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Expert recommendation

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Precision medicine in monogenic inflammatory bowel disease: proposed mIBD REPORT standards

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Abstract

Owing to advances in genomics that enable differentiation of molecular aetiologies, patients with monogenic inflammatory bowel disease (mIBD) potentially have access to genotype-guided precision medicine. In this Expert Recommendation, we review the therapeutic research landscape of mIBD, the reported response to therapies, the medication-related risks and systematic bias in reporting. The mIBD field is characterized by the absence of randomized controlled trials and is dominated by retrospective observational data based on case series and case reports. More than 25 off-label therapeutics (including small-molecule inhibitors and biologics) as well as cellular therapies (including haematopoietic stem cell transplantation and gene therapy) have been reported. Heterogeneous reporting of outcomes impedes the generation of robust therapeutic evidence as the basis for clinical decision making in mIBD. We discuss therapeutic goals in mIBD and recommend standardized reporting (mIBD REPORT (monogenic Inflammatory Bowel Disease Report Extended Phenotype and Outcome of Treatments) standards) to stratify patients according to a genetic diagnosis and phenotype, to assess treatment effects and to record safety signals. Implementation of these pragmatic standards should help clinicians to assess the therapy responses of individual patients in clinical practice and improve comparability between observational retrospective studies and controlled prospective trials, supporting future meta-analysis.

Sections

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Introduction

Inflammatory bowel diseases (IBD) are a group of disorders with heterogeneous genetic causes. Monogenic forms of IBD (mIBD) complement the 'classic' IBD triad of polygenic Crohn's disease, ulcerative colitis and IBD unclassified. Next-generation sequencing technologies are now central to the diagnostic work-up of patients with IBD at high risk of a monogenic aetiology[1]. Variants in >100 genes have been implicated in mIBD[2]. These pathogenic variants exhibit moderate or high disease penetrance and have variable expressivity for IBD[2]. The affected mIBD genes are expressed by a range of cell types including intestinal epithelial cells, fibroblasts, endothelial cells, phagocytes (that is, monocytes, macrophages and neutrophils) and lymphocytes. mIBD-causing gene variants affect diverse cellular pathways[2] and therefore trigger a plethora of pathologies. These pathologies include mucosal barrier defects that predispose to the translocation of luminal bacteria, defects in the antimicrobial functions of phagocytes, dysregulated innate and adaptive cellular immune responses, autoimmunity and syndromic features in other organ systems[3,4].

As the clinical phenotypes are so diverse, identifying patients with a likely monogenic condition and establishing the genetic diagnosis can be challenging[2,5,6]. The highest fraction of patients with mIBD is children with infant-onset IBD[2]. Key indications for genomic screening for mIBD are age at IBD onset under 2 years of age, or under 6 years of age if there are notable additional features. Those features that support genomic screening include: infection susceptibility or inflammatory features indicative of an inborn error of immunity as indicated by complex and severe multi-organ autoimmune disease or haemophagocytic lymphohistiocytosis (HLH); congenital intestinal atresias or congenital diarrhoea; early-onset malignancy (<25 years of age); family history of suspected mIBD, as well as the clinical decision process before interventions and/or therapies with irreversible consequences or high risk for adverse outcome, such as stem cell transplantation[1,7]. However, older children and even adults can present with mIBD, although this is less common[2,8]. Clinical position statements and guidelines for application of clinical genomics were established by the Porto group of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition[1], as well as by the British Society of Gastroenterology and the British Society of Paediatric Gastroenterology, Hepatology and Nutrition[7].

Patients with mIBD have a substantial unmet medical need for better treatments, because current 'standard' IBD medications frequently fail or are not approved, especially for use in very young patients[9,10]. The identification of a pathogenic variant in an mIBD gene can have an immediate effect on patients, as it constitutes a molecular diagnosis that can often provide a better mechanistic understanding of the condition. In addition, a molecular diagnosis can direct precision medicine such as pathway-directed medications, haematopoietic stem cell transplantation (HSCT) or gene therapy. In some mIBD disorders, a genetic diagnosis can help to predict the effect of surgery, to assess the potential benefit and risks of medication and to support palliation in those conditions for which no treatments are currently available[5,9].

The molecular pathways affected in mIBD involve inflammatory and barrier function mechanisms that are insufficiently corrected by licensed or emerging medicines in the field of classic IBD. When considering novel treatments for mIBD, there is a tension between the desire for all patients — who are often very young, sick and vulnerable — to have rapid access to novel and specific drugs and the regulatory imperative that new medicines be both safe and effective. The typical drug approval process around the world for classic IBD therapies (most of which are not yet approved for use in children) can be lengthy[10], which might not be optimal for rare or orphan mIBD disorders. Nevertheless, regulatory agencies such as the FDA and the European Medicines Agency have a strong interest in rigorously assessing and approving drugs for ultra-rare and rare diseases. Therefore, innovative approaches to clinical trial design are warranted, as are tools to assess therapeutic effectiveness in patients with mIBD in the real-world setting of clinical practice.

Aims

In this Expert Recommendation, our purpose was to review therapeutic interventions for mIBD, discuss therapeutic goals, assess the landscape of clinical trials and observational studies, review informative parameters that help to assess response to therapy, highlight adverse risks of medications in patients with mIBD, and stress the bias in current therapeutic research. On the basis of these considerations, we propose recommendations for standardized outcome reporting.

Our recommendations (for a detailed methodology, see Supplementary Information) are based on a wide representation of mIBD specialists, including investigators leading major research consortia (the VEO-IBD Consortium, COLORS in IBD and GENIUS), as well as paediatric and adult IBD clinical trial specialists. To reflect the complexities of multi-organ immunopathology, the group includes specialists in immunology, stem cell transplantation and gene therapy who have contributed to translational research relevant to the field of mIBD. To reduce bias, specialists with strong research contributions from multiple institutions, countries and regions worldwide, representing different health-care systems, contributed to these recommendations. The group includes physicians as well as non-clinical specialists at different career stages. Furthermore, we invited stakeholder patient organizations and charities representing paediatric and adult patients with IBD, or rare monogenic disorders that can present with IBD, to participate. These included the Crohn's in Childhood Research Association (CICRA), the XLP Research Trust and the Chronic Granulomatous Disorder Society (CGD Society).

Reports of treatments were initially selected from three different systematic analyses of mIBD. These analyses included patients with mIBD due to inborn errors of immunity (including 36 articles)[11] and patients with mIBD due to immune and epithelial defects (including 303 articles[9] and 395 articles[2]). Additional literature was reviewed, as cited in each selected article. Prospective clinical trials were identified in the ClinicalTrials.gov database or reported via the respective National Clinical Trial (NCT) number or the European Trials Registry identification.

Following this systematic literature review, mIBD REPORT (monogenic Inflammatory Bowel Disease Report Extended Phenotype and Outcome of Treatments) standards were proposed to the entire group for extensive discussion, followed by a first voting round of voting based on a five-point Likert scale of agreement (strongly disagree, disagree, neutral, agree, strongly agree) at the time of writing this Expert Recommendation (Supplementary Information). We discussed divergent positions and after rewording and modification, a second round of voting was performed. Agreement (either agree or strongly agree) of at least 80% participating scientists and clinicians was required for recommendations on reporting standards to be accepted. This Expert Recommendation represents the start of a process leading to recommendations for disease-specific therapeutic approaches for which agreement at this stage is not possible given the absent, incomplete, conflicting or biased evidence.

Therapeutic studies in mIBD: the research landscape

Studies on therapies for mIBD are dominated by real-world retrospective, observational clinical reports, whereas efficacy data from prospective clinical trials are lacking. As yet there are no randomized clinical trials that have evaluated intestinal response to therapy as a primary outcome (that is, induction or maintenance of remission, endoscopic, histological healing or long-term outcomes) in patients with mIBD. Few prospective studies have evaluated resolution of intestinal inflammation, even as a secondary outcome (for example, in individual patients after gene therapy)[12–14]. Several prospective clinical trials are investigating therapeutic interventions in monogenic conditions that can present with intestinal inflammation. One example is umbilical cord blood stem cell transplantation in patients with IL-10 receptor variants (NCT04170192). Other trials are not primarily focused on control of intestinal inflammation as primary outcome but will likely include patients with mIBD; these include: tadekinig alfa (a recombinant IL-18-binding protein; also known as rhIL-18BP) in X-linked inhibitor of apoptosis protein (XIAP) deficiency and NOD-, LRR- and CARD-containing 4 (NLRC4) variants (NCT03113760); pozelimab in CD55 deficiency with hyperactivation of complement, angiopathic thrombosis and severe protein-losing enteropathy (CHAPLE) disease (NCT04209634); empagliflozin in glycogen storage disease type 1B and G6PC3 deficiency (NCT04138251 and NCT05078879); tofacitinib in chronic granulomatous disorder (CGD)-associated inflammatory disease (NCT05104723); or abatacept in CTLA4 and LRBA deficiency (German Clinical Trials Register DRKS00017736).

Most published therapeutic reports in mIBD include fewer than five patients with intestinal inflammation per gene who were exposed to the interventions[2,9,11]. The studies focused on the induction of remission; there is often a lack of long-term data to assess maintenance of remission, although mIBD has lifelong implications once diagnosed. In most case series reporting interventions, therapy was directed at other disease manifestations such as infection susceptibility or multisystem inflammation[2], because intestinal inflammation has incomplete penetrance and/or expressivity. In patients with inborn errors of immunity, the focus of interventions was usually to reduce susceptibility to infection and/or to control immune dysregulation. In autoinflammatory conditions, the primary objective was to control the multisystem inflammation. In other disease groups, studies had a different focus (for example, to prevent neurological decline in patients with neurodegeneration such as Niemann–Pick disease type C), even though IBD has a major effect on quality of life in some patients.

Most of the published evidence on mIBD therapeutics involves patients in whom previous treatments have failed. In this setting, individual patients effectively serve as their individual, historical comparator. In many instances, biologically plausible interventions in patients with mIBD are initially described as case studies and are subsequently replicated in case series. For example, the curative effect of HSCT in patients with pathogenic IL-10 signalling variants was initially reported in individual patients in whom conventional therapies, such as anti-tumour necrosis factor (anti-TNF) therapy, had failed. After successful demonstration in patients with pathogenic variants in *IL10RA*, *IL10RB* and *IL10* (refs. 15,16), HSCT is now the de facto standard of care in patients with these gene variants. Another example is treatment with ruxolitinib in patients with *STAT1* gain-of-function variants. Ruxolitinib, a Janus kinase (JAK) inhibitor, was shown to be effective in patients in whom anti-IL-6 receptor treatment had failed[17,18] and is therefore regarded as the preferred therapeutic option. The clinical response in a single patient with XIAP deficiency after treatment with tadekinig alfa is remarkable because of the well-established mechanistic link with high IL-18 serum levels observed in patients with XIAP deficiency in whom conventional IBD therapies frequently fail[19]. Similarly, treatment of individuals with CTLA4 insufficiency with the CTLA4–Fc fusion protein abatacept has strong mechanistic support[20]. These examples illustrate the relevance of meticulous reporting of case studies and case series for orphan disorders in a field that lacks prospective studies.

Therapies for patients with mIBD

Multiple classes of therapeutics have been described in patients with mIBD (Table 1). This is because there are multiple pathophysiological mechanisms that drive the inflammation with diverse intestinal and extraintestinal disease presentations, and also because of the failure of classic IBD therapies. These interventions target several cellular compartments, but they are mainly focused on haematopoietic cells and immune mechanisms (Figs. 1,2). Thus far, the greatest therapeutic effect has been the introduction of allogeneic HSCT in selected patients with mIBD.

Small-molecule pharmaceuticals

Medical treatments including all drugs commonly used in classic IBD, such as 5-aminosalicylic acid, topical and systemic corticosteroids and immunomodulators licensed for use in children and adults with IBD (azathioprine and mercaptopurine; not approved in the USA for Crohn's disease), are used off-label in patients with mIBD. In paediatric patients with infantile or very-early-onset IBD, such first-line treatments are often used while waiting for a genetic diagnosis to be established[21]. However, many patients with mIBD are steroid-refractory or become steroid-dependent. The effects of treatments that are standard of care in Crohn's disease[22] and ulcerative colitis[23] are generally safe. However, these standard IBD therapies are unlicensed for use in patients with mIBD, and it is unknown whether there are similar risk–benefit profiles.

Consequently, patients with mIBD have been treated with a spectrum of medications (Table 1). These treatments not only include immunomodulatory and immunosuppressive medications such as mechanistic target of rapamycin (mTOR) inhibitors, thalidomide, the calcineurin inhibitor ciclosporin, mycophenolate mofetil, the immunophilin binding molecule tacrolimus[21] and JAK inhibitors, but also medications that target inflammasome activation (colchicine), angiotensin receptor signalling (losartan) and glucose metabolism (empagliflozin).

mTOR inhibitors. The mTOR inhibitor rapamycin has been used for the treatment of patients with intestinal inflammation due to *FOXP3* gene variants that cause immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) or IPEX-like syndrome caused by mutations in *CTLA4* or *LRBA*[20,24,25]. Although mTOR signalling is activated in patients with activated PI3Kδ syndrome (APDS) caused by mutations in *PIK3CD* or *PIK3R1*, treatment with sirolimus did not have strong efficacy for resolving colitis[26].

JAK inhibitors. Treatment with tofacitinib, the JAK1 and JAK3 inhibitor, has been reported in patients with *STAT3* (ref. 17) and *JAK1* (ref. 27) gain-of-function variants. The JAK1 and JAK2 inhibitor ruxolitinib has been used to treat patients with *STAT1* gain-of-function mutations[17,18], and baricitinib has been used in a patient with trichohepatoenteric syndrome and upper gastrointestinal tract infection[28]. Stronger evidence is needed to assess which JAK inhibitor is best suited in these individual conditions.

Table 1 | Examples of experimental treatments previously used in patients with mIBD

Treatment	Mechanism	Examples of affected genes
Small molecules		
Sirolimus	mTOR inhibitor	*CTLA4, LRBA, FOXP3, SKIV2L, PIK3CD, PIK3R1*
Thalidomide	Ubiquitinylation	*IL10RA, IL10RB, G6PC3, CYBB, NCF1, XIAP*
Tacrolimus	Calcineurin phosphatase inhibitor	*EPCAM, TTC37, SKIV2L, FOXP3, XIAP*
Tofacitinib	JAK1 and JAK3 inhibitor	*STAT3* and *JAK1* gain-of-function
Ruxolitinib	JAK1 and JAK2 inhibitor	*STAT1* gain-of-function
Baricitinib	JAK1 and JAK2 inhibitor	*SKIV2L*
Ciclosporin	Calcineurin inhibitor	*LRBA, XIAP*
Mycophenolate	Inosine monophosphate dehydrogenase inhibitor	*CTLA4, LRBA, STAT3* gain-of-function, among others
Colchicine	Block microtubule assembly	*IL10RA, XIAP*
Losartan	Angiotensin receptor 1 inhibitor	*TGFBR1, TGFBR2*
Empagliflozin	Sodium/glucose cotransporter 2 inhibitor	*SLC37A4*
D-Mannose	Replacement to control defect of glycosylation	*MPI*
Biologics		
Infliximab, adalimumab, golimumab	Anti-TNF	*IL10RA, IL10RB, CYBB, HPS1, TTC7A, IKBKG, G6PC3, RIPK1, TGFBR1, TGFBR2, WAS, CD55, SKIV2L, MPI, XIAP, CARD8*, among others
Etanercept	Recombinant TNF receptor	*XIAP*
Vedolizumab	Anti-α4β7 integrin	*CTLA4, NPC1, XIAP, SLC26A3*
Canakinumab	Anti-IL-1β	*MVK, XIAP*
Anakinra	IL-1 receptor antagonist	*IL10RB, CARD8, MVK, CYBB, NLRC4, XIAP*
Abatacept	CTLA fusion	*LRBA, CTLA4*
Tadekinig alfa	Recombinant IL-18 binding protein	*NLRC4, XIAP*
Rituximab	Anti-CD20	*IL10RB* (for B cell lymphoma), *XIAP*
Ustekinumab	Anti-IL-12/23p40	*NPC1, TGFBR2*
Tocilizumab	Anti-IL-6 receptor	*FOXP3, STAT3* gain-of-function, *XIAP*
Basiliximab	Anti-CD25	*TTC7A*
Eculizumab	Anti-complement C5	*CD55*
GCSF	GCSF growth factor	*G6PC3, SLC37A4*
Immunoglobulin	Replacement therapy	*LRBA, BTK, IL10RA*
HSCT		
Bone marrow	Haematopoietic stem cells	*IL10RB*[a], *IL10RA*[a], *IL10, RIPK1, NCF4, LRBA, MALT1, CYBB*[a], *FOXP3, NCF1*[a], *STAT3, XIAP*[a], *ICOS, NCF2, CTLA4, IKBA, DOCK2, G6PC3, WAS, CD3G, ITGB2, STAT1, ADA2, DCLRE1C, PIK3CD* gain-of-function, *FCHO1*
Umbilical cord	Haematopoietic stem cells	*IL10RA, ITGB2*
Gene therapy		
Retroviral transfer	Haematopoietic stem cells	*WAS, CYBB*
Lentiviral transfer	Haematopoietic stem cells	*WAS, CYBB*

The drugs and interventions listed illustrate published experience. Due to limited numbers of patients reported and heterogeneous reporting, inclusion of drugs and interventions in the table does not indicate a recommendation for use in a specific mIBD group. The medications listed are considered experimental and must be used both with caution and with appropriate off-label approval. Some drugs have been used as bridging treatment for intestinal disease prior to HSCT. Standard-of-care steroids (prednisolone, budesonide), aminosalicylic acids, immunomodulators (azathioprine, mercaptopurine), antibiotics and antifungals, and exclusive enteral nutrition are not included. Data are summarized as reported in the main text and in refs. 2,9,11,18–20,24,25,28,35,63,69,81,131–133. GCSF, granulocyte colony-stimulating factor; HSCT, haematopoietic stem cell transplantation; JAK, Janus kinase; mIBD, monogenic inflammatory bowel disease; mTOR, mechanistic target of rapamycin; TNF, tumour necrosis factor. [a]Interventions with reported therapeutic efficacy to resolve IBD-like intestinal inflammation in more than ten patients.

Other small molecules. Thalidomide has been used in children with mIBD caused by pathogenic IL-10 signalling variants[29], CGD[30] or congenital neutropenia[31,32]. The rationale for using thalidomide is its effect on inflammatory pathways, including its regulation of TNF.

Colchicine has been used in autoinflammatory disorders such as XIAP deficiency to block inflammasome activation[19]. Individual patients with intestinal inflammation associated with familial Mediterranean fever due to homozygous *MEFV* variants responded well to

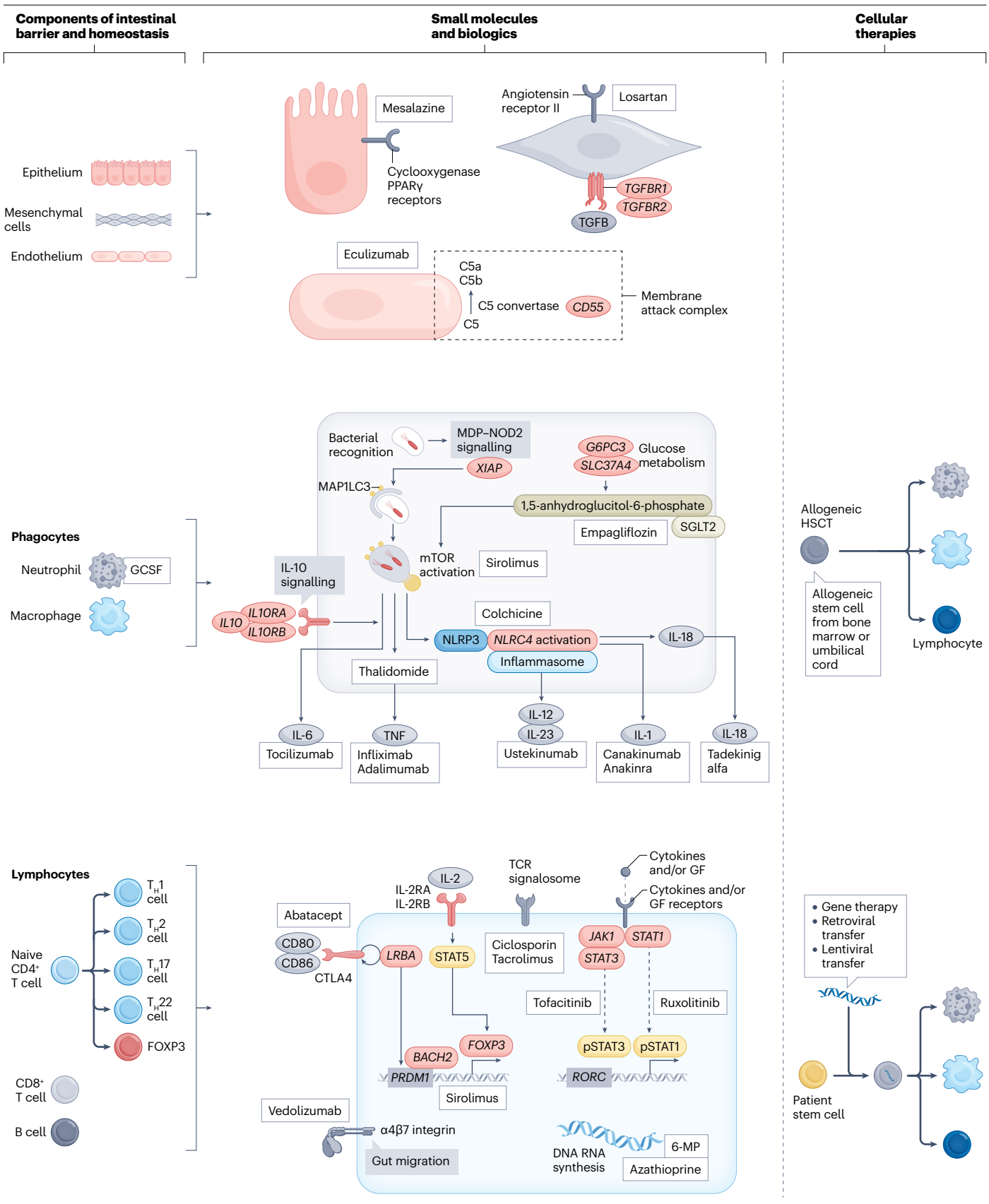

Components of intestinal barrier and homeostasis
Small molecules and biologics
Cellular therapies
Epithelium
Mesenchymal cells
Endothelium
Mesalazine
Cyclooxygenase PPARγ receptors
Angiotensin receptor II
Losartan
TGFBR1
TGFBR2
TGFB
Eculizumab
C5a
C5b
C5 convertase
CD55
C5
Membrane attack complex
Phagocytes
Neutrophil
GCSF
Macrophage
Bacterial recognition
MDP–NOD2 signalling
XIAP
MAP1LC3
G6PC3
SLC37A4
Glucose metabolism
1,5-anhydroglucitol-6-phosphate
Empagliflozin
SGLT2
mTOR activation
Sirolimus
IL-10 signalling
IL10
IL10RA
IL10RB
Colchicine
NLRP3
NLRC4 activation
Inflammasome
IL-18
Thalidomide
IL-6
Tocilizumab
TNF
Infliximab Adalimumab
IL-12
IL-23
Ustekinumab
IL-1
Canakinumab Anakinra
IL-18
Tadekinig alfa
Allogeneic HSCT
Allogeneic stem cell from bone marrow or umbilical cord
Lymphocyte
Lymphocytes
Naive CD4+ T cell
TH1 cell
TH2 cell
TH17 cell
TH22 cell
FOXP3
CD8+ T cell
B cell
IL-2
IL-2RA
IL-2RB
TCR signalosome
Cytokines and/or GF
Cytokines and/or GF receptors
Abatacept
CD80
CD86
CTLA4
LRBA
STAT5
Ciclosporin Tacrolimus
JAK1
STAT1
STAT3
Tofacitinib
Ruxolitinib
BACH2
FOXP3
PRDM1
Sirolimus
pSTAT3
pSTAT1
RORC
Vedolizumab
α4β7 integrin
Gut migration
DNA RNA synthesis
6-MP
Azathioprine
Gene therapy
Retroviral transfer
Lentiviral transfer
Patient stem cell

Fig. 1 | Proposed mechanisms of action for targeted therapies in mIBD. The use of several small-molecule therapeutics, biologics and cellular therapies, has been reported in patients with monogenic inflammatory bowel disease (mIBD). The potential mechanistic target of each therapeutic is highlighted. Although medications can affect several cellular compartments, one cellular group for each is highlighted. Inclusion of medications reflects literature reports and does not indicate a recommendation for use. 6-MP, 6-mercaptopurine; GCSF, granulocyte colony-stimulating factor; GF, growth factor; HSCT, haematopoietic stem cell transplantation; MAP1LC3, microtubule-associated protein 1A/1B-light chain 3; MDP, muramyl dipeptide; NOD2, nucleotide-binding oligomerization domain-containing protein 2; SGLT2, sodium/glucose cotransporter 2; TCR, T cell receptor.

colchicine treatment[33]. Whether patients with additional disorders (such as pathogenic *IL10RA* variants) respond to colchicine requires further investigation[34].

The use of mycophenolate mofetil, an inhibitor of inosine-5′-monophosphate dehydrogenase used to treat patients with solid organ transplantation, has been reported in individual patients with autoimmune conditions such as CTLA4 deficiency and colitis[35]. Caution is warranted as mycophenolate mofetil can induce colitis de novo[36]. In patients with autoimmune regulator deficiency, which is a defect of T cell selection causing inflammation in multiple organs and chronic diarrhoea but rarely colitis, mycophenolate mofetil seems to induce colitis, as reported in a case series[37].

Patients with Loeys–Dietz syndrome due to *TGFBR1* and *TGFBR2* mutations develop connective tissue abnormalities and intestinal inflammation[38]. The angiotensin receptor blocker losartan targets defective TGFβ signalling and has been primarily used to protect against cardiovascular connective tissue pathology in patients with Marfan syndrome or Loeys–Dietz syndrome[39]. Losartan also reduces disease activity in dextran sodium sulfate-induced[40] as well as 2,4,6-trinitrobenzenesulfonic acid-induced colitis in rodent models[41,42]. Preliminary reports suggest that losartan has no effect on colitis activity in patients with Loeys–Dietz syndrome[38].

Patients with disrupted glucose-6-phosphate metabolism due to *G6PC3* or *SLC37A4* variants develop severe forms of congenital neutropenia and, phenotypically, a Crohn's-like disease[2,43,44]. Glucose-6-phosphate translocase-deficient neutrophils accumulate 1,5-anhydroglucitol-6-phosphate, a structural analogue of glucose-6-phosphate, which impairs glycolysis[45]. Empagliflozin, an inhibitor of sodium/glucose cotransporter 2, rescued neutrophil function in a G6PC3-deficient mouse model[45]. Treatment of patients with SLC37A4 deficiency with empagliflozin improved neutrophil function and intestinal inflammation in individual patients[46,47].

Biologics in mIBD

Biologic therapies can target diverse molecules and pathways in patients with mIBD (Figs. 1,2 and Table 1). For example, they can target pro-inflammatory cytokines (such as TNF, IL-12 and IL-23, IL-1β and IL-1α, IL-6 and IL-18), cytokine receptors (such as the soluble and membrane-bound IL-6 receptor and the IL-2 receptor), and costimulatory molecules (CTLA4) (Table 1). Others, such as anti-CD20, deplete B cells or target immune cell migration by inhibiting the α4β7 integrin (Fig. 1 and Table 1). Further applications involve stimulation of granulopoiesis by granulocyte colony-stimulating factor (GCSF), inhibition of activation of complement C5 (using eculizumab) and restoring immunoglobulin levels in patients with humoral immunity disorders (Table 1).

As anti-TNF therapy is licensed for use in children and adults with IBD in several countries, anti-TNF therapy is the most widely used biologic therapy for patients with mIBD. TNF-targeting therapy (adalimumab, golimumab, infliximab and even etanercept (which is indicated for the treatment of psoriatic and rheumatoid inflammatory disease but not for IBD)) has been described in multiple mIBD conditions, with variable outcomes[2,9,11]. Clinical response has been observed in patients with pathogenic *HPS1*, *IKBKG*, *G6PC3*, *NPC1* or *BTK* variants in small case series or reports[9,48,49]. Low efficacy has been observed in patients with pathogenic *IL10RA*, *IL10RB* or *XIAP* variants (robust case series)[9]. No relevant therapeutic effects were reported in patients with pathogenic *TGFBR1*, *TGFBR2*, *WAS*, *MVK*, *TTC7A*, *SLCO2A1*, *SKIV2L* or *TTC37* variants (small case series or reports)[9].

Evidence for all other biologics licensed to treat classic IBD in patients over 18 years of age, including ustekinumab (anti-IL-12/23p40) and vedolizumab (anti-α4β7 integrin), is limited to a small number of mIBD gene variants and small numbers of patients (Table 1).

Dysregulated inflammasome activation and secretion of high levels of IL-1β and/or IL-18A are observed in several mIBD disorders. Patients with mevalonate kinase deficiency or CARD8 deficiency have been successfully treated with IL-1β blockade, using IL-1-targeting antibodies or the IL-1 receptor antagonist anakinra[50,51]. Anakinra therapy has also been reported in patients with pathogenic IL-10 signalling variants, CGD and *NLRC4* variants[52,53]. Likewise, gain-of-function variants in *NLRC4* and XIAP deficiency cause high levels of IL-18 (refs. 19,54,55). A patient with an *NLRC4* variant and a patient with XIAP deficiency-associated HLH and intestinal inflammation were successfully treated with tadekinig alfa[19,54].

CTLA4 insufficiency results in immune dysregulation due to defective inhibitory signalling between T cells and antigen-presenting cells. Abatacept, the fusion protein of CTLA4 and an immunoglobulin Fc region, can substitute for the lack of endogenous CTLA4, and it reduced inflammation in a small case series of patients with IBD due to CTLA4 insufficiency[20]. Similarly, as LPS-responsive beige-like anchor protein (LRBA) regulates CTLA4 protein degradation[56], abatacept also ameliorated IBD in a small case series of patients with LRBA deficiency[57].

In patients with complement regulatory protein CD55 deficiency, blocking activation of complement C5 using eculizumab has been reported consistently to resolve metabolic abnormalities and protein-losing enteropathy as well as Crohn's disease-like immunopathology in individual patients[58].

Advanced combination therapies

Emerging evidence suggests that advanced combination therapy with dual biologics can have positive therapeutic effects in patients with refractory IBD[59]. So far, the use of advanced combination therapies in children with mIBD is limited (examples include the anti-TNF infliximab plus ustekinumab in a patient with Niemann–Pick disease type C[60], anakinra plus infliximab, vedolizumab and/or tadekinig alfa in a patient with NLRC4-associated enterocolitis and HLH[54], and vedolizumab plus tadekinig alfa in a patient with XIAP deficiency[19]).

Growth factor substitution therapies

GCSF has been used to stimulate granulocyte numbers in patients with congenital neutropenia due to pathogenic *G6PC3* and *SLC37A4* variants, but intestinal inflammation is not effectively treated (small case numbers)[43,47,61].

Immunoglobulin replacement therapy

A number of mIBD disorders are associated with absent or reduced immunoglobulin levels (by definition agammaglobulinaemia, combined variable immunodeficiency disorders or combined immunodeficiencies). The role of immunoglobulin replacement therapy in the prevention of infections is established, but its effect for treatment or prevention of intestinal inflammation in patients with immunoglobulin deficiency, such as Bruton tyrosine kinase (BTK)-associated agammaglobulinaemia, is unclear[62].

Cellular therapies

Stem cell transplantation. Allogeneic HSCT corrects the haematopoietic cell compartment in several primary immunodeficiencies that cause intestinal inflammation. Therapeutic evidence to support the use of allogeneic HSCT in patients with mIBD caused by inborn errors of immunity has been described in at least 26 genetic aetiologies (*IL10RB*, *IL10RA*, *IL10*, *RIPK1*, *NCF4*, *LRBA*, *MALT1*, *CYBB*, *FOXP3*, *NCF1*, *STAT3*, *XIAP*, *ICOS*, *NCF2*, *CTLA4*, *IKBA*, *DOCK2*, *G6PC3*, *WAS*, *CD3G*, *ITGB2*, *STAT1*, *ADA2*, *DCLRE1C*, *PIK3CD* and *FCHO1*)[2,9,63]. HSCT is the de facto standard of care in patients with pathogenic variants associated with IL-10 signalling, CGD and IPEX syndrome, resolving immunodeficiency, intestinal inflammation and associated extraintestinal complications[64]. In addition to bone marrow as a source of stem cells, umbilical cord blood transplantation has also been reported in patients with *IL10RA* variants and infantile enterocolitis[65].

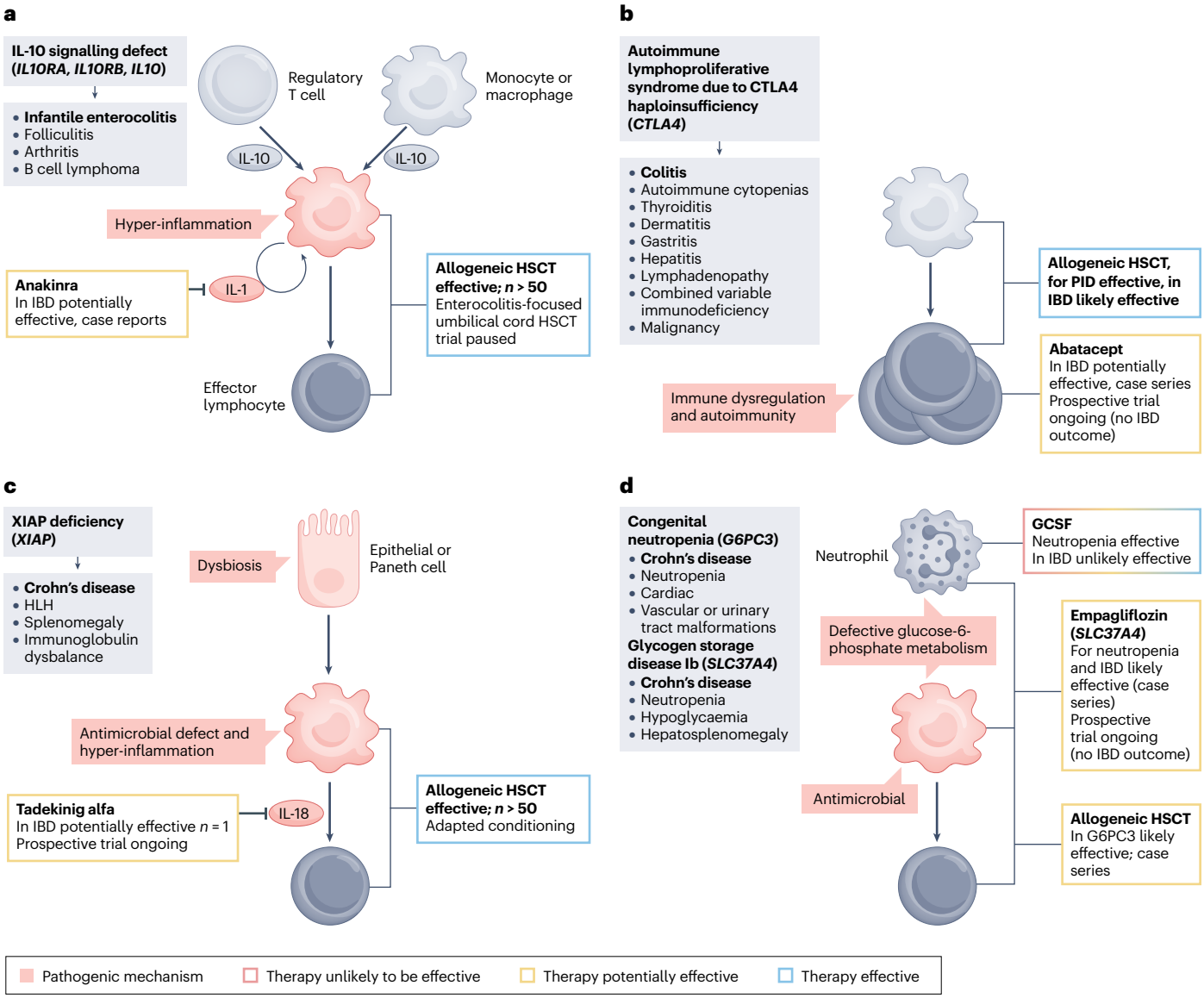


Fig. 2 | Examples of precision medicine in four mIBD groups. Disease manifestations, cellular and molecular mechanisms as well as precision medicine interventions are illustrated. Four monogenic inflammatory bowel disease (mIBD) groups are highlighted: IL-10 signalling defects (part **a**), CTLA4 haploinsufficiency (part **b**), X-linked inhibitor of apoptosis protein (XIAP) deficiency (part **c**) and pathogenic variants in glucose-6-phosphate metabolism (part **d**). GCSF, granulocyte colony-stimulating factor; HLH, haemophagocytic lymphohistiocytosis; HSCT, haematopoietic stem cell transplantation; IBD, inflammatory bowel disease; PID, primary immunodeficiency disease.

Some mIBD disorders, including those affecting epithelial and endothelial compartments (Fig. 1), are notably unsuitable for HSCT. In some disorders the gene product is expressed by a number of cell types, and intestinal inflammation might be driven by epithelial barrier defects, while infection susceptibility is caused by the immune defect, which explains why allogeneic HSCT can improve infection susceptibility but not intestinal inflammation, or why inflammation may recur after weaning off the immunosuppression after HSCT. For example, intestinal inflammation caused by NF-κB essential modulator (NEMO; encoded by *IKBKG*) or TTC7A deficiency is not corrected by HSCT, mostly due to persistent epithelial dysfunction[2]. Specialist advice, informed consent and multidisciplinary discussion are strongly advised before HSCT in patients without a genetic diagnosis and those with epithelial or combined immune–epithelial defects.

Somatic gene therapy. Somatic gene therapy that targets patient-derived stem cells offers advanced precision medicine as it corrects the underlying gene defect. This autologous approach enables replacement of the affected cellular compartment using less toxic conditioning regimens without risk of graft-versus-host-disease (GVHD), and hence avoids the need for subsequent immunosuppressive therapy. Successful resolution of intestinal inflammation has been described in patients with pathogenic *WAS* and *CYBB* variants after retroviral gene therapy of haematopoietic stem cells[12,13] (Table 1). Subsequently, patients with CGD and intestinal inflammation due to *CYBB* variants were successfully treated with lentiviral gene therapy in haematopoietic stem cells[14]. These studies provide proof of concept that gene therapy can resolve intestinal inflammation once the genetic defect is corrected in the appropriate cellular compartment.

Nutrition, microbiome and antibiotics in mIBD

Exclusive enteral nutrition is an established first-line treatment option for patients with paediatric-onset Crohn's disease[66]. Although many patients with mIBD have received exclusive enteral nutrition[21], there is limited evidence that exclusive enteral nutrition using polymeric or elemental diets has a consistent anti-inflammatory effect in mIBD. In some patients, exclusive enteral nutrition in combination with immunosuppressive and anti-inflammatory therapy might help by bridging to stem cell transplantation (*IL10RA* or *NCF1*)[67,68]. Nevertheless, dietetic support (by either enteral or total parenteral nutrition) has a major role in preventing nutrient deficiency and supporting growth. In disorders such as congenital sodium-losing diarrhoea or chloride-losing diarrhoea (due to variants in *GUCY2C*, *SLC9A3* or *SLC26A3*), electrolyte substitution therapy is essential[69–71].

Patients with mIBD frequently receive antibiotics and antifungal agents (such as itraconazole or posaconazole) to treat or prevent infections caused by an underlying primary immunodeficiency, or due to complications of intestinal pathology (perianal abscesses, fistulating disease)[72]. This can contribute to the bacterial and fungal dysbiosis observed in patients with mIBD[72–75]. Whether antibiotic treatments contribute to dysbiosis-induced inflammation or, conversely, are effective for treating or preventing the onset of intestinal inflammation in mIBD remains unclear.

Therapy response: outcome measures, risks and systematic bias

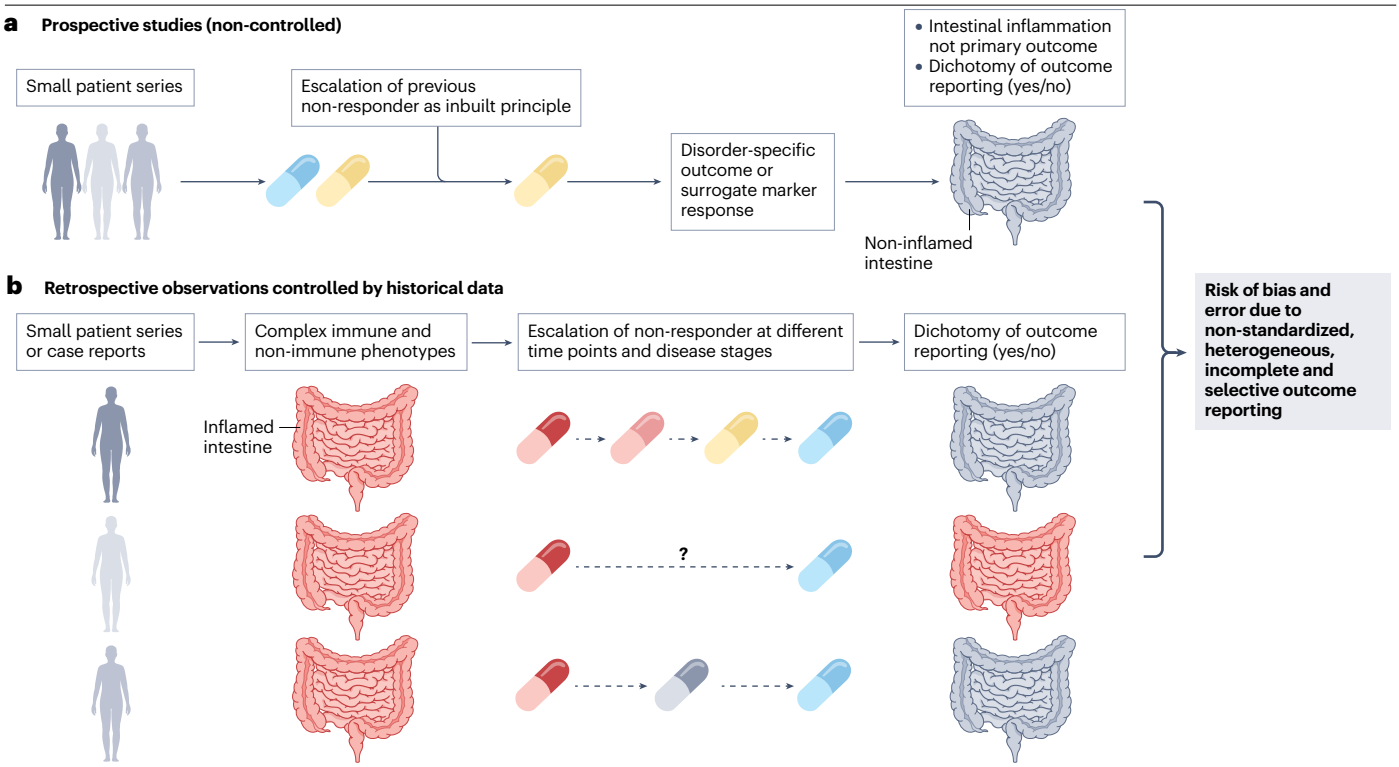
Reporting of treatment response in patients with mIBD

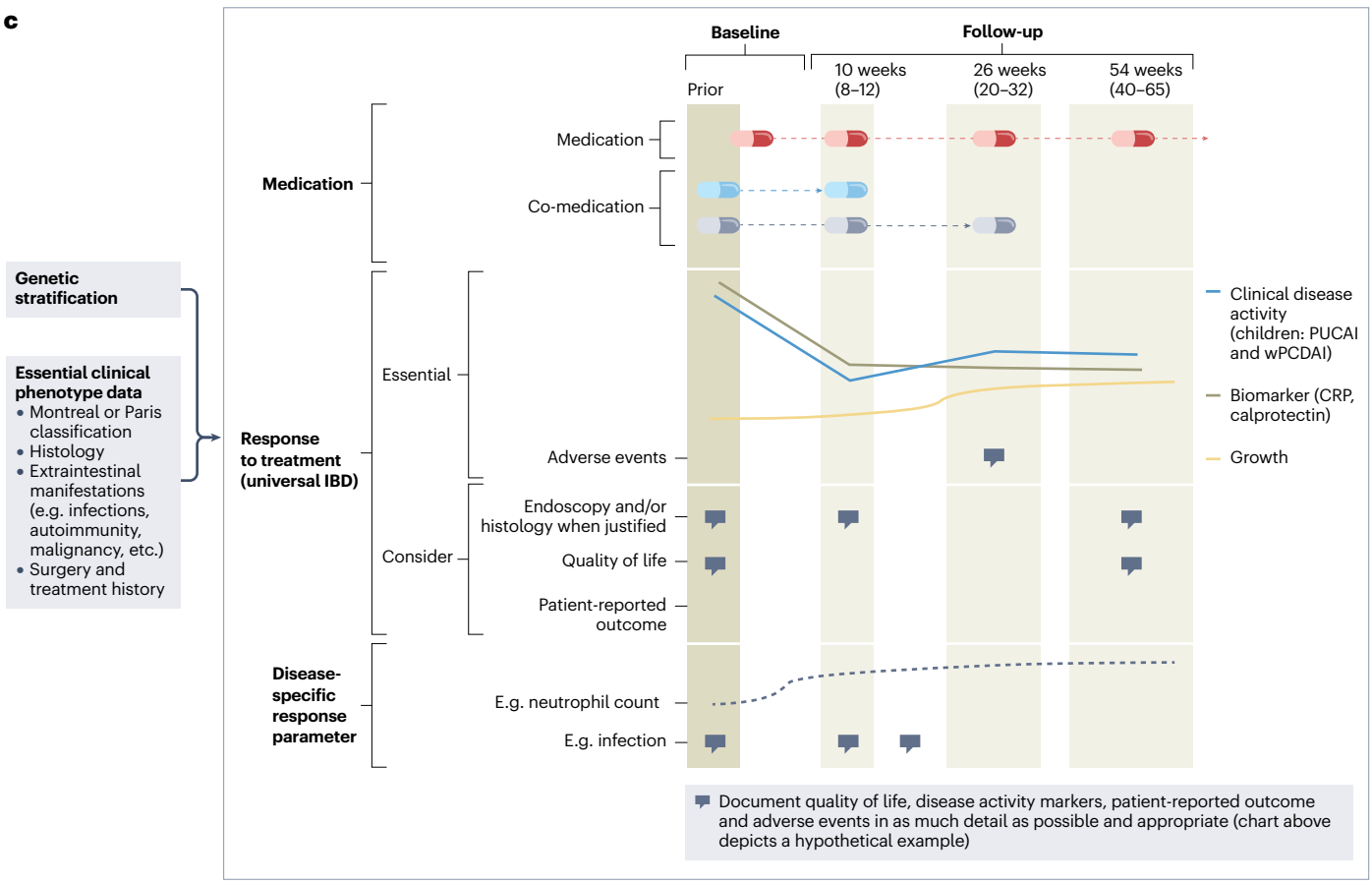
The reporting of response to treatment in patients with mIBD is heterogeneous. Variable details of baseline patient characteristics are provided, and heterogeneous parameters document response to therapy. Even essential baseline characteristics for mIBD, such as a clear description of the causative genetic variants, are not always reported. Patients are treated at different ages and at different stages of their disease (directly after disease onset as a neonate[76] or decades after disease onset[43,77]). Although intestinal inflammation has a complex immunopathology, many reports provide a single parameter and a dichotomous outcome (for example, 'inflammation resolved' or 'response' versus 'non-response' or 'successfully treated' versus 'failure'). Furthermore, studies that report outcomes of allogeneic HSCT often focus on a haematological perspective and report either a dichotomous outcome for intestinal inflammation, or none at all[78]. These descriptors are overly simplistic, lack precision and are likely to overlook critical clinical features relating to intestinal inflammation that are important for patient welfare.

There are established quantitative parameters to evaluate response to therapy in clinical trials or to define treat-to-target strategies in classic paediatric and adult IBD[79,80]. A few reports and case series in patients with mIBD suggest that it is feasible and informative to report symptomatic disease activity (for example, the Paediatric Ulcerative Colitis Activity Index (PUCAI) or the weighted Paediatric Crohn's Disease Activity Index (wPCDAI)) or inflammatory biomarkers (such as C-reactive protein (CRP) or faecal calprotectin) as quantitative markers of response[48,75,81]. Longitudinal analysis of inflammatory markers such as CRP before and after intervention can be a powerful tool to assess response to intervention[43,77]. Whereas these examples show the value of a quantitative assessment of therapy response in mIBD, most observational retrospective studies lack these data. Currently registered prospective studies investigating patients with monogenic conditions that are likely to include patients with an IBD phenotype do record intestinal inflammation as a secondary assessment criterion, but do not specify disease activity. For instance, a trial of tadekinig alfa in patients with XIAP deficiency and pathogenic *NLRC4* variants (NCT03113760) is assessing macrophage activation, systemic inflammation and gut dysfunction by stool frequency, but no quantitative IBD activity scores, biomarkers of intestinal inflammation or endoscopic appearance as specified secondary outcomes. Similarly, the evaluation of empagliflozin for neutropenia in glycogen storage disease type 1B and G6PC3 deficiency is highly relevant to patients with intestinal inflammation[46,47], but inflammatory complications are not a specified outcome measure (NCT04138251).

Longitudinal data are required to assess the efficacy of mIBD treatments, as medications used for classic IBD suggest that differences in the kinetics of therapeutic responses can be expected during induction therapy (for example, there are different kinetic response profiles between anti-TNF therapy and vedolizumab)[82], and long-term maintenance of remission is an important measure of overall health-related quality of life. Published mIBD case series rarely reflect this longitudinal perspective, and lack information on the overall period of medication exposure, making it difficult to assess the mid-term and long-term maintenance of clinical remission, as well as adverse events. Although corticosteroid-free remission is a universal therapeutic goal and outcome measure in IBD, many studies of mIBD do not confirm that remission or maintenance of remission is achieved without the use of corticosteroids. For pharmacological interventions, long-term outcome data based on years of follow-up are largely missing in patients with mIBD.

Despite being a fundamental goal of medical therapy, improvement of health-related quality of life and resolution or prevention of disability are rarely reported using standardized quantitative tools in


a Prospective studies (non-controlled)
Small patient series
Escalation of previous non-responder as inbuilt principle
Disorder-specific outcome or surrogate marker response
• Intestinal inflammation not primary outcome
• Dichotomy of outcome reporting (yes/no)
Non-inflamed intestine
b Retrospective observations controlled by historical data
Small patient series or case reports
Complex immune and non-immune phenotypes
Escalation of non-responder at different time points and disease stages
Dichotomy of outcome reporting (yes/no)
Inflamed intestine
?
Risk of bias and error due to non-standardized, heterogeneous, incomplete and selective outcome reporting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Genetic stratification
Essential clinical phenotype data
• Montreal or Paris classification
• Histology
• Extraintestinal manifestations (e.g. infections, autoimmunity, malignancy, etc.)
• Surgery and treatment history
Baseline
Follow-up
Prior
10 weeks (8–12)
26 weeks (20–32)
54 weeks (40–65)
Medication
Medication
Co-medication
Response to treatment (universal IBD)
Essential
Consider
Adverse events
Endoscopy and/or histology when justified
Quality of life
Patient-reported outcome
Disease-specific response parameter
E.g. neutrophil count
E.g. infection
Clinical disease activity (children: PUCAI and wPCDAI)
Biomarker (CRP, calprotectin)
Growth
Document quality of life, disease activity markers, patient-reported outcome and adverse events in as much detail as possible and appropriate (chart above depicts a hypothetical example)

Fig. 3 | Therapeutic studies in mIBD and the mIBD REPORT standards. a,**b**, Key aspects of published prospective trials and reported retrospective observational studies in patients with monogenic inflammatory bowel disease (mIBD). Both prospective studies and observational retrospective studies have investigated a small number of patients with heterogeneous phenotype. The intervention is therapy escalation in patients who did not previously respond to conventional treatments. The response to therapy is often provided as dichotomous outcomes (responder/non-responder) which fails to reflect the complexity of intestinal pathophysiology. **c**, Illustration (in the form of a hypothetical example of a patient's treatment course) of the proposed mIBD REPORT (monogenic Inflammatory Bowel Disease Report Extended Phenotype and Outcome of Treatments) standards that describe key parameters to characterize the patient and to assess response to therapies. These include genetics and essential clinical phenotype data, as well as medication, and a structured follow-up that reflects universal therapeutic goals in IBD and disease-specific response parameters. CRP, C-reactive protein; PUCAI, Paediatric Ulcerative Colitis Activity Index; wPCDAI, weighted Paediatric Crohn's Disease Activity Index.

patients with mIBD. There is a striking lack of patient or parent perspectives in the literature of mIBD, although qualitative parent perspectives are available for some disorders[83].

Risks and complications of treatment

Paediatric patients with mIBD are susceptible to complications and mortality due to their underlying genetic condition or treatment effects, or both. Increased susceptibility to infection and reduced survival have been described in patients with CGD-associated IBD treated with anti-TNF therapy[84,85]. Although potentially curative in several mIBD conditions, HSCT is associated with substantial morbidity and mortality, which is partially transplant-related (myeloablation-related, infection risk and GVHD) and partially influenced by the genotype. To differentiate disease-related and treatment-related risks, it is therefore important to compare the proportions of patients with acute gastrointestinal GVHD and short-term and mid-term survival between those with and without pretransplant IBD[64]. In patients with XIAP deficiency, which involves a gene expressed by haematopoietic and non-haematopoietic cells[2], HSCT can resolve intestinal inflammation, but intestinal complications and GVHD are more common than in those with other inborn errors of immunity, despite reduced toxicity regimens that have been introduced in the care of patients with XIAP deficiency[64,75,78]. Several patients who received retroviral vector gene therapy for both X-linked CGD and Wiskott–Aldrich syndrome developed leukaemias owing to genotoxic off-target effects[86].

It is also necessary to investigate and exclude other disease-specific and treatment-specific risks that could act synergistically. Several medications used to treat patients with mIBD carry generic risks that are particularly relevant to individual mIBD disorders. For example, azathioprine, which can cause clinically relevant lymphopenia[87], might further aggravate lymphopenia in patients with mIBD with hypomorphic (also known as 'leaky') severe combined immunodeficiency. Medications such as thalidomide have been used in patients with IL-10 signalling problems but are associated with exceptionally high risks of adverse events, such as severe developmental abnormalities requiring extreme caution in women of child-bearing age[34]. In patients with the neurodegenerative cholesterol storage disorder Niemann–Pick disease type C, as a result of which some patients develop a severe phenotype of Crohn's disease, it is particularly important to assess whether anti-TNF therapy is effective and to ensure that this treatment does not aggravate the neurological condition (anti-TNF therapy can cause rare but severe neurological side effects)[48].

Sources of bias in therapeutic mIBD studies

Reporting bias is common in the field of rare diseases. Reports or small case series are particularly prone to bias, as it is more likely that a successful outcome will be published and many studies will be under-powered[88]. For example, resolution of intestinal inflammation was reported for IL-1-targeting therapies in patients with CGD[89], but this was not observed in subsequent series[90].

A further confounder is reporting on the effect of treatment at different disease stages. In some case series, the initial stage is reported and in others late-stage disease is reported, at which point inflammation or intestinal resection, for example, might already have caused irreversible organ damage.

Treatment reports of patients with mIBD can reflect the health-care system in which patents are supported. Countries have different regulations regarding off-licence therapeutics, availability of adult-licensed medications in children, and availability of HSCT. Because of differences between health-care systems, insurance might cover treatments in some countries but not in others. In some systems, effective medication is not available to some patients due to unaffordability. This is relevant not only to individual patients and families, but becomes a source of bias in scientific analysis of genotype-related treatments, as genetic disorders are not homogeneously distributed worldwide. For example, pathogenic *IL10RA* variants are more prevalent in East Asia (China, Japan and Korea)[76,91] and a *HPS1* variant is prevalent in Puerto Rico[49].

There are further challenges. Novel therapeutics might be compared with 'best practice', or historical interventions. This can add bias, because best practice changes over time; for example, the success rates of HSCT in patients with XIAP deficiency changed after the introduction of reduced toxicity conditioning regimens[78,92]. All of these factors illustrate the complexity of the multiple mIBD conditions and of clinical decision-making in the real world.

Opportunities and systematic barriers to precision medicine

As discussed previously, the mIBD literature reveals exceptional opportunities for targeting biologically plausible pathways based on genetic information. Although preclinical and clinical pilot studies have suggested plausible treatments for a precision medicine approach, we have outlined major methodological difficulties in assessing the efficacy of medications (Fig. 3a,b). A systematic and comparative approach is required to assess response to therapy in the vast majority of >100 mIBD conditions, given that over 25 different interventions have already entered the clinical setting and many more are in preclinical development. Examples such as the use of HSCT for IL-10 signalling variants[16], recombinant human IL-18-binding protein for XIAP deficiency[19], CTLA4 fusion protein for CTLA4 insufficiency[93,94], empagliflozin for abnormalities in G6P metabolism[47] and gene therapy for CGD[14] illustrate that translating studies in preclinical models towards clinical studies can occur rapidly in all classes of therapeutics (Fig. 2).

However, there are systematic barriers to assessing the efficacy of therapeutic interventions in the field of mIBD (Box 1). Owing to the

small numbers of patients reported, diverse conditions and heterogeneous outcome measures, conclusive data on outcomes are currently restricted to a few interventions (such as anti-TNF therapy or HSCT) and a few gene variants (such as pathogenic IL-10 signalling variants, CGD, FOXP3-associated IPEX syndrome and XIAP deficiency). There is therefore an unmet need for more data before patient management recommendations for most interventions can be established[2,7,9,11].

It is important to note that patients with mIBD are excluded from high-quality prospective trials (usually per protocol) in classic IBD for two reasons: expected differences in pathophysiological mechanisms and uncertain safety profile. This omission means that prospective trials need to be encouraged for individual mIBD conditions. One difficulty is the rarity of patients with these orphan disorders. In addition, many patients with mIBD are very young at disease onset. Innovative study designs that aim to minimize the overall number of participants are needed whilst maximizing the data generated offer potential solutions. Potential approaches to generate stronger evidence include the use of biomarkers for response, crossover trials, adaptive trials, early

Box 1

Opportunities and barriers in the development of drugs for patients with mIBD

Need and opportunities for mIBD orphan disease precision drug development

- Monogenic inflammatory bowel disease (mIBD)-related genes control essential functions of the gastrointestinal barrier and immune system
- Protein-coding gene variants inform functional mechanisms, providing an opportunity to observe direct target engagement of medications with strong effect size
- Strong unmet clinical need because standard IBD care frequently fails
- mIBD provides an opportunity to develop precision medicine approaches guided by the gene defect present, the pathway affected and the pathology

Barriers in orphan drug development in mIBD

- mIBD conditions cause intestinal inflammation via diverse mechanisms
- Most mIBD conditions are ultra-rare, with a fragmented patient population
- High costs of prospective multicentre trials that involve multiple countries
- The mIBD patient populations have high numbers of patients with IBD onset under 2 years of age, a study population that is typically excluded from clinical trials for safety reasons
- Therapies have licence restrictions for use in infants or paediatric patients and lack safety data; off-licence use of medications is common practice due to lack of alternatives
- The likelihood is high that unforeseen side effects occur or that the expected natural history proceeds
- Lack of prospective data collection leads to missing data, causing outcome analysis based on incomplete data
- Heterogeneity of care due to different clinical standards and health-care system differences in geographical distribution in certain disorders (for example, *HPS1* variant in Puerto Rico, pathogenic *IL10RA* variants more common in East Asia) can become confounding factors
- IBD might only be one of many concurrent immunodeficiency and inflammatory processes that drive treatment selection (dermatitis, abscesses, endocrinopathy, etc.)
- Heterogeneity in outcome reporting due to differing focus of clinical specialities (immunology, haematology, metabolism, gastroenterology)
- Dichotomous outcome reporting is insufficient to assess response to therapy; quantitative outcome measures for disease activity and markers of inflammation recommended in classic IBD studies are often not applied; histopathological validation is lacking
- Clinical activity scores and biochemical markers to assess disease activity are rarely validated in very young children and might differ among different groups of patients with mIBD; assessment tools might be confounded by disease-specific manifestations (for example, clinical activity scores that use haemoglobin might be affected by bleeding due to intestinal inflammation as well as by coagulation defects, or hypoalbuminaemia might be caused by inflammation as well as by protein-losing enteropathy)
- Promising disease activity biomarkers need validation (IL-18 in XIAP deficiency, soluble IL-2 receptor in CTLA4 deficiency)
- Outcome reporting typically lacks assessment of quality of life
- For treatments such as haematopoietic stem cell transplantation (HSCT) and gene therapy, there is no standard reporting system to assess resolution of intestinal inflammation
- Comparability among treatments is difficult, due to different kinetics of interventions (biologics such as anti-TNF or ustekinumab (weeks to months), vedolizumab (months) and HSCT (months to years)), yet outcomes at a single time point are reported
- Variability of therapeutic responses in patients with mIBD might be influenced by confounding factors (for example, microbiome, antibiotics and diet)
- Lack of longitudinal and long-term outcomes data
- Reporting bias: reportedly successful treatment strategies become commonplace with the risk of creating de facto standards of care for individual genetic diseases based on weak and biased evidence

escape designs and repeat application[95,96]. For example, crossover repeat intervention trials can demonstrate statistically significant effects after starting and stopping an intervention in single patients. This increases the number of intervals in which patients are exposed to a drug, which enables individual and statistical evaluation (an extreme example of this is $n = 1$ trials).

Only international collaboration using standardized reporting of data will establish the data that are required to perform meta-analysis of prospective or retrospective series across disorders and across treatments. Owing to geographically dispersed patient populations, multicentre trials or observational studies are required to achieve sufficient patient recruitment. This recruitment can best be achieved by multinational research consortia (such as the VEO-IBD Consortium, COLORS in IBD, and the Genius group) or rare disease registries[97]. To increase the comparability of data, it is important to capture baseline demographic and disease-specific parameters in cohorts and rare disease database platforms[98] according to established standards, or to develop such standards.

One strategy to increase the quality of datasets and the number of patients with mIBD included is to assess the effects of medications across groups of patients with similar phenotypes and shared functional mechanisms across genotypes[2]. For example, it would be legitimate to assess therapeutics that target the IL-10 signalling pathway in patients with *IL10RA* as well as *IL10RB* variants who present with infantile enterocolitis and perianal disease. Similarly, it would be a useful approach to assess the effects of therapies in patients with complex immune dysregulation presenting as IPEX or IPEX-like syndrome due to *FOXP3* and *IL2RA* variants, in patients with multiple intestinal atresia due to pathogenic *TTC7A* and *PI4KA* variants[99], and in patients with Loeys–Dietz syndrome due to defective TGFβ signalling caused by *TGFBR1* or *TGFBR2* variants. These are limited examples, but the principle of exploratory evaluation across diseases with similar functional pathogenesis needs to be recognized by the clinical community, ethical committees and regulatory authorities.

Best practice curative approaches exist for some mIBD conditions, such as HSCT for IL-10 receptor variants. Nonetheless, some patients decline HSCT because of the risks (which include transplant-associated lethality and concerns about future fertility), or there may be an absence of a suitable stem cell donor. In some health-care systems, patients might not be offered HSCT due to financial constraints. Consequently, research is required to identify additional effective medications even in disorders for which a standard of care has been established. Trials or observations assessing novel pharmacological medications in these disorders should therefore focus on the 'bridging' window between genetic diagnosis and potential HSCT, enabling collection of therapeutic evidence while offering evidence-based management for the condition.

Many patients with mIBD receive targeted, precision-directed treatments, but are managed in the context of a clinically oriented assessment of their best interests, rather than a formal trial setting. This is, in principle, at odds with the established ethical practice of research, which distinguishes between biomedical research and the practice of accepted therapy[100]. To ensure that the best interests of patients are met, ethical opinion can help to clarify where off-licence or compassionate use of medications and observational translational research can overlap[101]. Care is defined with reference to best practice, based on an evaluation of published literature and specialist input. Observational studies such as case reports or series are an incomplete surrogate for controlled prospective studies, but nevertheless they reflect real-world evidence that must be collected with the aim of drawing generalizable conclusions. Measuring each patient's response using accepted parameters that are in use, for and against a set of parameters that are accepted in classic IBD, seems to be a pragmatic step to improve the quality of care. In addition, such an approach might generate the type of real-world evidence that would also benefit retrospective observational studies investigating those patients who consent to research.

Assessment of therapeutic off-licence interventions as part of best practice in real-world settings is an overarching systematic problem in mIBD as it can compromise the generalizability of observational studies. Standardized reporting of data and study design features represent a mechanism for providing quality assurance, enhancing generalizability and minimizing bias in clinical research (for example, CONSORT criteria, STROBE criteria or reporting $n = 1$ trials)[102].

Defining therapeutic goals in mIBD

Defining therapeutic goals, and measures to quantify whether goals are achieved, is an emerging concept in classic IBD. On the basis of clinical evidence, targets to treat can be defined and clinically relevant outcome measures can be used in observational and clinical studies. In mIBD, defining essential therapeutic goals and using pragmatic quantitative measures will be a step forward.

Overall health-related quality of life is the key consideration for supporting patients with mIBD. Despite clear differences between mIBD and polygenic IBD patient populations in terms of age at onset and diverse extraintestinal manifestations, several IBD-centric therapeutic goals for classic IBD can be adapted for use in patients with mIBD.

Although resolving intestinal inflammation, enabling appropriate growth and normalizing quality of life are universal therapeutic goals in patients with IBD, including mIBD (Box 2), additional considerations need to be implemented to reflect problems specific to the underlying inborn errors of immunity, mucosal barrier function defects or other organ pathologies seen in mIBD. Disease-specific aims should include prevention of infections, prevention and treatment of autoimmunity, HLH and malignancy, numerical and functional normalization of immune cell populations, and prevention of neurological decline.

Standardized reporting

There are two critical factors in evaluating treatment response in patients with mIBD: the availability of data that allow the assessment of genetic and phenotypic heterogeneity of patients, and standardized parameters that can measure whether a therapeutic response was observed. To facilitate this, we propose a reporting standard to assess genetic and disease-specific data, integrated with a catalogue to assess interventional medical treatments.

As part of this Expert Recommendation, we have created 'mIBD REPORT' (monogenic Inflammatory Bowel Disease Report Extended Phenotype and Outcome of Treatments) standards to help clinicians, patients and their family assess response to therapy, based on a range of relevant parameters (Box 2 and Fig. 3c).

Parameters of the mIBD REPORT standards are molecular diagnostics, intestinal and extraintestinal disease characteristics, descriptors of the intervention, and criteria to assess therapeutic goals after starting the intervention and whether adverse events occurred (Box 3). Molecular diagnostics include details of suspected pathogenic genetic variants and any related functional data, while

clinical characteristics should include age at IBD onset, Paris or Montreal criteria, endoscopic and histological assessments to confirm the diagnosis, disease extent and activity, and a record of extraintestinal manifestations and comorbidities (which is particularly relevant to inborn errors of immunity). Regarding the intervention, relevant parameters reflect therapeutic goals and recommendations of the STRIDE-II position statement[80], including measures of disease activity as a framework for mIBD. Documentation should include the intervention and changes in co-medication during the intervention, as these can indicate therapeutic success (for example, ability to reduce steroids or achieve steroid-free status) or failure (stopping the interventional medication, or the use of rescue co-medications). Therapeutic goals include clinical remission and biomarker response (CRP and faecal calprotectin), the maintenance of remission, restoring growth, preventing IBD-related disability and normalizing health-related quality of life. The mIBD REPORT standards include a proposal to record potential adverse events, whether or not they are considered probably related or attributable to the intervention.

The parameters overlap with evidence-based recommendations for clinical trial design in paediatric IBD, as formulated by the paediatric European Crohn's and Colitis Organisation (P-ECCO) committee[79] and PIBDnet[103]. The recommendations reflect the importance of assessing induction and maintenance of steroid-free clinical remission and mucosal healing, the use of validated disease activity indices, the role of quantitative biological markers of inflammatory disease activity, and safety. As patients with mIBD can present with Crohn's disease, ulcerative colitis or unclassified IBD phenotypes[28], a pragmatic approach is to record both the PUCAI and the wPCDAI in paediatric patients with mIBD. The endoscopic and histological assessment defines mucosal disease activity, although surrogate markers do correlate with disease activity[104,105]. In adults, the Simple Clinical Colitis Activity Index and the Ulcerative Colitis Endoscopic Index of Severity are recommended for ulcerative colitis, and the Harvey–Bradshaw Index and the Simple Endoscopic Score are recommended for Crohn's disease[106].

The set of parameters are based on practicality and comparability across clinical care settings in the world, and limiting invasiveness for the individual patient while collecting the dataset most likely to be meaningful. We acknowledge the limitations that few markers of response to therapy used in classic IBD are validated in infants or patients with mIBD. Indeed, due to the heterogeneous molecular basis of mIBD, it is possible that in certain conditions, such as pathogenic IL-10 signalling variants, CGD or XIAP deficiency with monocyte, macrophage and neutrophil activation, biological parameters, such as CRP or faecal calprotectin, have different weights in mIBD than they do in epithelial disorders with mild lymphocytic infiltration (such as those caused by *EPCAM* mutations).

Box 2

mIBD REPORT standards: expert recommendations

1. Therapeutic goals for treating patients with monogenic inflammatory bowel disease (mIBD) should reflect the individual patient's health-related quality of life (including emotional and social functioning, intestinal and extraintestinal inflammatory problems, etc.) as well as disorder-specific prognostic considerations (for example, infection susceptibility, organ damage due to autoimmunity, need for enteral and parenteral nutrition, development and growth, tumour susceptibility, effect of available therapies, etc.) (agreement 96%)
2. In principle, the therapeutic goals defined for conventional IBD do apply in patients with mIBD (for example, to achieve clinical and endoscopic remission to normalize inflammatory biomarkers, to improve quality of life and to enable normal growth); treatment options need to be considered as these therapeutic goals may be challenging to achieve, some of the tools to assess response to therapy may not be valid in the youngest age group, and treatment of extraintestinal disease needs to be balanced (agreement 96%)
3. mIBD REPORT (monogenic Inflammatory Bowel Disease Report Extended Phenotype and Outcome of Treatments) standards are a set of parameters (molecular diagnostics including genetics, phenotype, intestinal inflammation and extraintestinal disease, treatment and adverse events) aiming to characterize the patient's disease burden and activity at baseline and describe the intestinal response to therapy over time (there is insufficient evidence for uniform outcome targets based on mIBD that disproportionately affect very young patients, components of the mIBD REPORT parameters will be of differential value for individual disorders, and additional parameters might be relevant to the characterization of disease activity for the individual patient and disorder) (agreement 92%)
4. Off-licence treatment of patients with mIBD in clinical practice should be documented via mIBD REPORT standards to assess whether universal IBD treatment goals are achieved; a standardized documentation will allow a patient's response to be compared with response to medications in the patient's history as well as with published responses to interventions (agreement 92%)
5. Observational studies, including case reports, on therapies in patients with mIBD should report standardized outcomes; mIBD REPORT standards may complement study-specific parameters and these may be provided as supplementary information (agreement 96%)
6. Performers of prospective clinical trials that investigate therapies for intestinal inflammation in patients with monogenic disorders are encouraged to implement mIBD REPORT standards as outcome measures, or to report mIBD REPORT parameters as supplementary information; in prospective trials that do not focus on intestinal disease but that are likely to recruit patients with mIBD, the collection of mIBD REPORT standards as descriptive supplementary information is encouraged (agreement 96%)

Box 3

mIBD REPORT standards

Molecular diagnostics

- Monogenic inflammatory bowel disease (mIBD) variant(s) identified (protein, cDNA and DNA sequence variant nomenclature requested) pathogenic or likely pathogenic classification system (for example, ACMG guidelines or in silico scoring system(s))
- Any associated functional data such as protein expression, signalling activity, etc.

Clinical characteristics

- Diagnosis (Crohn's disease, ulcerative colitis, IBD unclassified); disease extent and behaviour according to Paris or Montreal classification and histological confirmation of IBD; recent endoscopic disease activity; preferably measured with validated tools (UCEIS, SES-CD)[a]
- Age at IBD onset and diagnosis (year/month)
- History of surgery (in particular resections)
- Previous IBD-related medications (and why discontinued: primary or secondary lack of activity or side effects; steroid dependence)
- Comorbidities and extraintestinal manifestations (infections, autoimmunity, skin, joints, liver, neurological disorders) with age at onset

IBD-related response to therapy

Baseline prior to therapy (or intervention)

- Clinical disease activity (paediatric patients PUCAI and wPCDAI[b], preferably both; adult patients PRO2)
- Inflammatory disease activity (serum CRP, and faecal calprotectin)[b]
- Current medication and co-medication (including corticosteroids, antibiotics and exclusive enteral nutrition)
- Growth (paediatric patients according to WHO charts)
- Other disease-specific markers if applicable and clinically justified

Follow up after start of the therapy at week 10 (8–12), week 26 (20–32) and week 52 (40–65)

- Define the therapy setting (off-licence clinical setting, retrospective analysis, prospective trial, compassionate use of unauthorized medicine, and its respective approval and consent processes)
- Define the intervention (medication name, dose, route)[c,d]
- Report changes in medication and co-medication (including corticosteroids, antibiotics and exclusive enteral nutrition, confirm steroid-free intervals)
- Report disease activity index (paediatric patient PUCAI, wPCDAI, preferably both; adults PRO2)[b]
- Report IBDQ or other validated quality of life assessment[e]
- Report biomarker response (serum CRP, and faecal calprotectin)[b]
- Consider endoscopy, report endoscopic disease activity and histological healing if procedure clinically indicated and justified[a]
- Growth (paediatric patients) according to WHO charts
- Report all potential side effects and adverse events
- Report the overall period of the intervention (months on medication), and preferably record long-term structured updates (annual)
- Consider parent and patient perspective

Report response to therapy in regard to disease-specific manifestations and biomarkers (examples)

- Neutropenia in congenital neutropenia
- Liver function tests in autoimmune liver disease
- Infection events in inborn errors of immunity
- Serum IL-18 level in XIAP deficiency or if pathogenic *NLRC4* variants are present
- Serum soluble IL-2 receptor in *CTLA4* haploinsufficiency

ACMG, American College of Medical Genetics and Genomics; CBC, complete blood count; CRP, C-reactive protein; HSCT, haematopoietic stem cell transplantation; IBDQ, Inflammatory Bowel Disease Questionnaire; mIBD REPORT, monogenic Inflammatory Bowel Disease Report Extended Phenotype and Outcome of Treatments; PRO2, two-item patient-reported outcome; PUCAI, Paediatric Ulcerative Colitis Activity Index; SES-CD, Simple Endoscopic Score for Crohn's Disease; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; wPCDAI, weighted Paediatric Crohn's Disease Activity Index; XIAP, X-linked inhibitor of apoptosis protein. [a]Endoscopy when clinically justified; preferred to confirm mucosal healing over pure biomarker assessment or imaging such as ultrasonography or MRI. [b]Suggested minimal clinical activity indices: PUCAI or wPCDAI; and laboratory assessment CBC, CRP, ESR, albumin and faecal calprotectin. [c]For HSCT report type of donor and degree of HLA compatibility, conditioning chimerism after HSCT, and evidence for graft-versus-host disease. [d]Where relevant, consider specifying if intervention-specific precautions were applied (for example, prophylactic antibiotics or special vaccines required for certain immunosuppressive medications). [e]Health-related quality of life is a target to treat, but no validated quantitative parameter in the group of very young children with mIBD.

To incorporate a longitudinal element into clinical reporting, we suggest measuring the effect of the intervention at four intervals, covering at least 1 year of follow-up (baseline, 10 weeks, 26 weeks and 52 weeks). This will enable different response kinetics of interventions to be assessed in relation to short-term and mid-term therapeutic goals.

Completeness of reporting should be documented in observational studies, so that no treated patient is omitted, thereby reducing reporting bias.

Endoscopic response or histological healing is important information. As this requires endoscopic and histological investigation before and after the intervention, obtaining this information will depend on clinical need or a defined study protocol in prospective trials. Additional investigations (such as measuring IL-18 levels in the serum of patients with XIAP deficiency or *NLRC4* variants) might provide disease-specific biomarkers for assessment of disease activity, but such investigations might affect feasibility in clinical practice and

are therefore restricted to research studies until the biomarkers are validated as markers of disease activity.

Implementing a patient and family perspective is a key consideration in clinical practice and is highly valuable in research studies. Patient-reported and/or parent-reported outcomes that complement mIBD reports are desirable. Improving quality of life is a fundamental goal of all medical practice, but is difficult to quantify in a standardized way, especially with the extremely variable challenges faced by patients with mIBD disorders and their family. A validated generic instrument (such as EQ5D-5L, the IBDQ or SF-12/36, or parent-completed survey SF10) is preferred, in the absence of a disease-specific instrument. Patients or family might collect these data themselves using digital systems[107].

We hope that this framework for mIBD REPORT standards will enable assessment of therapeutic responses in patients managed in routine clinical care, and facilitate comparability of observational studies or prospective trials.

Limitations and future directions

This Expert Recommendation has several limitations. Among these, as our analysis acknowledges, is the limited biological understanding of many of these mIBD disorders and that for most therapies the evidence is fragmented. In light of these limitations, we have proposed recommendations to guide principles of precision medicine for patients with mIBD and reached a consensus on mIBD reporting to assess response in clinical practice and to support research. We suggest a set of recording parameters, acknowledging that some of the parameters suggested have limitations (which need to be specified in future studies). For example, the wPCDAI and PUCAI scores are not yet validated measures in patients with IBD under 2 years of age. In addition, CRP is only useful in mIBD conditions in which systemic inflammation is a component. Stool calprotectin has limited sensitivity in very young infants or in some regions in the world where very high faecal calprotectin levels are observed in healthy children (for instance, due to the high prevalence of subclinical infections)[108].

Although we tried carefully to reduce systematic bias in the selection of specialists involved, the process was not based on an open call and the recommendations were not established under the umbrella of an established medical society or organization. Patient organizations were consulted, but were not included as active participants in the recommendation process.

Our analysis highlights a number of future directions. Use of large-scale health-care data can help to analyse disease presentations, confounders and treatment responses[36]. Meta-analysis of standardized case reports and access to prospective and retrospective registries as well as patient-reported data will enable linking of genetics, phenotype, disease progression and treatment over time. Greater availability of standardized data will inform more specific recommendations for treatment selection. In addition to overarching recommendations for mIBD as a diverse and heterogeneous group, it will be essential to establish recommendations for individual treatments at the levels of the disease group, the affected genes and in some cases the variants present. A functionally supported variant-level analysis and stratification is particularly important in disorders for which a spectrum of expressivity exists and gain-of-function and loss-of-function variants have been described.

Next-generation analytical tools are essential to harmonize complex clinical datasets such as imaging or multiomics analysis[109]. Artificial intelligence and machine-learning approaches will potentially help to develop new endoscopic[110,111] and histopathological[112] models of disease pattern and activity. There is a need for harmonized efficacy and safety end points in mIBD studies as well as in paediatric IBD studies in general[113]; in the mIBD setting these need to be complemented by additional disease-specific markers. Multiomics analysis such as proteomics and transcriptomics, including single-cell approaches and spatial analysis of classic and monogenic forms of IBD, are likely to help identify functional modules, allowing patient stratification with implications for mechanistically informed treatment approaches[114,115].

A standardized genetic variant annotation might help to identify the monogenic and polygenic landscape in each patient. This is relevant as a bigenic, oligogenic or polygenic risk probably contributes to disease susceptibility and also to therapy response in some genetic disorders with incomplete penetrance of intestinal inflammation[116].

The availability of validated biomarkers of disease activity will aid researchers in assessing a range of new therapeutic concepts and indications in the field of mIBD. Findings from preclinical models indicate a large number of therapeutics with potential relevance for mIBD disorders. For instance, leflunomide corrected cellular defects observed in vitro using human cell lines and in a zebrafish model of TTC7A deficiency[117]. SYK inhibitors can inhibit inflammation induced by gain-of-function *SYK* variants in human cell lines as well as in a mouse model[74]. Increased mTOR signalling has been observed in patients with G6PC3 deficiency, glycogen storage disease type 1b (*SLC37A4*), LACC1 deficiency and APDS (caused by variants in *PIK3CD* and *PIK3R*), and in the IL-10 signalling cascade, and mTOR inhibitors such as rapamycin might have a role in the management of these disorders[2,26,118–120].

A preclinical stage precision medicine concept relevant to the field of mIBD is the replacement of defective cytokines. Synthetic cytokines such as recombinant IL-10 with a longer half-life[121], intestinal delivery of wild-type human IL-10 via transgenic bacteria that encode IL-10 (such as *Lactococcus lactis*)[122,123] or delivery of a transgenic human IL-10 molecule to the site of inflammation via a stroma-targeting anchor (Dekavil, also known as F8-IL-10)[124] are interesting potential treatment options for patients with IL-10 deficiency.

Mesenchymal or epithelial stem cell transplantation therapies might become relevant for some forms of mIBD, especially those characterized by wound-healing problems, or some epithelial disorders. Although mesenchymal or epithelial transplantation therapies are unlikely to allow a complete exchange of the cellular compartment, these therapies might still be feasible in patients in whom segmental or mosaic engraftment might be sufficient. Mouse models suggest the feasibility of epithelial organoid transplantations as proof of principle[125]. Mesenchymal stem cell therapies might have a role in the treatment of perianal Crohn's disease[126].

Several mIBD conditions are likely to benefit from gene therapy, as it would enable less toxic conditioning regimens (for example, for XIAP deficiency) compared with allogeneic HSCT. Some conditions, such as IL-10 deficiency, might only require moderate chimerism to resolve or prevent intestinal inflammation. Technological advances in the field of gene therapy such as genome editing using the CRISPR–Cas9 system could allow precise correction of genetic lesions in situ, thereby allowing gene-specific endogenous regulatory elements and cell-specific gene expression to be retained[127].

There is a clear need to better understand microbial–host interactions in the field of mIBD. Mouse models illustrate the complexity of potential interventions, as continuous antibiotic administration (either ciprofloxacin, or neomycin and metronidazole) prevented intestinal

inflammation in *Il10*-knockout mice[128], whereas intermittent antibiotic administration aggravated disease in these mice[129]. Although discovery in the field of mIBD will remain challenging, knowledge might emerge from seemingly unrelated fields such as checkpoint inhibitor treatment in immune oncology. For example, anti-CTLA4-induced antitumour immune responses (and adverse effects such as colitis) depend on the microbiome composition[130]. Microbiome studies in patients with anti-CTLA4 have clear potential for translation in patients with CTLA4 haploinsufficiency.

Conclusions

There is an unmet need to develop effective therapies for patients with mIBD. This presents an opportunity to drive precision medicine approaches. A major limitation of published research is heterogeneous reporting of responses to therapy. In this Expert Recommendation, we propose reporting standards to measure responses to therapies. These standards will enable estimates of effect size and kinetics in patients with mIBD, in an intestinal inflammation-centric but adjustable therapeutic framework that reflects established therapeutic goals for IBD while enabling disease-specific applications. mIBD REPORT standards can be implemented in clinical practice, will improve comparability between observational studies and trials, and facilitate meta-analysis. We highlight the importance of standardized, quantitative generic markers of treatment outcome as a first and important step, but we also recognize the need for additional disease-specific markers to assess the quality of life of patients with specific disorders and to assess treatments based on validated biomarkers that reflect disease-specific molecular and cellular outcomes. Precise data will promote precision medicine and, hopefully, improve the quality of care in patients with mIBD.

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References

1. Uhlig, H. H. et al. Clinical genomics for the diagnosis of monogenic forms of inflammatory bowel disease: a position paper from the Paediatric IBD Porto group of European Society of Paediatric Gastroenterology, Hepatology and Nutrition. *J. Pediatr. Gastroenterol. Nutr.* **72**, 456–473 (2021).
2. Bolton, C. et al. An integrated taxonomy for monogenic inflammatory bowel disease. *Gastroenterology* **122**, 859–876 (2022).
3. Uhlig, H. H. & Powrie, F. Translating immunology into therapeutic concepts for inflammatory bowel disease. *Annu. Rev. Immunol.* **36**, 755–781 (2018).
4. Charbit-Henrion, F., Parlato, M., Malamut, G., Ruemmele, F. & Cerf-Bensussan, N. Intestinal immunoregulation: lessons from human mendelian diseases. *Mucosal Immunol.* **14**, 1017–1037 (2021).
5. Sullivan, K. E., Conrad, M. & Kelsen, J. R. Very early-onset inflammatory bowel disease: an integrated approach. *Curr. Opin. Allergy Clin. Immunol.* **18**, 459–469 (2018).
6. Ouahed, J. et al. Very early onset inflammatory bowel disease: a clinical approach with a focus on the role of genetics and underlying immune deficiencies. *Inflamm. Bowel Dis.* **26**, 820–842 (2020).
7. Kammermeier, J. et al. Genomic diagnosis and care co-ordination for monogenic inflammatory bowel disease in children and adults: consensus guideline on behalf of the British Society of Gastroenterology and British Society of Paediatric Gastroenterology, Hepatology and Nutrition. *Lancet Gasteroenterol. Hepatol.* **8**, 271–286 (2023).
8. Crowley, E. et al. Prevalence and clinical features of inflammatory bowel diseases associated with monogenic variants, identified by whole-exome sequencing in 1000 children at a single center. *Gastroenterology* **158**, 2208–2220 (2020).
9. Nambu, R. et al. A systematic review of monogenic inflammatory bowel disease. *Clin. Gastroenterol. Hepatol.* **20**, e653–e663 (2022).
10. Crowley, E. et al. Impact of drug approval pathways for paediatric inflammatory bowel disease. *J. Crohns Colitis* **23**, 331–335 (2021).
11. Both, T. et al. Inflammatory bowel disease in primary immunodeficiency disorders is a heterogeneous clinical entity requiring an individualized treatment strategy: a systematic review. *Autoimmun. Rev.* **20**, 102872 (2021).
12. Boztug, K. et al. Stem-cell gene therapy for the Wiskott–Aldrich syndrome. *N. Engl. J. Med.* **363**, 1918–1927 (2010).
13. Kawai, T. et al. A gene therapy clinical study of a patient with X-linked chronic granulomatous disease. *Mol. Ther.* **24**, S87–S88 (2016).
14. Kohn, D. B. et al. Lentiviral gene therapy for X-linked chronic granulomatous disease. *Nat. Med.* **26**, 200–206 (2020).
15. Glocker, E.-O. et al. Infant colitis – it's in the genes. *Lancet* **376**, 1272 (2010).
16. Glocker, E. O. et al. Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. *N. Engl. J. Med.* **361**, 2033–2045 (2009).
17. Forbes, L. R. et al. Jakinibs for the treatment of immune dysregulation in patients with gain-of-function signal transducer and activator of transcription 1 (STAT1) or STAT3 mutations. *J. Allergy Clin. Immunol.* **142**, 1665–1669 (2018).
18. Rudra, S. et al. Ruxolitinib: targeted approach for treatment of autoinflammatory very early onset inflammatory bowel disease. *Clin. Gastroenterol. Hepatol.* **20**, 1408–1410 (2022).
19. Geerlinks, A. V., Dvorak, A. M. & XIAP Deficiency Treatment Consortium. A case of XIAP deficiency successfully managed with tadekinig alfa (rhIL-18BP). *J. Clin. Immunol.* **42**, 901–903 (2022).
20. Egg, D. et al. Therapeutic options for CTLA-4 insufficiency. *J. Allergy Clin. Immunol.* **149**, 736–746 (2022).
21. Kammermeier, J. et al. Phenotypic and genotypic characterisation of inflammatory bowel disease presenting before the age of 2 years. *J. Crohns Colitis* **11**, 60–69 (2017).
22. Torres, J. et al. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. *J. Crohns Colitis* **14**, 4–22 (2020).
23. Raine, T. et al. ECCO guidelines on therapeutics in ulcerative colitis: medical treatment. *J. Crohns Colitis* **16**, 2–17 (2022).
24. Passerini, L. et al. Treatment with rapamycin can restore regulatory T-cell function in IPEX patients. *J. Allergy Clin. Immunol.* **145**, 1262–1271.e13 (2020).
25. Azizi, G. et al. New therapeutic approach by sirolimus for enteropathy treatment in patients with LRBA deficiency. *Eur. Ann. Allergy Clin. Immunol.* **49**, 235–239 (2017).
26. Maccari, M. E. et al. Disease evolution and response to rapamycin in activated phosphoinositide 3-kinase δ syndrome: the European Society for Immunodeficiencies–Activated Phosphoinositide 3-Kinase δ Syndrome Registry. *Front. Immunol.* **9**, 543 (2018).
27. Gruber, C. N. et al. Complex autoinflammatory syndrome unveils fundamental principles of JAK1 kinase transcriptional and biochemical function. *Immunity* **53**, 672 (2020).
28. Talbot, J. W. et al. Management of enteritis associated with tricohepatoenteric syndrome due to SKIV2L mutation using the combination of JAK1/2 inhibition and azathioprine. *JPGN Rep.* **3**, e264 (2022).
29. Ye, Z. et al. Clinical and genetic spectrum of children with congenital diarrhea and enteropathy in China. *Genet. Med.* **21**, 2224–2230 (2019).
30. Noel, N. et al. Efficacy and safety of thalidomide in patients with inflammatory manifestations of chronic granulomatous disease: a retrospective case series. *J. Allergy Clin. Immunol.* **132**, 997–1000.e4 (2013).
31. Dai, R. et al. Altered functions of neutrophils in two Chinese patients with severe congenital neutropenia type 4 caused by *G6PC3* mutations. *Front. Immunol.* **12**, 699743 (2021).
32. Sokol, H. et al. Thalidomide as a treatment for refractory CGD colitis. *Am. J. Gastroenterol.* **104**, 1069 (2009).
33. Kuloglu, Z. et al. An infant with severe refractory Crohn's disease and homozygous MEFV mutation who dramatically responded to colchicine. *Rheumatol. Int.* **32**, 783–785 (2012).
34. Veenbergen, S. et al. IL-10 signaling in dendritic cells controls IL-1β-mediated IFNγ secretion by human $CD4^+$ T cells: relevance to inflammatory bowel disease. *Mucosal Immunol.* **12**, 1201–1211 (2019).
35. Egg, D. et al. Increased risk for malignancies in 131 affected CTLA4 mutation carriers. *Front. Immunol.* **9**, 2012 (2018).
36. Uhlig, H. H. Mendelian diseases and inflammatory bowel disease – data mining for genetic risk and disease-associated confounders. *Inflamm. Bowel Dis.* **24**, 467–470 (2018).
37. Schmitt, M. M. et al. Mycophenolate-induced colitis in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy patients. *JPGN Rep.* **2**, e131 (2021).
38. Naviglio, S. et al. Severe inflammatory bowel disease associated with congenital alteration of transforming growth factor beta signaling. *J. Crohns Colitis* **8**, 770–774 (2014).
39. van Andel, M. M. et al. Long-term clinical outcomes of losartan in patients with Marfan syndrome: follow-up of the multicentre randomized controlled COMPARE trial. *Eur. Heart J.* **41**, 4181–4187 (2020).
40. Asgharzadeh, F. et al. The beneficial effect of combination therapy with sulfasalazine and valsartan in the treatment of ulcerative colitis. *EXCLI J.* **20**, 236–247 (2021).
41. Wengrower, D. et al. Losartan reduces trinitrobenzene sulphonic acid-induced colorectal fibrosis in rats. *Can. J. Gastroenterol.* **26**, 33–39 (2012).
42. Liu, T. J., Shi, Y. Y., Wang, E. B., Zhu, T. & Zhao, Q. AT1R blocker losartan attenuates intestinal epithelial cell apoptosis in a mouse model of Crohn's disease. *Mol. Med. Rep.* **13**, 1156–1162 (2016).
43. Bolton, C. et al. Remission of inflammatory bowel disease in glucose-6-phosphatase 3 deficiency by allogeneic haematopoietic stem cell transplantation. *J. Crohns Colitis* **14**, 142–147 (2020).

44. Dieckgraefe, B. K., Korzenik, J. R., Husain, A. & Dieruf, L. Association of glycogen storage disease 1b and Crohn disease: results of a North American survey. *Eur. J. Pediatr.* **161**, S88–S92 (2002).
45. Veiga-da-Cunha, M. et al. Failure to eliminate a phosphorylated glucose analog leads to neutropenia in patients with G6PT and G6PC3 deficiency. *Proc. Natl Acad. Sci. USA* **116**, 1241–1250 (2019).
46. Wortmann, S. B. et al. Treating neutropenia and neutrophil dysfunction in glycogen storage disease type Ib with an SGLT2 inhibitor. *Blood* **136**, 1033–1043 (2020).
47. Grunert, S. C. et al. Improved inflammatory bowel disease, wound healing and normal oxidative burst under treatment with empagliflozin in glycogen storage disease type Ib. *Orphanet J. Rare Dis.* **15**, 218 (2020).
48. Williams, I. et al. Anti-TNF therapy for inflammatory bowel disease in patients with neurodegenerative Niemann–Pick disease type C. *Wellcome Open Res.* **7**, 11 (2022).
49. O'Brien, K. J. et al. Inflammatory bowel disease in HermanskyPudlak syndrome: a retrospective single-centre cohort study. *J. Intern. Med.* **290**, 129–140 (2021).
50. Mao, L. et al. Loss-of-function CARD8 mutation causes NLRP3 inflammasome activation and Crohn's disease. *J. Clin. Invest.* **128**, 1793–1806 (2018).
51. Levy, M. et al. Severe early-onset colitis revealing mevalonate kinase deficiency. *Pediatrics* **132**, e779–e783 (2013).
52. Shouval, D. S. et al. Interleukin 1β mediates intestinal inflammation in mice and patients with interleukin 10 receptor deficiency. *Gastroenterology* **151**, 1100–1104 (2016).
53. Li, J., Shouval, D. S., Doty, A. L., Snapper, S. B. & Glover, S. C. Increased mucosal IL-22 production of an IL-10RA mutation patient following anakin treatment suggests further mechanism for mucosal healing. *J. Clin. Immunol.* **37**, 104–107 (2017).
54. Canna, S. W. et al. Life-threatening NLRC4-associated hyperinflammation successfully treated with IL-18 inhibition. *J. Allergy Clin. Immunol.* **139**, 1698–1701 (2017).
55. Wada, T. et al. Sustained elevation of serum interleukin-18 and its association with hemophagocytic lymphohistiocytosis in XIAP deficiency. *Cytokine* **65**, 74–78 (2014).
56. Lo, B. et al. Patients with LRBA deficiency show CTLA4 loss and immune dysregulation responsive to abatacept therapy. *Science* **349**, 436–440 (2015).
57. Tesch, V. K. et al. Long-term outcome of LRBA deficiency in 76 patients after various treatment modalities as evaluated by the immune deficiency and dysregulation activity (IDDA) score. *J. Allergy Clin. Immunol.* **145**, 1452–1463 (2020).
58. Ozen, A. et al. Broadly effective metabolic and immune recovery with C5 inhibition in CHAPLE disease. *Nat. Immunol.* **22**, 128–139 (2021).
59. Danese, S., Solitano, V., Jairath, V. & Peyrin-Biroulet, L. The future of drug development for inflammatory bowel disease: the need to ACT (advanced combination treatment). *Gut* **71**, 2380–2387 (2022).
60. Hudson, A. A., Almeida, P. & Huynh, H. Dual biologic therapy in a patient with Niemann–Pick type C and Crohn disease: a case report and literature review. *JPGN Rep.* **3**, e225 (2022).
61. Goenka, A. et al. Neutrophil dysfunction triggers inflammatory bowel disease in G6PC3 deficiency. *J. Leukoc. Biol.* **109**, 1147–1154 (2021).
62. Barmettler, S. et al. Gastrointestinal manifestations in X-linked agammaglobulinemia. *J. Clin. Immunol.* **37**, 287–294 (2017).
63. Aydemir, S. et al. Inflammatory bowel disease and Guillain Barre syndrome in FCHO1 deficiency. *J. Clin. Immunol.* **41**, 1406–1410 (2021).
64. Marsh, R. A. et al. Chronic granulomatous disease-associated IBD resolves and does not adversely impact survival following allogeneic HCT. *J. Clin. Immunol.* **39**, 653–667 (2019).
65. Peng, K. et al. Umbilical cord blood transplantation corrects very early-onset inflammatory bowel disease in Chinese patients with IL10RA-associated immune deficiency. *Inflamm. Bowel Dis.* **24**, 1416–1427 (2018).
66. Ashton, J. J., Gavin, J. & Beattie, R. M. Exclusive enteral nutrition in Crohn's disease: evidence and practicalities. *Clin. Nutr.* **38**, 80–89 (2019).
67. Murugan, D. et al. Very early onset inflammatory bowel disease associated with aberrant trafficking of IL-10R1 and cure by T cell replete haploidentical bone marrow transplantation. *J. Clin. Immunol.* **34**, 331–339 (2014).
68. Freudenberg, F. et al. Therapeutic strategy in p47-phox deficient chronic granulomatous disease presenting as inflammatory bowel disease. *J. Allergy Clin. Immunol.* **125**, 943–946.e1 (2010).
69. Norsa, L. et al. Inflammatory bowel disease in patients with congenital chloride diarrhoea. *J. Crohns Colitis* **15**, 1679–1685 (2021).
70. Janecke, A. R. et al. Reduced sodium/proton exchanger NHE3 activity causes congenital sodium diarrhea. *Hum. Mol. Genet.* **24**, 6614–6623 (2015).
71. Fiskerstrand, T. et al. Familial diarrhea syndrome caused by an activating *GUCY2C* mutation. *N. Engl. J. Med.* **366**, 1586–1595 (2012).
72. Sokol, H. et al. Intestinal dysbiosis in inflammatory bowel disease associated with primary immunodeficiency. *J. Allergy Clin. Immunol.* **143**, 775–778.e6 (2019).
73. Xue, A. J. et al. Intestinal dysbiosis in pediatric Crohn's disease patients with *IL10RA* mutations. *World J. Gastroenterol.* **26**, 3098–3109 (2020).
74. Wang, L. et al. Gain-of-function variants in *SYK* cause immune dysregulation and systemic inflammation in humans and mice. *Nat. Genet.* **53**, 500–510 (2021).
75. Ono, S. et al. Hematopoietic cell transplantation rescues inflammatory bowel disease and dysbiosis of gut microbiota in XIAP deficiency. *J. Allergy Clin. Immunol. Pract.* **9**, 3767–3780 (2021).
76. Huang, Z. et al. Mutations in interleukin-10 receptor and clinical phenotypes in patients with very early onset inflammatory bowel disease: a Chinese VEO-IBD Collaboration Group survey. *Inflamm. Bowel Dis.* **23**, 578–590 (2017).
77. Quaranta, M. et al. Consequences of identifying XIAP deficiency in an adult patient with inflammatory bowel disease. *Gastroenterology* **155**, 231–234 (2018).
78. Arnold, D. E. et al. Reduced-intensity/reduced-toxicity conditioning approaches are tolerated in XIAP deficiency but patients fare poorly with acute GVHD. *J. Clin. Immunol.* **42**, 36–45 (2022).
79. Ruemmele, F. M. et al. Outcome measures for clinical trials in paediatric IBD: an evidence-based, expert-driven practical statement paper of the paediatric ECCO committee. *Gut* **64**, 438–446 (2015).
80. Turner, D. et al. STRIDE-II: an update on the selecting therapeutic targets in inflammatory bowel disease (STRIDE) initiative of the International Organization for the Study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. *Gastroenterology* **160**, 1570–1583 (2021).
81. Opréa, A. C.-F. et al. Therapeutic approach of very early-onset inflammatory bowel disease in a Loeys–Dietz syndrome child. *JPGN Rep.* **3**, e139 (2022).
82. Attauabi, M. et al. Comparative onset of effect of biologics and small molecules in moderate-to-severe ulcerative colitis: a systematic review and network meta-analysis. *EClinicalMedicine* **57**, 101866 (2023).
83. Dike, C. R., Bernat, J., Bishop, W. & DeGeeter, C. Niemann–Pick disease type C presenting as very early onset inflammatory bowel disease. *BMJ Case Rep.* **12**, e229780 (2019).
84. Uzel, G. et al. Complications of tumor necrosis factor-α blockade in chronic granulomatous disease-related colitis. *Clin. Infect. Dis.* **51**, 1429–1434 (2010).
85. Conrad, A. et al. Infections in patients with chronic granulomatous disease treated with tumor necrosis factor alpha blockers for inflammatory complications. *J. Clin. Immunol.* **41**, 185–193 (2021).
86. Braun, C. J. et al. Gene therapy for Wiskott-Aldrich syndrome – long-term efficacy and genotoxicity. *Sci. Transl Med.* **6**, 227–233 (2014).
87. Vogelin, M. et al. The impact of azathioprine-associated lymphopenia on the onset of opportunistic infections in patients with inflammatory bowel disease. *PLoS ONE* **11**, e0155218 (2016).
88. Nori, M. 'Negative' clinical trials in rare diseases and beyond: reclassification and potential solutions. *Future Rare Dis.* **1**, 10.2217/frd-2020-0005 (2021).
89. de Luca, A. et al. IL-1 receptor blockade restores autophagy and reduces inflammation in chronic granulomatous disease in mice and in humans. *Proc. Natl Acad. Sci. USA* **111**, 3526–3531 (2014).
90. Hahn, K. J. et al. Treatment with anakinra, a recombinant IL-1 receptor antagonist, unlikely to induce lasting remission in patients with CGD colitis. *Am. J. Gastroenterol.* **110**, 938–939 (2015).
91. Aschenbrenner, D. et al. Pathogenic interleukin-10 receptor alpha variants in humans – balancing natural selection and clinical implications. *J. Clin. Immunol.* **43**, 495–511 (2023).
92. Marsh, R. A. et al. Allogeneic hematopoietic cell transplantation for XIAP deficiency: an international survey reveals poor outcomes. *Blood* **121**, 877–883 (2013).
93. Kuehn, H. S. et al. Immune dysregulation in human subjects with heterozygous germline mutations in *CTLA4*. *Science* **345**, 1623–1627 (2014).
94. Schubert, D. et al. Autosomal dominant immune dysregulation syndrome in humans with *CTLA4* mutations. *Nat. Med.* **20**, 1410–1416 (2014).
95. Gagne, J. J., Thompson, L., O'Keefe, K. & Kesselheim, A. S. Innovative research methods for studying treatments for rare diseases: methodological review. *BMJ* **349**, g6802 (2014).
96. Whicher, D., Philbin, S. & Aronson, N. An overview of the impact of rare disease characteristics on research methodology. *Orphanet J. Rare Dis.* **13**, 14 (2018).
97. Santoro, M. et al. Rare disease registries classification and characterization: a data mining approach. *Public Health Genomics* **18**, 113–122 (2015).
98. European Commission. Set of common data elements for rare diseases registration. *EU RD Platform* https://eu-rd-platform.jrc.ec.europa.eu/set-of-common-data-elements_en (2023).
99. Salter, C. G. et al. Biallelic PI4KA variants cause neurological, intestinal and immunological disease. *Brain* **144**, 3597–3610 (2021).
100. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (US Department of Health and Human Services, 1979).
101. Borysowski, J., Ehni, H. J. & Gorski, A. Ethics review in compassionate use. *BMC Med.* **15**, 136 (2017).
102. Vohra, S. et al. CONSORT extension for reporting N-of-1 trials (CENT) 2015 Statement. *J. Clin. Epidemiol* **76**, 9–17 (2016).
103. Turner, D. et al. Designing clinical trials in paediatric inflammatory bowel diseases: a PIBDnet commentary. *Gut* **69**, 32–41 (2020).
104. Faingelernt, Y. et al. Correlation between the Nancy Histopathology Index and markers of disease activity in pediatric ulcerative colitis. *J. Pediatr. Gastroenterol. Nutr.* **76**, 782–785 (2023).
105. Ricciuto, A. et al. Prospective evaluation of endoscopic and histologic indices in pediatric ulcerative colitis using centralized review. *Am. J. Gastroenterol.* **116**, 2052–2059 (2021).
106. Walsh, A. J., Bryant, R. V. & Travis, S. P. Current best practice for disease activity assessment in IBD. *Nat. Rev. Gastroenterol. Hepatol.* **13**, 567–579 (2016).

107. Tran, F. et al. Patient reported outcomes in chronic inflammatory diseases: current state, limitations and perspectives. *Front. Immunol.* **12**, 614653 (2021).
108. Grassly, N. C. et al. The effect of azithromycin on the immunogenicity of oral poliovirus vaccine: a double-blind randomised placebo-controlled trial in seronegative Indian infants. *Lancet Infect. Dis.* **16**, 905–914 (2016).
109. Subbiah, V. The next generation of evidence-based medicine. *Nat. Med.* **29**, 49–58 (2023).
110. Raine, T. et al. Establishment of a validated central reading system for ileocolonoscopy in an academic setting. *Gut* **71**, 661–664 (2022).
111. Byrne, M. F. et al. Application of deep learning models to improve ulcerative colitis endoscopic disease activity scoring under multiple scoring systems. *J. Crohns Colitis* **19**, 463–471 (2023).
112. Sutton, R. T., Zai Ane, O. R., Goebel, R. & Baumgart, D. C. Artificial intelligence enabled automated diagnosis and grading of ulcerative colitis endoscopy images. *Sci. Rep.* **12**, 2748 (2022).
113. Crowley, E., Griffiths, A. M. & Jairath, V. pIBD Clinical Trials Outcome Group Heterogeneity in efficacy and safety endpoints for pediatric clinical trials in inflammatory bowel disease: a need for harmonization. *Gastroenterology* **163**, 1137–1144 (2022).
114. Cavounidis, A. et al. Hermansky-Pudlak syndrome type 1 causes impaired anti-microbial immunity and inflammation due to dysregulated immunometabolism. *Mucosal Immunol.* **15**, 1431–1446 (2022).
115. 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).
116. Huang, C. et al. Genetic risk for inflammatory bowel disease is a determinant of Crohn's disease development in chronic granulomatous disease. *Inflamm. Bowel Dis.* **22**, 2794–2801 (2016).
117. Jardine, S. et al. Drug screen identifies leflunomide for treatment of inflammatory bowel disease caused by TTC7A deficiency. *Gastroenterology* **158**, 1000–1015 (2020).
118. Ip, W. K. E., Hoshi, N., Shouval, D. S., Snapper, S. & Medzhitov, R. Anti-inflammatory effect of IL-10 mediated by metabolic reprogramming of macrophages. *Science* **356**, 513–519 (2017).
119. Omarjee, O. et al. LACC1 deficiency links juvenile arthritis with autophagy and metabolism in macrophages. *J. Exp. Med.* **218**, e20201006 (2021).
120. Coulter, T. I. & Cant, A. J. The treatment of activated PI3Kδ syndrome. *Front. Immunol.* **9**, 2043 (2018).
121. Minshawi, F. et al. The generation of an engineered interleukin-10 protein with improved stability and biological function. *Front. Immunol.* **11**, 1794 (2020).
122. Zurita-Turk, M. et al. Attenuation of intestinal inflammation in IL-10 deficient mice by a plasmid carrying *Lactococcus lactis* strain. *BMC Biotechnol.* **20**, 38 (2020).
123. Braat, H. et al. A phase I trial with transgenic bacteria expressing interleukin-10 in Crohn's disease. *Clin. Gastroenterol. Hepatol.* **4**, 754–759 (2006).
124. Bruijnen, S. T. G. et al. F8-IL10: a new potential antirheumatic drug evaluated by a PET-guided translational approach. *Mol. Pharm.* **16**, 273–281 (2019).
125. Watanabe, S. et al. Transplantation of intestinal organoids into a mouse model of colitis. *Nat. Protoc.* **17**, 649–671 (2022).
126. Ko, J. Z., Johnson, S. & Dave, M. Efficacy and safety of mesenchymal stem/stromal cell therapy for inflammatory bowel diseases: an up-to-date systematic review. *Biomolecules* **11**, 82 (2021).
127. Sweeney, C. L. et al. Correction of X-CGD patient HSPCs by targeted *CYBB* cDNA insertion using CRISPR/Cas9 with 53BP1 inhibition for enhanced homology-directed repair. *Gene Ther.* **28**, 373–390 (2021).
128. Madsen, K. L. et al. Antibiotic therapy attenuates colitis in interleukin 10 gene-deficient mice. *Gastroenterology* **118**, 1094–1105 (2000).
129. Li, S. et al. Intermittent antibiotic treatment accelerated the development of colitis in IL-10 knockout mice. *Biomed. Pharmacother.* **146**, 112486 (2021).
130. Vetizou, M. et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. *Science* **350**, 1079–1084 (2015).
131. de la Morena-Barrio, M. E. et al. MPI-CDG with transient hypoglycosylation and antithrombin deficiency. *Haematologica* **104**, e79–e82 (2019).
132. Yang, L. et al. Phenotype, genotype, treatment, and survival outcomes in patients with X-linked inhibitor of apoptosis deficiency. *J. Allergy Clin. Immunol.* **150**, 456–466 (2022).
133. Čechová, A. et al. Consensus guideline for the diagnosis and management of mannose phosphate isomerase-congenital disorder of glycosylation. *J. Inherit. Metab. Dis.* **43**, 671–693 (2020).

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