroxine (T3/T4) ratio predict therapeutic outcome to anti-TNF therapies in biologic-naïve patients with active luminal Crohn's disease? *Aliment Pharmacol Ther* **56**, 783–793 (2022).

102. Frei, R. *et al.* Early initiation of anti-TNF is associated with favourable long-term outcome in Crohn's disease: 10-year-follow-up data from the Swiss IBD cohort study. *J Crohns Colitis* **13**, 1292–1301 (2019).

103. Ding, N. S. *et al.* Metabonomics and the gut microbiome associated with primary response to anti-TNF therapy in Crohn's disease. *J Crohns Colitis* **14**, 1090–1102 (2020).

104. Lee, J. W. J. *et al.* Multi-omics reveal microbial determinants impacting responses to biologic therapies in inflammatory bowel disease. *Cell Host Microbe* **29**, 1294-1304.e4 (2021).

105. Martin, J. C. *et al.* Single-cell analysis of Crohn's disease lesions identifies a pathogenic cellular module associated with resistance to anti-TNF therapy. *Cell* **178**, 1493-1508.e20 (2019).

106. Dai, Z. *et al.* Single-cell sequencing-based validation of T cell-associated diagnostic model genes and drug response in Crohn's disease. *Int J Mol Sci* **24**, 6054 (2023).

107. Bincy P. Abraham, M. D. *et al.* Real-World Impact of Infliximab Precision-Guided Dosing on Management of Patients With IBD. (2023).

108. Dierckx, T., Verstockt, B., Vermeire, S. & van Weyenbergh, J. GlycA, a Nuclear Magnetic Resonance Spectroscopy Measure for Protein Glycosylation, is a Viable Biomarker for Disease Activity in IBD. *J. Crohns Colitis* **13**, 389–394 (2019).

109. Arkko, A. *et al.* Automatic detection of Crohn's disease using quantified motility in magnetic resonance enterography: initial experiences. *Clin Radiol* **77**, 96–103 (2022).

110. Bossuyt, P. *et al.* Automatic, computer-aided determination of endoscopic and histological inflammation in patients with mild to moderate ulcerative colitis based on red density. *Gut* **69**, 1778–1786 (2020).

111. Kuo, C.-Y. *et al.* Implementing precision medicine in endoscopy practice. *J. Gastroenterol. Hepatol.* **37**, 1455–1468 (2022).

112. Javdan, B. *et al.* Personalized Mapping of Drug Metabolism by the Human Gut Microbiome. *Cell* **181**, 1661-1679.e22 (2020).

113. Gui, X. *et al.* PICaSSO Histologic Remission Index (PHRI) in ulcerative colitis: development of a novel simplified histological score for monitoring mucosal healing and predicting clinical outcomes and its applicability in an artificial intelligence system. *Gut* **71**, 889–898 (2022).

114. Vitali, R. *et al.* Proteomic Analysis Identifies Three Reliable Biomarkers of Intestinal Inflammation in the Stools of Patients With Inflammatory Bowel Disease. *J. Crohns Colitis* **17**, 92–102 (2023).

115. Guimarães, P. *et al.* Artificial-intelligence-based decision support tools for the differential diagnosis of colitis. *Eur. J. Clin. Invest.* **53**, e13960 (2023).

116. Afonso, J. *et al.* Automated detection of ulcers and erosions in capsule endoscopy images using a convolutional neural network. *Med. Biol. Eng. Comput.* **60**, 719–725 (2022).

117. Gardiner, L.-J. *et al.* Combining explainable machine learning, demographic and multi-omic data to inform precision medicine strategies for inflammatory bowel disease. *PloS One* **17**, e0263248 (2022).

118. Del Amor, R. *et al.* Constrained multiple instance learning for ulcerative colitis prediction using histological images. *Comput Methods Programs Biomed* **224**, 107012 (2022).

119. Bhambhvani, H. P. & Zamora, A. Deep learning enabled classification of Mayo endoscopic subscore in patients with ulcerative colitis. *Eur. J. Gastroenterol. Hepatol.* **33**, 645–649 (2021).

120. Nguyen, T. B. *et al.* Identification of potential crucial genes and key pathways shared in Inflammatory Bowel Disease and cervical cancer by machine learning and integrated bioinformatics. *Comput. Biol. Med.* **149**, 105996 (2022).

121. Stankovic, B. *et al.* Machine Learning Modeling from Omics Data as Prospective Tool for Improvement of Inflammatory Bowel Disease Diagnosis and Clinical Classifications. *Genes* **12**, 1438 (2021).

122. Ozawa, T. *et al.* Novel computer-assisted diagnosis system for endoscopic disease activity in patients with ulcerative colitis. *Gastrointest. Endosc.* **89**, 416-421.e1 (2019).

123. Villanacci, V. *et al.* OP15 A new simplified histology artificial intelligence system for accurate assessment of remission in Ulcerative Colitis. *J. Crohns Colitis* **16**, i015–i017 (2022).

124. Barash, Y. *et al.* Ulcer severity grading in video capsule images of patients with Crohn's disease: an ordinal neural network solution. *Gastrointest Endosc* **93**, 187–192 (2021).

125. Vande Casteele, N. *et al.* Utilizing deep learning to analyze whole slide images of colonic biopsies for associations between eosinophil density and clinicopathologic features in active ulcerative colitis. *Inflamm Bowel Dis* **28**, 539–546 (2022).

126. Jovic, D. *et al.* Single-cell RNA sequencing technologies and applications: A brief overview. *Clin Transl Med* **12**, (2022).

127. Mukherjee, P. K. *et al.* Stricturing Crohn's disease single-cell RNA sequencing reveals fibroblast heterogeneity and intercellular interactions. *Gastroenterology* **165**, 1180–1196 (2023).

128. Mitsialis, V. *et al.* Single-cell analyses of colon and blood reveal distinct immune cell signatures of ulcerative colitis and Crohn's disease. *Gastroenterology* **159**, 591-608.e10 (2020).

129. Hou, Q., Huang, J., Ayansola, H., Masatoshi, H. & Zhang, B. Intestinal stem cells and immune cell relationships: Potential therapeutic targets for inflammatory bowel diseases. *Front Immunol* **11**, (2021).

130. Lian, G. *et al.* Diagnosis and prognosis of epidemic inflammatory bowel disease under convolutional neural network algorithm and nonlinear equation model. *Results Phys* **22**, 103912 (2021).

131. Stidham, R. W. *et al.* Performance of a Deep Learning Model vs Human Reviewers in Grading Endoscopic Disease Severity of Patients With Ulcerative Colitis. *JAMA Netw. Open* **2**, e193963 (2019).

132. Tepus, M. & Yau, T. O. Non-Invasive Colorectal Cancer Screening: An Overview. *Gastrointest. Tumors* **7**, 62–73 (2020).

133. Liu, D., Saikam, V., Skrada, K. A., Merlin, D. & Iyer, S. S. Inflammatory bowel disease biomarkers. *Med Res Rev* **42**, 1856–1887 (2022).

134. CFR - Code of Federal Regulations Title 21. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=866.5180.

135. Torres, J., Mehandru, S., Colombel, J.-F. & Peyrin-Biroulet, L. Crohn's disease. *The Lancet* **389**, 1741–1755 (2017).

136. Krugliak Cleveland, N., Torres, J. & Rubin, D. T. What Does Disease Progression Look Like in Ulcerative Colitis, and How Might It Be Prevented? *Gastroenterology* **162**, 1396–1408 (2022).

137. Gergely, M., Prado, E. & Deepak, P. Management of refractory inflammatory bowel disease. *Curr. Opin. Gastroenterol.* **38**, 347–357 (2022).

138. Colombel, J.-F., D'haens, G., Lee, W.-J., Petersson, J. & Panaccione, R. Outcomes and Strategies to Support a Treat-to-target Approach in Inflammatory Bowel Disease: A Systematic Review. *J. Crohns Colitis* **14**, 254–266 (2020).

139. Pariente, B. *et al.* Validation and Update of the Lémann Index to Measure Cumulative Structural Bowel Damage in Crohn's Disease. *Gastroenterology* **161**, 853-864.e13 (2021).

140. Parigi, T. L. *et al.* Difficult-to-treat inflammatory bowel disease: results from an international consensus meeting. *Lancet Gastroenterol. Hepatol.* **8**, 853–859 (2023).

141. Rogler, G., Singh, A., Kavanaugh, A. & Rubin, D. T. Extraintestinal Manifestations of Inflammatory Bowel Disease: Current Concepts, Treatment, and Implications for Disease Management. *Gastroenterology* **161**, 1118–1132 (2021).

142. Barberio, B. *et al.* Prevalence of Primary Sclerosing Cholangitis in Patients With Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. *Gastroenterology* **161**, 1865–1877 (2021).

143. Shah, S. C. & Itzkowitz, S. H. Colorectal Cancer in Inflammatory Bowel Disease: Mechanisms and Management. *Gastroenterology* **162**, 715-730.e3 (2022).

144. Ungaro, R. C. *et al.* Deep Remission at 1 Year Prevents Progression of Early Crohn's Disease. *Gastroenterology* **159**, 139–147 (2020).

145. Berre, C. L. *et al.* Selecting End Points for Disease-Modification Trials in Inflammatory Bowel Disease: the SPIRIT Consensus From the IOIBD. *Gastroenterology* **160**, 1452-1460.e21 (2021).

146. Rudbaek, J. J. *et al.* Deciphering the different phases of preclinical inflammatory bowel disease. *Nat. Rev. Gastroenterol. Hepatol.* 1–15 (2023) doi:10.1038/s41575-023-00854-4.

147. Turpin, W. *et al.* Increased Intestinal Permeability Is Associated With Later Development of Crohn's Disease. *Gastroenterology* **159**, 2092-2100.e5 (2020).

148. Vestergaard, M. V., Allin, K. H., Poulsen, G. J., Lee, J. C. & Jess, T. Characterizing the pre-clinical phase of inflammatory bowel disease. *Cell Rep. Med.* **4**, 101263 (2023).

149. Choung, R. S. *et al.* Serologic microbial associated markers can predict Crohn's disease behaviour years before disease diagnosis. *Aliment. Pharmacol. Ther.* **43**, 1300–1310 (2016).

150. Chan, A. T. Inflammatory Bowel Disease Findings From the Nurses' Health Study I and II. *Gastroenterol. Hepatol.* **11**, 767–769 (2015).

151. Santos, M. P. C., Gomes, C. & Torres, J. Familial and ethnic risk in inflammatory bowel disease. *Ann. Gastroenterol.* **31**, 14–23 (2018).

152. Saravanarajan, K. *et al.* Genomic profiling of intestinal T-cell receptor repertoires in inflammatory bowel disease. *Genes Immun.* **21**, 109–118 (2020).

153. Hong, S. N. *et al.* Reduced diversity of intestinal T-cell receptor repertoire in patients with Crohn's disease. *Front. Cell. Infect. Microbiol.* **12**, 932373 (2022).

154. Wu, J. *et al.* Expanded TCRβ CDR3 clonotypes distinguish Crohn's disease and ulcerative colitis patients. *Mucosal Immunol.* **11**, 1487–1495 (2018).

155. Singh, S. *et al.* AGA Clinical Practice Guideline on the Role of Biomarkers for the Management of Ulcerative Colitis. *Gastroenterology* **164**, 344–372 (2023).

156. Fairbrass, K. M., Costantino, S. J., Gracie, D. J. & Ford, A. C. Prevalence of irritable bowel syndrome-type symptoms in patients with inflammatory bowel disease in remission: a systematic review and meta-analysis. *Lancet Gastroenterol. Hepatol.* **5**, 1053–1062 (2020).

157. Chang, J. *et al.* Impaired Intestinal Permeability Contributes to Ongoing Bowel Symptoms in Patients With Inflammatory Bowel Disease and Mucosal Healing. *Gastroenterology* **153**, 723-731.e1 (2017).

158. Chiriac, S. *et al.* Impaired Intestinal Permeability Assessed by Confocal Laser Endomicroscopy—A New Potential Therapeutic Target in Inflammatory Bowel Disease. *Diagnostics* **13**, 1230 (2023).

159. Raine, T. *et al.* ECCO Guidelines on Therapeutics in Ulcerative Colitis: Medical Treatment. *J. Crohns Colitis* **16**, 2–17 (2022).

160. Feuerstein, J. D. *et al.* AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. *Gastroenterology* **158**, 1450–1461 (2020).

161. Nguyen, N. H., Singh, S. & Sandborn, W. J. Positioning Therapies in the Management of Crohn's Disease. *Clin. Gastroenterol. Hepatol.* **18**, 1268–1279 (2020).

162. Cushing, K. & Higgins, P. D. R. Management of Crohn Disease: A Review. *JAMA* **325**, 69–80 (2021).

163. Verstockt, B., Parkes, M. & Lee, J. C. How Do We Predict a Patient's Disease Course and Whether They Will Respond to Specific Treatments? *Gastroenterology* **162**, 1383–1395 (2022).

164. Honig, G., Heller, C. & Hurtado-Lorenzo, A. Defining the Path Forward for Biomarkers to Address Unmet Needs in Inflammatory Bowel Diseases. *Inflamm. Bowel Dis.* **26**, 1451–1462 (2020).

165. Straatmijer, T. *et al.* Effectiveness and safety of tofacitinib for ulcerative colitis: two-year results of the ICC Registry. *Aliment. Pharmacol. Ther.* **57**, 117–126 (2023).

166. Ben-Horin, S. & Chowers, Y. Review article: loss of response to anti-TNF treatments in Crohn's disease. *Aliment. Pharmacol. Ther.* **33**, 987–995 (2011).

167. Fuentes-Valenzuela, E. *et al.* Influence of HLADQA1*05 Genotype in Adults With Inflammatory Bowel Disease and Anti-TNF Treatment With Proactive Therapeutic Drug Monitoring: A Retrospective Cohort Study. *Inflamm. Bowel Dis.* **29**, 1586–1593 (2023).

168. Sethi, S. *et al.* Meta-analysis: The efficacy of therapeutic drug monitoring of anti-TNF-therapy in inflammatory bowel disease. *Aliment. Pharmacol. Ther.* **57**, 1362–1374 (2023).

169. Sparrow, M. P. *et al.* Therapeutic Drug Monitoring of Biologics During Induction to Prevent Primary Non-Response. *J. Crohns Colitis* **14**, 542–556 (2020).

170. Li, L. *et al.* A Novel Model Based on Serum Biomarkers to Predict Primary Non-Response to Infliximab in Crohn's Disease. *Front. Immunol.* **12**, 646673 (2021).

171. Chen, Y., Li, H., Feng, Q. & Shen, J. Development and Validation of an Interleukin-6 Nomogram to Predict Primary Non-response to Infliximab in Crohn's Disease Patients. *Front. Pharmacol.* **12**, (2021).

172. Pauwels, R. W. M. *et al.* Prediction of Relapse After Anti–Tumor Necrosis Factor Cessation in Crohn's Disease: Individual Participant Data Meta-analysis of 1317 Patients From 14 Studies. *Clin. Gastroenterol. Hepatol.* **20**, 1671-1686.e16 (2022).

173. Song, J. H. *et al.* Long-term Outcomes after the Discontinuation of Anti-Tumor Necrosis Factor-α Therapy in Patients with Inflammatory Bowel Disease under Clinical Remission: A Korean Association for the Study of Intestinal Disease Multicenter Study. *Gut Liver* **15**, 752–762 (2021).

174. Jaeger, N. *et al.* Single-cell analyses of Crohn's disease tissues reveal intestinal intraepithelial T cells heterogeneity and altered subset distributions. *Nat. Commun.* **12**, 1921 (2021).

175. Ruf, B., Jenkinson, P., Armour, D., Fraser, M. & Watson, A. J. Videoconference clinics improve efficiency of inflammatory bowel disease care in a remote and rural setting. *J. Telemed. Telecare* **26**, 545–551 (2020).

176. Borg-Bartolo, S. P., Boyapati, R. K., Satsangi, J. & Kalla, R. Precision medicine in inflammatory bowel disease: concept, progress and challenges. *F1000Research* **9**, F1000 Faculty Rev-54 (2020).

177. Lamb, C. A., Saifuddin, A., Powell, N. & Rieder, F. The Future of Precision Medicine to Predict Outcomes and Control Tissue Remodeling in Inflammatory Bowel Disease. *Gastroenterology* **162**, 1525–1542 (2022).

178. Fiocchi, C. *et al.* Results of the Seventh Scientific Workshop of ECCO: Precision Medicine in IBD—What, Why, and How. *J. Crohns Colitis* **15**, 1410–1430 (2021).

179. Klein, O. *et al.* Classification of Inflammatory Bowel Disease from Formalin-Fixed, Paraffin-Embedded Tissue Biopsies via Imaging Mass Spectrometry. *PROTEOMICS – Clin. Appl.* **14**, 1900131 (2020).

180. Garrido-Trigo, A. *et al.* Macrophage and neutrophil heterogeneity at single-cell spatial resolution in human inflammatory bowel disease. *Nat. Commun.* **14**, 4506 (2023).

181. Iacucci, M. *et al.* Artificial Intelligence Enabled Histological Prediction of Remission or Activity and Clinical Outcomes in Ulcerative Colitis. *Gastroenterology* **164**, 1180-1188.e2 (2023).

182. Najdawi, F. *et al.* Artificial Intelligence Enables Quantitative Assessment of Ulcerative Colitis Histology. *Mod. Pathol.* **36**, 100124 (2023).

183. Lawrence, D. F., Manjelievskaia, J., Chrones, L., McCue, M. & Touya, M. Adherence and persistence among patients with major depressive disorder enrolled in the vortioxetine tAccess Patient Support Program. *Curr. Med. Res. Opin.* **37**, 1385–1392 (2021).

184. Rudrapatna, V. A. & Butte, A. J. Opportunities and challenges in using real-world data for health care. *J. Clin. Invest.* **130**, 565–574 (2020).

185. Vazquez, E. *et al.* Characteristics of available studies and dissemination of research using major clinical data sharing platforms. *Clin. Trials* **18**, 657–666 (2021).

186. Raffals, L. E. *et al.* The Development and Initial Findings of A Study of a Prospective Adult Research Cohort with Inflammatory Bowel Disease (SPARC IBD). *Inflamm. Bowel Dis.* **28**, 192–199 (2022).

187. Yau, T. O. *et al.* Hyperactive neutrophil chemotaxis contributes to anti-tumor necrosis factor-α treatment resistance in inflammatory bowel disease. *J. Gastroenterol. Hepatol.* **37**, 531–541 (2022).

188. Cobos, F. A. *et al.* Effective methods for bulk RNA-seq deconvolution using scnRNA-seq transcriptomes. *Genome Biol.* **24**, 177 (2023).

189. Dart, R. J. *et al.* Conserved γδ T cell selection by BTNL proteins limits progression of human inflammatory bowel disease. *Science* **381**, eadh0301 (2023).

190. Gerassy-Vainberg, S. *et al.* A personalized network framework reveals predictive axis of anti-TNF response across diseases. *Cell Rep. Med.* 101300 (2023) doi:10.1016/j.xcrm.2023.101300.

191. Woodcock, J. & Woosley, R. The FDA Critical Path Initiative and Its Influence on New Drug Development. *Annu. Rev. Med.* **59**, 1–12 (2008).

192. Menetski, J. P. *et al.* The FNIH Biomarkers Consortium embraces the BEST. *Nat. Rev. Drug Discov.* **18**, 567–568 (2019).

193. Vatn, S. S. *et al.* Mucosal Gene Transcript Signatures in Treatment Naïve Inflammatory Bowel Disease: A Comparative Analysis of Disease to Symptomatic and Healthy Controls in the European IBD-Character Cohort. *Clin. Exp. Gastroenterol.* **15**, 5–25 (2022).

194. Samuels, A., Whaley, K. G. & Minar, P. Precision Dosing of Anti-TNF Therapy in Pediatric Inflammatory Bowel Disease. *Curr. Gastroenterol. Rep.* **25**, 323–332 (2023).

195. Nicolaides, N. C., O'Shannessy, D. J., Albone, E. & Grasso, L. Co-Development of Diagnostic Vectors to Support Targeted Therapies and Theranostics: Essential Tools in Personalized Cancer Therapy. *Front. Oncol.* **4**, (2014).

196. Twomey, J. D. & Zhang, B. Cancer Immunotherapy Update: FDA-Approved Checkpoint Inhibitors and Companion Diagnostics. *AAPS J.* **23**, 39 (2021).

197. Benatar, M. *et al.* Biomarker Qualification for Neurofilament Light Chain in Amyotrophic Lateral Sclerosis: Theory and Practice. *Ann. Neurol.* **n/a**,.

198. Gromova, M., Vaggelas, A., Dallmann, G. & Seimetz, D. Biomarkers: Opportunities and Challenges for Drug Development in the Current Regulatory Landscape. *Biomark. Insights* **15**, 1177271920974652 (2020).

199. Bradshaw, A. *et al.* Data sharing in neurodegenerative disease research: challenges and learnings from the innovative medicines initiative public-private partnership model. *Front. Neurol.* **14**, 1187095 (2023).

200. Carter, A. B. *et al.* Electronic Health Records and Genomics: Perspectives from the Association for Molecular Pathology Electronic Health Record (EHR) Interoperability for Clinical Genomics Data Working Group. *J. Mol. Diagn.* **24**, 1–17 (2022).

201. Bornstein, K., Gryan, G., Chang, E. S., Marchler-Bauer, A. & Schneider, V. A. The NIH Comparative Genomics Resource: addressing the promises and challenges of comparative genomics on human health. *BMC Genomics* **24**, 575 (2023).

202. Shah, S. J., Butler, J., Shah, S. H., Kamphaus, T. N. & Sachdev, V. Accelerating therapeutic discoveries for heart failure: a new public–private partnership. *Nat. Rev. Drug Discov.* **21**, 781–782 (2022).