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

Jochen Kammermeier, Christopher A Lamb*, Kelsey D J Jones, Carl A Anderson, Emma L Baple, Chrissy Bolton, Helen Braggins, Tanya I Coulter, Kimberly C Gilmour, Vicki Gregory, Sophie Hambleton, David Hartley, A Barney Hawthorne, Sarah Hearn, Arian Laurence, Miles Parkes, Richard K Russell, R Alexander Speight, Simon Travis, David C Wilson, Holm H Uhlig*

Genomic medicine enables the identification of patients with rare or ultra-rare monogenic forms of inflammatory bowel disease (IBD) and supports clinical decision making. Patients with monogenic IBD frequently experience extremely early onset of treatment-refractory disease, with complex extraintestinal disease typical of immunodeficiency. Since more than 100 monogenic disorders can present with IBD, new genetic disorders and variants are being discovered every year, and as phenotypic expression of the gene defects is variable, adaptive genomic technologies are required. Monogenic IBD has become a key area to establish the concept of precision medicine. Clear guidance and standardised, affordable applications of genomic technologies are needed to implement exome or genome sequencing in clinical practice. This joint British Society of Gastroenterology and British Society of Paediatric Gastroenterology, Hepatology and Nutrition guideline aims to ensure that testing resources are appropriately applied to maximise the benefit to patients on a national scale, minimise health-care disparities in accessing genomic technologies, and optimise resource use. We set out the structural requirements for genomic medicine as part of a multidisciplinary team approach. Initiation of genomic diagnostics should be guided by diagnostic criteria for the individual patient, in particular the age of IBD onset and the patient's history, and potential implications for future therapies. We outline the diagnostic care pathway for paediatric and adult patients. This guideline considers how to handle clinically actionable findings in research studies and the impact of consumer-based genomics for monogenic IBD. This document was developed by multiple stakeholders, including UK paediatric and adult gastroenterology physicians, immunologists, transplant specialists, clinical geneticists, scientists, and research leads of UK genetic programmes, in partnership with patient representatives of several IBD and rare disease charities.

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*Joint first authors

Department of Paediatric Gastroenterology, Evelina London Children's Hospital, London, UK (J Kammermeier PhD); **Translational & Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK** (C A Lamb PhD, Prof S Hambleton DPhil, R A Speight MD); **Department of Gastroenterology, Royal Victoria Infirmary, Newcastle upon Tyne, UK** (C A Lamb, R A Speight); **Department of Gastroenterology, Great Ormond Street Hospital for Children, London, UK** (K D J Jones PhD); **Kennedy Institute of Rheumatology, Nuffield Department of Orthopaedics** (K D J Jones), **Translational Gastroenterology Unit and Biomedical Research Centre** (S Hearn, Prof S Travis DPhil, Prof H H Uhlig MD), **and Department of Paediatrics** (Prof H H Uhlig), **University of Oxford, Oxford, UK; Wellcome Sanger Institute, Hinxton, Cambridgeshire, UK** (C A Anderson PhD); **University of Exeter Medical School, Royal Devon & Exeter Hospital, Exeter, UK** (E L Baple PhD); **Department of Infection, Immunity and Inflammation, UCL Great Ormond Street Institute of Child Health, London, UK** (C Bolton MRCPCH); **Department of Immunology** (H Braggins), **and Clinical Immunology Laboratory** (K C Gilmour PhD), **Great**

Introduction

Translational genomic research has had a transformative effect on the mechanistic understanding of immune-mediated diseases. Implementation of these genetic discoveries into clinical practice is vital for patients to benefit from personalised or precision medicine. Research on inflammatory bowel disease (IBD), a group of chronic relapsing inflammatory disorders including Crohn's disease, ulcerative colitis, and IBD unclassified (IBDu), has identified the polygenic contribution of hundreds of associated loci.[1,2] A small group of patients with severe forms of IBD harbour highly penetrant pathogenic variants in a single gene that are summarised as monogenic IBD.[1,3] For these patients, identification of the precise genetic cause explains aspects of the disease and can provide prognostic information (eg, on infection susceptibility, disease progression, or malignancy risk). A molecular diagnosis might enable prediction of response to conventional therapy (eg, anti-TNF therapy or surgery), and might suggest highly specific mechanistically guided therapies (eg, allogeneic haematopoietic stem-cell transplantation [HSCT][4,5] or gene therapy).[6]

On surveying approximately 2500 people living with IBD, the incorporation of precision medicine strategies in routine clinical practice was identified as a highly important theme for research prioritisation.[7] Genomic medicine has the potential to achieve this approach for some patients. National and international guidance supports the use of genomic testing to diagnose monogenic causes of IBD.[3,7] This marks the transition of next-generation sequencing technology from a research modality to a diagnostic tool in routine clinical care. Sequencing technologies required for genome-wide sequencing have been approved for use in clinical practice, and new technologies are emerging. However, testing resources, legal requirements, and ethical considerations are country or region specific. The field is complex, since genomic health data are generated from not only the clinical health-care sector, but also clinical research (such as the 100 000 Genomes Project, and numerous IBD research studies and consortia) and consumer genomics.[8–14] Preconditions for pragmatic implementation of genomic technologies are to identify patient groups that benefit the most from testing, to provide appropriate genetic counselling before testing

Ormond Street Hospital of Children NHS Foundation Trust and NIHR Great Ormond Street Hospital Biomedical Research Centre, London, UK; Chronic Granulomatous Disorder Society, Dartford, UK (H Braggins)**; Regional Immunology Service for Northern Ireland, Belfast, UK** (T I Coulter FRCPath)**; Crohn's & Colitis UK, Hatfield, UK** (V Gregory BMBS)**; Department of Paediatric Immunology, Great North Children's Hospital, Newcastle upon Tyne, UK** (S Hambleton)**; XLP Research Trust, Romsey, Hampshire, UK** (D Hartley BSc)**; Department of Gastroenterology, University Hospital of Wales, Cardiff, UK** (A B Hawthorne MD)**; Department of Clinical Immunology, Royal Free Hospital, London, UK** (A Laurence PhD)**; Department of Haematology and Bone Marrow Transplantation, University College Hospital, London, UK** (A Laurence)**; Department of Gastroenterology, Addenbrooke's Hospital, Cambridge, UK** (M Parkes DM)**; Child Life and Health, University of Edinburgh; Department of Paediatric Gastroenterology** (Prof R K Russell PhD, Prof D C Wilson PhD)**; Department of Paediatric Gastroenterology, The Royal Hospital for Children & Young People, Edinburgh, UK** (Prof R K Russell, Prof D C Wilson)

Correspondence to:
Prof Holm H Uhlig, Translational Gastroenterology Unit, Department of Paediatrics and Biomedical Research Centre, University of Oxford, Oxford OX3 9DU, UK
holm.uhlig@ndm.ox.ac.uk

and on review of the results, and to manage the expectations of patients or clinicians (panel 1). This guideline provides a tool for clinicians who care for patients with suspected monogenic IBD to support the implementation of genomics into clinical care. The guideline also discusses the handling of potentially actionable results at the interface of research and consumer genomics.

Methods

This guideline was developed according to Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology,[15] in accordance with the principles of the AGREE II tool,[16] and in compliance with the British Society of Gastroenterology (BSG) guideline development process, accredited by the National Institute for Health and Care Excellence (NICE).[17]

Guideline development group membership

A guideline development group (GDG) was selected to cover expertise in paediatric and adult IBD, clinical immunology, clinical and molecular genetics, and HSCT. The group was recruited via the British Society of Paediatric Gastroenterology Hepatology and Nutrition (BSPGHAN) IBD Working Group, and the BSG Inflammatory Bowel Disease Section, and supplemented with additional paediatric and adult IBD specialists, clinical immunology, clinical genetics, and haematology transplant specialists. In addition to clinical specialties, the group included representation from key IBD research consortia, including UK adult and paediatric IBD BioResource,[9] colitis of early onset—rare diseases within IBD (COLORS in IBD) group,[10] the Oxford IBD cohort, and the PETIT study.[12] To reduce bias, we considered gender balance, geographical representation from all four UK nations, and early career stage clinician contribution and non-clinical representation.

Participation of UK patient organisations and charities

Stakeholder UK patient organisations and charities were invited to participate, which represent paediatric and adult patients with IBD, or rare monogenic disorders that can present with IBD. These groups included the Crohn's in Childhood Research Association (CICRA), Crohn's & Colitis UK, the X-linked Lymphoproliferative Syndrome (XLP) Research Trust, and the Chronic Granulomatous Disorder (CGD) Society.

Scope and purpose of guideline

A guideline proposal was endorsed by the leads for clinical guidelines of both BSG and BSPGHAN. After commissioning the guideline, a Chair for the GDG (JK) was appointed to oversee any potential conflicts of interest within the group. Scope and purpose of the guideline were prospectively defined (panel 2). Clinical questions structured by population, intervention, comparator, and outcome (PICO) or population, exposure, and outcome (PEO) were designed, including consideration of patient populations impacted, to

Panel 1: **Establishing need for a monogenic IBD guideline**

- If applied to the appropriate patient at the right time, genomic medicine can enable the selection of effective treatments to achieve precision medicine; a molecular genetic diagnosis might offer patients mechanistically informed, or even curative treatment options, and the potential for genetic counselling.
- Monogenic forms of IBD are a heterogenous group of disorders; coordinated multidisciplinary care is essential.
- Compared with other groups of genetic disorders (eg, syndromal developmental disorders) the rate of actionable genetic findings in patients with IBD overall is low, hence robust eligibility criteria are required for genomic testing to determine whom to investigate.
- A specific and practical guide is required to support implementation of genomic medicine for monogenic IBD diagnostics for both paediatric and adult patients.
- In the UK gastroenterologists and immunologists caring for paediatric and adult patients are eligible to request genomic testing; education and guidance on how to interpret and act on genetic results is lacking.
- Clear consensus guidance will reduce regional and age-dependent (paediatrics *vs* adult medicine) disparities, and disparities due to ethnicity in accessing genomic testing.
- Input from patients is critical for implementing personalised genomic medicine pathways effectively; consulting multiple patient organisations and charities is essential.

Panel 2: **Scope and purpose of monogenic IBD guideline**

- Outline the setting of genomic medicine for monogenic inflammatory bowel disease (IBD) in paediatric and adult gastroenterology
- Beyond infantile and very-early-onset IBD, to define eligibility criteria for genomic medicine in patients with IBD onset beyond age 6 years and in adult patients
- Define the patient diagnostic pathway in paediatric and adult medicine (eg, UK National Health Service clinical genomics pathway); identify which patients should be offered genomic analysis to investigate for monogenic IBD
- Determine the role of the multidisciplinary team in coordinating genomic diagnostics and subsequent care in patients with suspected monogenic IBD
- Identify training and continuing education requirements in genomic medicine for paediatric and adult gastroenterologists
- Guide the handling and clinical use of potentially actionable findings arising from research studies
- Summarise guideline recommendations for patients

assimilate evidence and draft statements (appendix p 9). Health economic implications were not formally assessed. Due to limited evidence arising largely from small case series or case reports, an assessment of treatment for individual gene defects was not considered a key topic for these guidelines.[5,18,19]

Search strategy and selection criteria

Definitions of relevance to this guideline are presented in the appendix (pp 9–11). Literature searches were designed using MEDLINE in January, 2022. No date or study design limits were incorporated into searches. Searches were restricted to English language. It was agreed that where up-to-date systematic reviews exist (diagnostic yield of genomic studies, age of onset in different genetic defects, and treatment of patients with monogenic IBD),[3,5,18] extensive systematic reviews would not be performed, but data would be summarised. Where previous guidance existed with respect to monogenic IBD, this was highlighted to encourage best practice.[3] GDG members were able to add papers (including reviews, guidelines, and case reports) or electronic documents (eg, NICE guidance) for inclusion in the literature dataset throughout the guideline development process.

Statement drafting and Delphi consensus

Statement recommendations were formulated according to the BSG consensus guidelines on the management of IBD in adults.[7] Draft statements were prepared on the basis of importance to patients and considering potential health benefits and risks. A first round of open discussion of draft statements by the GDG was undertaken via virtual meeting in January, 2022. Revised draft statements were then categorised according to the GRADE system for grading quality of evidence and strength of recommendations. Consideration was given to study type, risk of bias, inconsistency, indirectness, imprecision, publication bias, effect size, and plausible confounding variables. Quality of evidence was then considered as high (further research is very unlikely to change confidence in the estimate of effect), moderate (further research is likely to have an important impact on confidence in the estimate of effect, and may change the estimate), low (further research is very likely to have an important impact on confidence in the estimate of effect, and is likely to change the estimate), or very low (any estimate of effect is very uncertain). The strength of recommendation was assessed on the basis of considerations of desirable and undesirable anticipated effects, the certainty of the evidence of effects, any important uncertainty about or variability in how much people value the outcome, whether the balance of these effects favours the intervention or comparison, the acceptability of intervention to key stakeholders, and the feasibility of intervention implementation. The strength of each recommendation was then recorded as strong (meaning that benefits clearly outweigh risks and burdens, or that burdens clearly outweigh risks) with use of the phrase we recommend within statements; whereas weak recommendations were recorded as conditional (where benefits, risks, and burdens are closely balanced or uncertain) and used the phrase we suggest.

Following the preparation of draft statements, two rounds of anonymous online voting with commenting, using the tool eDelphi, were undertaken to facilitate refinement and consensus. Three patient representatives contributed to the Delphi process. Statements were scored by voting participants using a 5-point Likert scale (ranging from strongly disagree, disagree, neither agree nor disagree, agree, or strongly agree). Statements conforming to a consensus rate of 80% agree or strongly agree were accepted. Where statements did not conform to PICO or PEO (eg, subjective interventions or where outcomes were multiple) and evidence was indirect or of low quality, recommendations to inform clinical practice were presented as practice points and listed separately to GRADE recommendations, but still underwent consensus voting. Participants were able to abstain from voting on any individual statement or practice point. Final numbers of votes and abstentions are shown in the appendix (p 4). A patient summary of the guideline is presented in the appendix (pp 6–8).

See Online for appendix

Implementation of genomic medicine in a health-care system

Although exceptionally rare, monogenic causes of IBD should be considered in patients with IBD since optimal care pathways and treatment may differ from that of classical IBD (table 1). Implementation of genomic medicine in the field of monogenic IBD requires a health-care system that facilitates patient-centred personalised clinical care, that adapts in a timely fashion to advances in the field of genomic research and technology, and provides clinical genomic services including genetic counselling, genomic testing, analysis and reporting within an agreed timeframe, and ethical and legal frameworks. The clinical care for patients with suspected monogenic IBD is challenging and can require extensive interdisciplinary support with sufficient resources to enable the complex genomic diagnostic process, and subsequent individualised therapies to be provided within the health-care system.

In monogenic IBD, the individual rarity of the disorders, the heterogeneity of extraintestinal phenotypes, and the continually expanding list of potential disease genes favours the use of parallel sequencing, rather than stepwise candidate sequencing, as the primary genetic diagnostic modality.[3] The diagnostic value of next-generation sequencing for diagnosis of diverse monogenic IBD disorders has been described in multiple research studies.[10–14,20–33] Since the proposal of large-scale sequencing panels in 2013, the number of genes associated with monogenic IBD has

	GRADE	Strength of recommendation	Agreement
Statement 1			
Although exceptionally rare, monogenic IBD should be considered in patients with IBD since optimal treatment might differ substantially from that of classical IBD	High quality	Strong	90%
Statement 2			
We recommend that genomic testing to investigate monogenic IBD should be offered as part of the clinical diagnostic service in an accredited laboratory	Low quality	Strong	95%
Statement 3			
We suggest genomic testing for patients with suspected monogenic IBD is best coordinated by a GIM, which should include at least one specialist in the diagnosis and treatment of monogenic IBD	Low quality	Conditional	95%
Statement 4			
When genetic results suggest a monogenic IBD diagnosis, we recommend that communication of results to patients (or parents or guardians), functional validation of plausible variants, and setup of personalised care plans should be coordinated with support from the GIM	Low quality	Strong	100%
Statement 5			
We recommend clinicians consider genomic testing in all patients with infantile-onset (age <2 years) IBD	High quality	Strong	100%
Statement 6			
We recommend clinicians consider genomic testing in patients with very-early-onset (age <6 years) IBD particularly in the presence of one or more additional testing criteria*	High quality	Strong	100%
Statement 7			
We suggest that genomic testing should only be offered in exceptional circumstances to patients with IBD onset after age 6 years; these patients should meet at least one of the genomic testing criteria*	Moderate quality	Conditional	100%
Statement 8			
To prevent avoidable harm, we recommend that a monogenic IBD diagnosis should be considered in advance of performing autologous and allogeneic haematopoietic stem-cell transplantation in patients with IBD	Low quality	Strong	100%
Statement 9			
We suggest that genomic testing to investigate monogenic IBD uses a curated adaptable gene panel approach, best facilitated by whole genome sequencing to allow an updated analysis when new evidence becomes available	Moderate quality	Conditional	100%

GRADE=Grading of Recommendations Assessment, Development, and Evaluation. IBD=inflammatory bowel disease. GIM=genomics inflammatory bowel disease multidisciplinary team. *See panel 5.

Table 1: **GRADE recommendations regarding genomic diagnosis and care coordination for monogenic IBD in children and adults**

increased to over 100 genes.[5,34] Targeted panel sequencing reaches its limits in such an environment because gene panels must be redesigned and undiagnosed patients resequenced each time new gene discoveries are made. This limitation highlights the value of exome or whole genome sequencing, where defined virtual panels can be analysed at the time of initial submission but re-analysis can be undertaken in situations such as evolution of the patient phenotype, new monogenic IBD gene discoveries, and bioinformatic pipeline improvements over time. Diagnostic genomic testing is not universally accessible, but is increasingly available in high-income and middle-income economies.[35]

Several solutions to provide genomic services for people with potentially monogenic IBD have been proposed on an institutional level, as part of genomic medicine clinics or at clinics for patients with very-early-onset IBD.[36,37] In England, the National Health Service (NHS) Genomic Medicine Service (GMS) supports scalable and equitable diagnostic genomic testing (panel 3). The health-care system in England takes this strategy into account by commissioning whole genome and exome sequencing, where diagnostic gene panels are publicly accessible and reviewed at regular intervals.[38] This strategy allows input and critical review by the specialist community, aiming for coordinated efforts to ensure standardised analysis and reporting of genomic testing. Genomic testing to investigate monogenic IBD should be offered as part of the clinical diagnostic service (table 1).

The turnaround time of genomic analysis from sample submission to genomic report in many institutions is expected to be in the range of several weeks to months (panel 3). This information is important for patients, parents or guardians, and clinicians to manage expectations. If, in exceptional cases, a report is required more urgently, then rapid genomic sequencing with a turnaround of days can be considered.[39] In principle, technological advances allow a genetic diagnosis to be established by ultra-rapid genome sequencing within 8 h.[40]

Genomic medicine: a multidisciplinary team (MDT) approach

All patients with IBD benefit from care as part of an IBD MDT.[7] This approach is particularly relevant for patients with exceptional presentations, such as very early onset of inflammation (age <6 years), infection susceptibility or autoimmunity, multiorgan involvement, and lack of response to multiple conventional therapies; all characteristics that have been previously described in patients with underlying monogenic IBD conditions.

Genomic medicine MDTs can complement such a multidisciplinary approach by supporting the diagnostic genomic process in individuals with rare disorders, including those with monogenic IBD.[37] A genomic IBD MDT (GIM) can provide specialist advice at several key decision points in the care of patients with suspected monogenic IBD: (1) the decision to investigate for a monogenic cause in more complex or ambiguous cases and the most appropriate technologies, (2) variant interpretation and clinicogenetic correlation, and (3) the clinical care strategy of patients with established monogenic IBD (figure 1).

The heterogeneity of underlying genetic conditions and clinical presentations means that the GIMs should have a core structure with adaptive contribution from local

Panel 3: **Overview of the National Health Service Genomic Medicine Service (NHS GMS) and the monogenic inflammatory bowel disease (IBD) genomics setup**

- The NHS GMS offers a standardised genomic testing directory (the National Genomic Test Directory), including targeted, exome, or genome sequencing. The directory provides informatics and data storage aligned with ethical and legal frameworks in the UK. Funding of clinical genomics is provided by the NHS.
- The national genomic testing service is delivered to 55 million people in England by a network of seven NHS Genomic Laboratory Hubs (GLHs), each responsible for coordinating services for a particular part of the country.
- Common national standards across different institutions include counselling and clinical geneticist support aiming for a standardised analysis and reporting of genetic variants.
- A genomics education programme is embedded in the system.
- A National Genomic Test Directory for rare and inherited disease defines specific genomic tests commissioned by NHS England from its NHS GLHs, the technology by which they are available, and the patients who will be eligible to access to a test.
- Eligibility criteria for monogenic IBD testing are as follows. Suspected monogenic IBD diagnosed by a consultant paediatric gastroenterologist, gastroenterologist, or immunologist: (1) infantile onset IBD at younger than 2 years or (2) very-early-onset IBD (<6 years) with severe course (ie, requiring biologics or surgery) or relevant comorbidities and extraintestinal manifestations. Testing might occasionally be appropriate outside these criteria following discussion in a specialist multidisciplinary team (eg, paediatric or young-adult IBD with documented severity criteria [ie, relevant family history, comorbidities, and extraintestinal manifestations, such as infection susceptibility]).
- The NHS GMS Panels Resource is the repository for virtual gene panels that relate to genomic tests listed in the NHS National Genomic Test Directory. This platform is curated and regularly updated, and contains only genes and regions that have been approved for diagnostic testing in the NHS in England.
- Since about a fifth of more than 400 inborn errors of immunity can present with IBD or enteropathy, the NHS GMS has chosen a partially overlapping pipeline to analyse primary immunodeficiencies and monogenic IBD. This decision acknowledges that some monogenic IBD disorders are not considered as inborn errors of immunity (eg, Niemann Pick disease type C or the group of congenital diarrhoea disorders). Distinct reporting of monogenic IBD and inborn errors of immunity panels avoids potential inflation of the number of reported variants of unknown significance in genes that are of no relevance to the patient phenotype.
- Very-early-onset IBD clinics are integrated in the NHS paediatric gastroenterology service.
- Pilot genomic MDTs are set up to facilitate diagnostics for rare disorders, such as monogenic IBD and inborn errors of immunity.
- A joint primary immunodeficiency and monogenic IBD virtual gene panel (R15 test) is applied to trio, duo, or proband only whole genome sequencing data (current turnaround weeks to months).
- Trio sequencing (patient and both parents) can enhance the interpretation of zygosity and pathogenicity and empower gene agnostic analysis beyond panel (not currently supported within R15).
- Rapid whole genome sequencing for acutely unwell children with a likely monogenic disorder (R14 test) is available in exceptional instances (eg, a baby or child on intensive care with hemophagocytic lymphohistiocytosis presentation and suspected monogenic IBD, mean turnaround time 9 days).
- Prenatal genetic testing, including preimplantation genetic diagnosis, might be sought for very restricted indications such as couples with a previous child diagnosed with a fully penetrant IL-10 signalling defect.
- Functional screening assays, such as lymphocyte subsets or dihydrorhodamine oxidative burst assay, or XIAP FACS fluorescence-activated cell sorting assay are available through clinical standard immunology laboratories. Specialised validation tests, such as IL-10 stimulation assays (IL-10 signalling defects), soluble IL-2 receptor (haemophagocytic lymphohistiocytosis), oligoclonal expansion (hypomorphic SCID defects), and telomere length (RTEL defects) are available via centralised NHS laboratories.
- Additional or incidental findings are reported to patients and families according to national standards.
- The NHS GMS offers potential intersection with research programmes such as Genomics England 100 000 Genome Project, the National Institutes of Health Research IBD BioResource, or research projects with focus on monogenic IBD such as the colitis of early onset—rare diseases within IBD project.
- Re-analysis of direct-to-consumer genomic testing is not commissioned by the NHS UK health system.
- Patient support groups recognise the need to help patients with paediatric and adult onset IBD who are potentially affected by a monogenic IBD diagnosis (eg, Crohn's in Childhood Research Association and Crohn's and Colitis UK) and provide support for patients and families with specific monogenic conditions (eg, the CGD society, the XLP Research Trust, the Primary Immune-deficiency Patient Support Charity UKPIPS, or Immunodeficiency UK).

For more on the **genomics education programme** see https://www.genomicseducation.hee.nhs.uk/

For more on the **National Genomic Test Directory** see https://www.england.nhs.uk/publication/national-genomic-test-directories/

For more on **prenatal diagnostics for IL10 signalling defects** see http://www.labs.gosh.nhs.uk/media/1389892/il10_v10.pdf

For more on the **virtual gene panel resource** see https://nhsgms-panelapp.genomicsengland.co.uk/

clinicians, including the patient's lead consultant and external specialists depending on the patient's presentation and genetic findings (figure 1; panel 4). Organisation will vary, but the GIM will typically co-opt internal and external representatives to specific case discussions from clinical genetics, immunology,

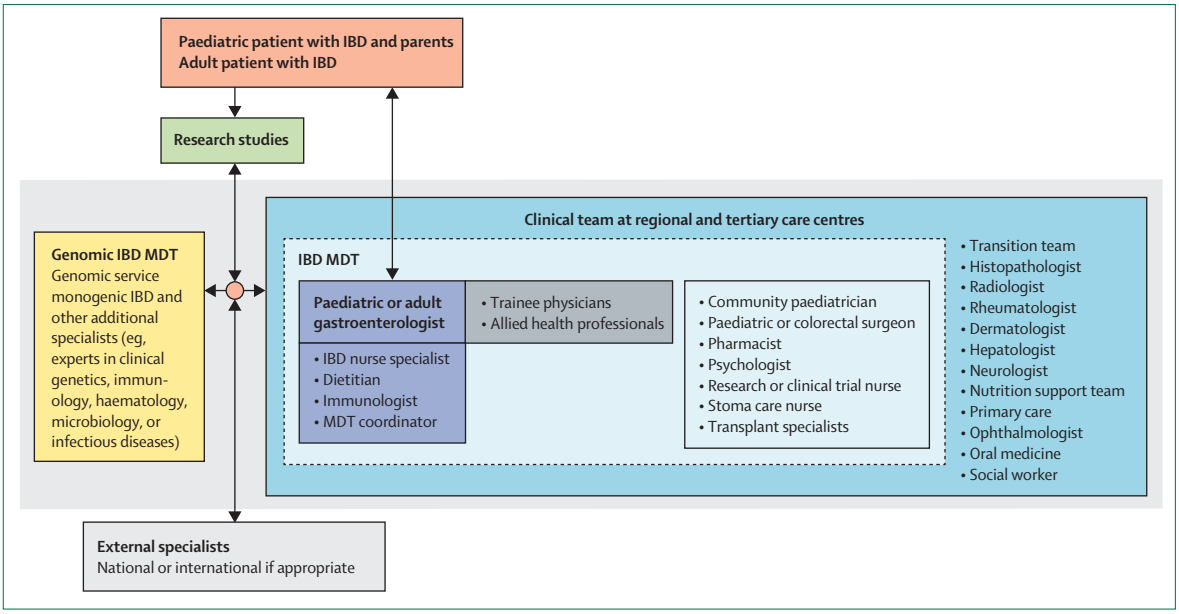

Figure 1: **The genomic IBD MDT**
Each patient with IBD is supported by a number of specialties depending on age and course of the disease (core IBD MDT support; dark blue).[7] To assess a potential monogenic cause of the problems, an additional focus on genomic medicine can be facilitated by a team, including the lead consultant and additional specialists, who will review key risk factors and consider whether to request clinical genomics support, review genetic findings, and discuss potential treatment options that are outside of the standard of care (in particular allogeneic haematopoietic stem-cell transplantation; yellow). Trainee physicians should attend MDT meetings as a valuable part of their training. Research studies (green) and external disease specific specialists (grey) can provide valuable input and complement the team. IBD=inflammatory bowel disease. MDT=multidisciplinary team.

haematology, and microbiology or infectious diseases, and should include at least one specialist in the diagnosis and treatment of monogenic IBD (table 1). Advice from external experts will typically be based on anonymised information to maintain patient confidentiality.

A hybrid format of face-to-face and virtual meetings can combine the strengths of local, holistic, in-depth knowledge of the patient with specialist knowledge of monogenic IBD available in tertiary institutions or national consortia. Inviting trainees to GIM meetings will enhance educational exposure to this developing field, and might generate interest in the genetic and immunological basis of monogenic IBD and the opportunities of precision medicine—thereby ultimately serving the interests of patients. Communication of results to patients (or their parents or guardians), coordination of functional validation of plausible variants, and setup of personalised care plans should be coordinated with support from the GIM (table 1).

Genomic testing criteria

Clinical genomics in the paediatric setting

Most patients with monogenic IBD present to paediatric services.[5,18] About a third of gene defects tend to cause intestinal inflammation in the infantile period (<2 years), a further third tend to present as very early onset (<6 years) and the remaining third present in children aged 6 years and older (figure 2). Clinicians should consider genomic testing in all patients with infantile-onset IBD and in very-early-onset IBD, particularly in the presence of one or more additional testing criteria (table 1; panel 5). Due to the variable phenotype and course of different genetic conditions, some patients will present directly to paediatric gastroenterologists whereas those with extraintestinal features (see later) might first present to other services, including paediatric immunology. For patients originally presenting with IBD, a careful history of intestinal and extraintestinal manifestations and comorbidities, the family history, and a limited set of laboratory tests (eg, full blood count, inflammatory markers, lymphocyte subsets, and immunoglobulin levels) should be undertaken at baseline since these can provide a clear signal for underlying inborn errors of immunity.[3,4] Characterising patients by Montreal or Paris classifications and using endoscopic, histological, and radiological features is considered standard of care although it has limited predictive power to identify monogenic IBD.[5,18,41,42]

A systematic taxonomy of 102 monogenic disorders associated with intestinal inflammation suggests some key classes of monogenic diseases based on phenotypic characteristics, laboratory assays, response to HSCT, single-cell gene expression, and biochemical pathways. Those classes highlight a diverse set of disorders, including defects with impaired IL-10 signalling, defective antimicrobial activity in phagocytes, defective cytoskeleton formation, autoinflammation, defective lymphocyte differentiation, dysfunctional regulatory T-cell activity, or epithelial predominant defects.

Panel 4: **Genomic inflammatory bowel disease multidisciplinary team (GIM) to evaluate patients with suspected or potential monogenic inflammatory bowel disease (IBD)**

GIM team structure

- The patient's lead consultant (typically a paediatric or adult gastroenterologist or immunologist, who coordinates care)
- An expert experienced in diagnosis and care of monogenic IBD
- Clinical geneticist or genetic counsellor
- Consider other specialists and allied health-care professionals involved in the patient's care (figure 1), specialty trainees, external experts with experience in the disease and gene function (maintaining patient confidentiality), and research participation (maintaining patient confidentiality)

The GIM discussion, the recommendation to the patient and family, as well as the response and consent of patient and families should be documented in the patient care record

Recommended information to be included in the documentation

Decision to investigate for monogenic cause

- IBD phenotype (current age, main diagnosis, type and location, including age of IBD onset and history of complications, surgery and medication)
- Extraintestinal manifestations and comorbidities
- Presence of features listed in the genomics testing criteria (panel 5)
- List of suspected candidate genes before genetic analysis
- Identification of who is discussing the diagnostics and potential findings with the family
- Initiate patient's consent to the diagnostic process, information on genetic counselling, information returned, and incidental findings
- Confirm test indication is commissioned for funding

Variant interpretation stage

- Genetic sequencing technology and analysis strategy (including the panel of genes investigated)
- Identify pathogenic, likely pathogenic variants, or variants of uncertain significance in monogenic-IBD-associated genes, and evidence that these variants are causative
- Confirm whether additional genetic, clinical, or functional tests are required
- Identify the likely pathological mechanism and potential implications
- Record any unexpected findings

Clinical care of patients with established monogenic IBD

- Identify implications for therapy and prevention of complications (and perform an iterative update based on the patient's condition and emerging scientific evidence)
- Perform an iterative update on implications for therapy and prevention of complications
- Identify whether additional specialist input is required (locally, nationally, or internationally)
- Identify whether genetic counselling is required

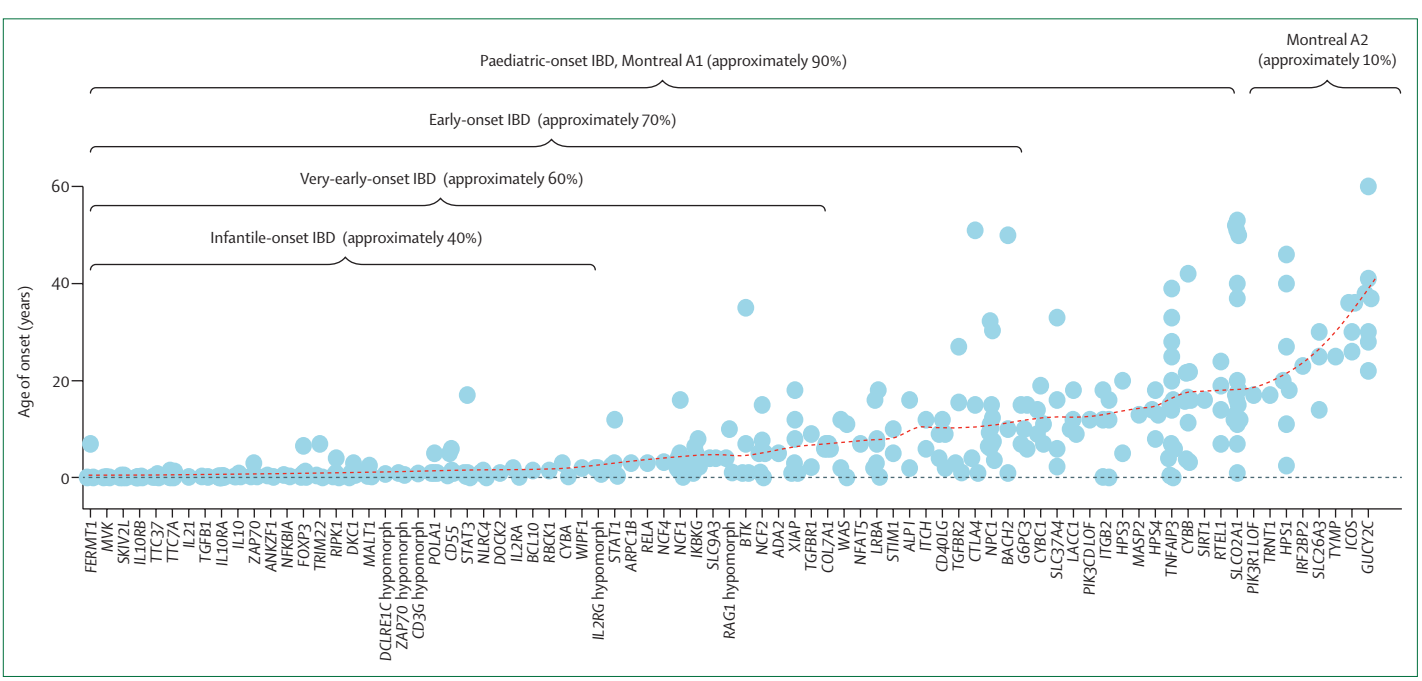

Figure 2: **Age of onset of IBD in patients with monogenic IBD**

Age of onset of patients with 102 monogenic conditions is shown. The median onset is highlighted in red. Data summarised based on Bolton et al 2021.[5] IBD=inflammatory bowel disease.

Panel 5: **Genomic testing criteria for monogenic inflammatory bowel disease (IBD)**

Genomic testing criteria

(1) Age of IBD onset: younger than 2 years or younger than 6 years particularly when additional criteria are observed
(2) Infection susceptibility (eg, due to recurrent sinopulmonary infections, systemic infections, meningitis, gastrointestinal infections, or cutaneous infections) in the presence of abnormal laboratory tests (eg, congenital lymphopenia or neutropenia, or combined immunoglobulin concentration abnormalities) meeting diagnostic criteria of an inborn error of immunity (ie, primary immunodeficiency)*
(3) Inflammatory features indicative for an inborn error of immunity, such as complex autoimmune features (especially features of IPEX syndrome in the paediatric population or severe multiorgan autoimmune disease in the adult population) or haemophagocytic lymphohistiocytosis
(4) Congenital multiple intestinal atresias or congenital diarrhoea
(5) Early-onset malignancy (age <25 years)
(6) Family history of suspected monogenic IBD (criteria 1–5)
(7) In advance of interventions or therapies with irreversible consequences and high risk for adverse outcome, such as haematopoietic stem-cell transplantation with transplantation-associated mortality or patients with a history of multiple intestinal resections and associated risk of short bowel syndrome, and total parenteral nutrition requirement

Supportive features

(1) Family history (ie, context of consanguinity, or multigeneration occurrence suggestive of recessive, X-linked, or highly penetrant dominant disorder)
(2) Failure to thrive, growth delay
(3) Severe perianal disease and impaired wound healing
(4) IBD refractory to multiple therapies†

*Criteria not explained by immunosuppressive or immunomodulatory IBD medication. †IBD refractory to multiple IBD therapies is a poorly defined term, and in isolation should not trigger genetic screening because the prevalence of monogenic IBD and the effect or benefit of clinical genomics in this cohort are unknown.

A large group of patients with monogenic IBD present with extraintestinal symptoms and complications (either independently driven by the underlying monogenetic disorder or related to the inflammatory activity), particularly features of primary immunodeficiency. Patients within monogenic IBD might present with (atypical) infection, immune activation syndromes (eg, haemophagocytic lymphohistiocytosis), or systemic autoimmunity.[3,5] Extraintestinal disease comprises diverse and sometimes pathognomonic features that suggest a particular potential monogenic IBD cause. These causes include infantile enterocolitis with perianal disease (due to mutations in *IL10RA*, *IL10RB*, or *IL10*), abscesses with bacterial or fungal infections (chronic granulomatous disorder [CGD]; *CYBB*, *CYBA*, *NCF1*, *NCF2*, *NCF4*, *PRKCD*, or *CYBC1*), eczema and thrombocytopenia (Wiskott Aldrich syndrome-like features; *WAS*, *WIPF1*, or *ARPC1B*), congenital neutropenia in the presence or absence of metabolic or syndromic features (*G6PC3* or *SLC37A4*), small and large bowel enteropathies, and dermatitis (immunodysregulation polyendocrinopathy enteropathy X-linked [IPEX] or IPEX-like syndrome, *FOXP3*, *IL2RA*, *IL2RB*, *STAT1*, or *STAT3*) or brittle hair, and chronic liver disease or cirrhosis, as well as immunodeficiency (tricho-hepatoenteric syndrome; *TTC37*, or *SKIV2L*). Laboratory features based on the recommended limited number of functional screening assays (panel 3) include numeric cellular abnormalities such as primary lymphopenia and neutropenia (*G6PC3* or *SLC37A4*), agammaglobulinaemia (*BTK*), or defective neutrophil function test (dihydrorhodamine assay to test for CGD; *CYBB*, *CYBA*, *NCF1*, *NCF2*, *NCF4*, *PRKCD*, or *CYBC1*).[5]

Congenital (non-bloody) diarrhoea with and without villous atrophy and multiple intestinal atresias are other distinctive symptoms arising in certain monogenic IBD conditions (*TTC7A*, *PI4KA*, *AGR2*, *SLC9A3*, *SLC26A3*, *GUCY2C*, *TTC37* or *SKIV2L*).[5] Several monogenic IBD conditions are associated with increased risk of malignancy such as lymphoma (IL-10 signalling defects; *CTLA4* or *SYK*).[43–45] Additional laboratory tests are relevant to characterise different organ involvement (ie, hepatitis or pancreatitis), autoinflammatory disease, or haemophagocytic lymphohistiocytosis.

Very young age of onset, specific symptoms, and laboratory features that suggest inborn errors of immunity, congenital intestinal dysfunction, and malignancy, as well as a family history of suspected monogenic IBD, are the strongest predictors of monogenic IBD and were therefore classified as monogenic IBD genomic testing criteria (panel 5). Other features, such as a family history of classical IBD, linear or ponderal growth delay, or severe or multiple treatment-refractory disease (ie, failure to respond to multiple biological therapies) are less specific and are therefore regarded as supportive features (panel 5). A limited set of immunological tests (full blood count, serum immunoglobulin levels, lymphocyte subsets, and neutrophil oxidative burst assay) are recommended to assess for a set of inborn errors of immunity (table 2).

For children and adolescents with IBD, it is important to discuss the opportunities of genomic medicine with their parents or guardians, while also highlighting the low probability that a monogenic diagnosis will be made with current technologies. Genomic testing that does not yield a molecular diagnosis can also be meaningful, as it provides reassurance that standard therapeutic approaches are indicated. Adolescents need to be involved in discussions about genetic testing and results. The views of adolescents regarding predictive gene variants for adult-onset disease and unexpected (ie, incidental)

findings should be carefully considered and respected in the decision-making process related to genomic medicine.[46] Patient views might differ from those of their physicians, or those of their parents or guardians. Complexities around individual consent for testing should be discussed with the clinical genetics team.

There is no formal cost–benefit analysis for the field of monogenic IBD. The overall costs of genome sequencing include sample preparation, sequencing, bioinformatic processing, analysis, and reporting.[47,48] Multiple studies of different rare diseases suggest that exome and genome sequencing can be more cost effective compared with targeted approaches.[49] There are major cost-saving opportunities if exome and genome sequencing are performed in a standardised manner and on a national scale.[50] Two published cases of monogenic IBD in the UK provide an estimate of potential cost-effectiveness. The first involved a patient aged 11 years who developed therapy-refractory Crohn's disease. This initial diagnosis was followed by 30 years of increasing therapy-refractory disease activity with exceptional health-care costs, until an XIAP defect was identified and appropriate therapy initiated.[20] Another patient with infantile-onset IBD, who was considered for HSCT, was diagnosed with an EPCAM defect.[11] The genetic diagnosis of this epithelial defect prevented progression with the HSCT and saved more than £220 000.

Clinical genomics in the adult setting

Adult gastroenterologists and immunologists see patients with monogenic forms of IBD typically after a genetic diagnosis has been established in the paediatric setting and when those patients are transitioned to adult care. In addition, two settings might require genomic diagnostics in adulthood: in the rare instance that patients develop adult-onset IBD, or the more common scenario of suspected paediatric-onset monogenic IBD where a diagnosis has not been reached during childhood (eg, as testing was not available, or genomic testing was incomplete due to the increasing number of novel monogenic IBD genes over time or a suspected false negative result in light of the more sensitive technologies available [panel 6]).[51–56] In both instances, discussion with a GIM is recommended to inform the decision to offer testing.

Onset of monogenic IBD during adulthood is a rare event, but is well recognised with several individual monogenic causes (figure 2). For example, patients with congenital diarrhoea due to *SLC26A3* variants or *GUCY2C* gain-of-function defects typically develop diarrhoea during early childhood and IBD as young adults (figure 2). Even if a monogenic IBD diagnosis is established in adulthood, this has profound implications for patient care (panel 6).

Genomic testing has a low yield in patients who are older than 6 years at the onset of IBD, but might be considered in patients who meet at least one of the genomic testing criteria (table 1; panel 5).

	Recommendation	Agreement
Practice point 1	In patients with very-early-onset IBD and, in particular, all those with infantile-onset IBD, we recommend a limited set of immunological tests (ie, complete blood count, serum immunoglobulin levels, lymphocyte subsets, and neutrophil oxidative burst assay) to assess for a set of inborn errors of immunity.	100%
Practice point 2	Therapy-refractory perianal or non-perianal fistulising Crohn's disease with collections can be a presentation of chronic granulomatous disease or XIAP deficiency, even in the absence of additional diagnostic signs of inborn errors of immunity. Since these two rare conditions are relevant differential diagnoses in male patients with adolescent or young adult-onset Crohn's disease, we suggest that a neutrophil function test and XIAP expression assay are considered in patients with those presentations.	100%
Practice point 3	Before genomic analysis, clinicians should discuss the potential effect of a genetic diagnosis with the patient, or the patient's parents or guardians depending on age. Genetic counselling should be offered if pathogenic variants have been established.	100%
Practice point 4	The treatment of patients with monogenic IBD is individualised and dependent on the genotype, the functional mechanisms that cause intestinal inflammation, the age and phenotype of the patient, and prognostic factors.	100%
Practice point 5	Patients with suspected or confirmed monogenic IBD should be offered the opportunity to participate in research studies.	100%
Practice point 6	Research studies in patients with IBD that perform genomic analysis into potential monogenic causes should have operating procedures in place to clarify the variant prioritisation process, and how potentially clinically relevant findings are communicated to patients and their clinical team who wish to receive genetic information. The clinical team should facilitate confirmatory clinical genetics testing and consider GIM input to ensure patient benefit.	100%
Practice point 7	In resource-limited settings, where access to genomic medicine is not available as clinical care, patient care will be guided by locally available resources and might be complemented by access to national and international specialist networks and research studies.	95%
Practice point 8	Consumer-based genetics is not recommended in a care setting where clinical genomic resources are available.	90%

IBD=inflammatory bowel disease. GIM=genomics inflammatory bowel disease multidisciplinary team.

Table 2: **Suggested good practice regarding genomic diagnosis and care coordination for monogenic inflammatory bowel disease in children and adults**

Genomic testing in patients with therapy-refractory IBD and need of interventions with high-risk impact

Results of genetic testing can help the therapeutic decision-making process, particularly for therapeutic interventions that come with a high risk of therapy-associated morbidity and mortality (eg, HSCT). Autologous HSCT has been proposed as a therapeutic option in adult patients with severe and therapy-refractory IBD.[57–59] Allogeneic HSCT has been used in some paediatric patients with potential undiagnosed monogenic conditions as a last resort.[11] Either approach could be futile without genetic testing—it is critical to exclude a monogenic IBD variant affecting the haematopoietic compartment in patients considered for autologous HSCT, and to exclude a monogenic epithelial (or mesenchymal or endothelial) monogenic IBD variant in patients potentially considered for allogeneic HSCT. Given the significant risk of HSCT-related morbidity and even mortality, avoiding harm caused by a futile transplant in the case of a relevant monogenic defect should be a key consideration in pretransplant planning (table 1).

Panel 6: **Case examples of monogenic inflammatory bowel disease (IBD) defects diagnosed in late adolescence and adulthood**

- A panel of monogenic IBD genes was investigated by exome sequencing performed in 503 patients aged 7–40 years who had a history of surgery and biological prescription.[20] A diagnosis of XIAP deficiency was made in one patient, 30 years after IBD onset (at age 11 years) who had undergone numerous operations, and spent more than 1000 days in hospital.[20]
- A diagnosis of X-linked chronic granulomatous disorder (CGD) was made in a patient aged 16 years, after he presented with a liver abscess. He had difficult-to-treat Crohn's disease since age 3 years and had previously developed neck abscesses and pneumonia. He underwent an allogeneic haematopoietic stem-cell transplantation (HSCT) after the CGD diagnosis was established (case included in Cole et al[54] and personal communication with TIC).
- A diagnosis of XIAP deficiency was detected for a patient aged 17 years, who was experiencing recurrent infections (particularly skin infections) and severe Crohn's disease since age 9 years.[55]
- In a patient with congenital neutropenia, severe infection susceptibility, ileocolic inflammation, and a Crohn's disease diagnosis, a diagnosis of *G6PC3* defect was established by genome sequencing at age 18 years. A subsequent allogeneic HSCT completely resolved intestinal symptoms of Crohn's disease.[56]
- In a patient aged 15 years with a history of infantile enterocolitis and relapse of B-cell lymphoma after two rounds of chemotherapy, an IL-10 receptor defect was established, which changed therapy from planning an autologous HSCT to allogeneic HSCT.[44] Non-Epstein-Barr virus related diffuse large B-cell lymphoma as well as Epstein-Barr virus associated lymphoma have been reported in patients with IL-10 receptor signalling defects between age 5·3 years and 16·5 years.[44,57,58]
- Identification of novel genes allows testing of patient with years of ongoing intestinal inflammation. Gain-of-function SYK variants were identified in adult patients after the molecular defect was functionally characterised.[43]
- An essential loss-of-function variant in the *LRBA* gene was identified by exome sequencing in a patient aged 37 years with a history of diarrhoea, duodenitis with villous atrophy, colonic abnormalities, arthritis, hepatitis, and a relevant family history.[59]

Some monogenic conditions, in particular XIAP deficiency or CGD, can present with severe Crohn's disease including severe therapy-refractory perianal disease, collections, and exceptional wound healing problems after surgery. Poorly controlled disease can lead to multiple intestinal resections, or complications after surgery such as collections, septic episodes, and short bowel syndrome. However, patients with adolescent-onset or adult-onset therapy-refractory ulcerative colitis or perianal Crohn's disease are not uncommon (eg, about 60% of patients with perianal Crohn's disease relapse during 1 year of anti-TNF therapy).[54] This means that the number of patients needed to test is probably very high; hundreds of patients might need to be screened to identify one patient with XIAP or CGD.[20,60] Since XIAP deficiency and CGD can be investigated by reliable functional tests with high sensitivity and specificity, functional tests are a fast and cost-effective way to investigate these disorders in clinical practice.[61,62] A neutrophil function test and XIAP expression assay might be diagnostic (table 2).

Future studies are required to establish the best initial diagnostic strategy that allows cost-effective and reliable testing in patient cohorts with expected low diagnostic yield (limited functional tests *vs* small targeted genetic panels or more comprehensive genomic testing as default option).

Which genes should be investigated?

The list of genes investigated as part of the analysis panel depends on cumulative evidence of published genotype–phenotype associations (number of patients described with each gene defect and the strength of the association, supported by functional data and model systems), and availability of treatment options.

In an European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) position statement, 75 genes were selected based on expert consensus.[3] Since then, additional genes have been described and quantitative parameters for IBD associations were proposed.[5] Defects in 102 genes show strong or moderate expressivity of intestinal inflammation.[5] For some monogenic conditions, the evidence is restricted to small case series or individual case reports, suggesting that further data are required to confirm genotype–phenotype associations. A regular panel review will allow for adoption of increasing numbers of genes over time and the collective evidence (panel 3). Genomic testing using such an adaptable gene panel approach provides an updated analysis when new evidence becomes available (table 1).

Interpreting genetic results

Interpreting the clinical significance of genetic variants is a complex process that requires plausible correlation of the patient history, the clinical presentation, and laboratory results. Variant classification can be established as recommended by the American College of Medical Genetics and the Association for Clinical Genomic Science. This variant classification framework includes assessing the previous evidence in variant or mutation databases, conducting literature searches, quantifying the variant frequency in disease cohorts and population datasets (eg, gnomAD), and the use of in silico tools to predict variant pathogenicity.[63,64] This

enables classification of sequence variants into one of five groups (appendix pp 9–11).[63]

The diagnostic genomic report will reflect the indication for sequencing and samples sequenced (eg, proband only or parent–child trio), the panel of genes investigated, the classification of any reportable variants, and might also summarise the evidence that was available to classify the variant and any additional testing or evidence (ie, genetic, clinical, or functional) that might aid variant reclassification to likely pathogenic or pathogenic. The report will typically comment on whether predictive testing or carrier testing is appropriate. Regional, national, or international specialist input might be required to decide whether further functional tests are required, and to discuss the implications of the genetic variant.

Actioning of results for the management of patients

A precise genetic diagnosis is likely to provide patients and clinicians with a greater understanding of the disease, inform on potential disease progression, allow discussion about targeted therapies, and guide genetic counselling. A genetic diagnosis might necessitate a refocus of support by individual care teams, such as increased input from the immunology team where a primary immunodeficiency is identified. It might enable the individual to receive information from patient support groups that specifically focus on individual monogenic conditions (panel 3).

A genetic diagnosis might also guide treatment decisions by informing the likelihood of response to commonly used therapies in IBD. For example, patients with IL-10 signalling defects are unlikely to respond to anti-TNF therapy, but might benefit from off-label treatment with IL-1 targeting treatments.[65] Patients with XIAP deficiency can be informed of the risk of fistulising disease and wound healing problems after surgery.[66] For patients with CGD, the increased risk of infection during anti-TNF therapy might influence treatment choice.[67]

Patients could be enrolled into clinical research trials that include personalised therapeutics or might consider off-licence treatment strategies under expert advice, based on molecular rationale (eg, IL-1 blockade in mevalonate kinase deficiency, or treatment with abatacept in patients with CTLA4 and LRBA deficiency, or IL18BP in XIAP deficiency).[68–70]

The most important change in management arising from a monogenic IBD diagnosis is currently the potential for allogeneic HSCT that is curative for some conditions (in particular IL-10 signalling defects, CGD, IPEX syndrome, and XIAP deficiency), although by no means all.[5,18] For some of the inborn errors of immunity, such as CGD due to *CYBB* variants,[6] gene therapies are in clinical development. Such highly specialised treatment strategies might best be provided with the support of national and international clinical networks involving paediatric and adult gastroenterologists and clinical immunology specialists. Overall, evidence for the therapeutic effectiveness of most medications and interventions is scarce. Consequently, no formal recommendations for treatment can be made, and an individualised approach is required based on the disease gene, the genetic variants identified, age of the patient, intestinal and extraintestinal manifestations, history of previous medications, organ damage, and the perspective of the patient or family.[5,18,71,72]

The availability of genetic counselling is paramount. Genetic counsellors are highly skilled in discussing genetic information with patients and their families while maintaining confidentiality and adherence to legal standards. The prediction of recurrence risk for a monogenic disorder can be highly relevant to parents and guardians with affected children. Genetic findings might also be relevant to the wider family (adult siblings or non-first degree relatives). Before genomic analysis, clinicians should discuss the potential effect of a genetic diagnosis with the patient, or their parent or guardian, and consider genetic counselling (table 2).

In some instances, parents or guardians might wish to consider prenatal testing or preimplantation diagnosis for a fully penetrant form of monogenic IBD (such as IL-10 signalling defects), services that are available in the UK and several other countries.[73]

In summary, the treatment of patients with monogenic IBD is individualised and dependent on the genotype, the functional mechanisms that cause intestinal inflammation, and the patient's age, phenotype, and prognostic factors (table 2). Where no genetic diagnosis can be established, a pragmatic approach is required: (1) to follow the established paediatric and adult IBD guidelines, (2) to consider immunomodulatory or immunosuppressive therapies based on clinical and immunological similarities with known monogenic defects, while (3) carefully considering potential benefit and risks of the therapies, and (4) be guided by the quality of life of the patient.

Training requirements in genomics for paediatric and adult gastroenterologists

The successful implementation of genomic medicine for monogenic IBD is dependent on the awareness of doctors to recognise potential monogenic IBD. Doctors need to recognise the benefits and pitfalls of clinical genomics and seek expert advice when appropriate. Training requirements formalised in the syllabus of paediatric gastroenterology organisations such as ESPGHAN, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, or national organisations such as the Royal College of Paediatrics and Child Health recognise the need to establish a genetic diagnosis, but scarcely cover the underlying principles of genomic medicine in the training

curriculum.[74] Adult gastroenterology curricula are even less specific.[75] Not surprisingly, a web-based nationwide survey of UK gastroenterology specialty trainees conducted in 2017 found that 91% of trainees considered that their local training programme did not adequately cover the field of genomic medicine.[76]

Identification of potential actionable monogenic IBD variants in the research setting

In the past decade, monogenic IBD diagnoses were often established by next-generation sequencing in the context of translational research studies.[3] The emerging availability of genomic medicine means that the role of research studies needs to be redefined. Whereas clinical genomics aims to establish a timely diagnosis in a patient with suspected monogenic IBD, research aims to explore beyond this clinical standard of care to identify novel genes and mechanisms, characterise interactions between genes, facilitate population-based studies, and develop and evaluate novel therapies.

Nevertheless, potentially actionable genetic variants might emerge from research studies that are relevant to the care of a specific patient. Clear pathways are needed to explain how research-derived genetic variants are prioritised and subsequently validated. A steering group is best suited to assess potentially clinically relevant variants and to suggest how those variants are, in line with the individual study protocol, communicated to patients. This process should follow defined operating procedures including initial and potentially reaffirmed patient consent.[9] Although the research team might provide the patient's lead consultant with the available evidence and recommendations, the final decision regarding discussion within a GIM, communication of results with patient, confirmation in a clinical setting, counselling, and therapeutic implications should remain with the local clinical team (table 2). A suggested pathway to integrate research findings in clinical care is depicted in the appendix (p 12).

Since research is essential for closing relevant knowledge gaps and to improve patient care, patients with suspected or confirmed monogenic IBD should be offered the opportunity to participate in research studies (table 2). All patients in England tested using whole genome sequencing through the NHS GMS are offered the opportunity to consent for their data to be submitted to the National Genomic Research Library (NGRL). The NGRL is managed by Genomics England and enables approved researchers to access the data. A mechanism is in place to enable findings from research to be communicated to the NHS, to inform clinical practice.

Establishing a genomic diagnosis in a resource-limited setting

Although there is increased availability of genomic technologies in many parts of the world, patients may be excluded as a consequence of resource-limited health-care systems, partial coverage of genomic medicine by some health-care insurers, or poor access of some individuals to health-care insurance. In these settings, access to research studies that investigate monogenic IBD causes, and virtual centralised national and international monogenic IBD clinics can help provide access to diagnostics (table 2).[3] Even in settings where treatments such as HSCT are not feasible due to insufficient resources, a positive genetic diagnosis might be partially clinically actionable via the provision of targeted antimicrobial chemoprophylaxis or considering therapy with off-label and repurposed drugs with some plausible mechanistic specificity (eg, thalidomide in IL-10 receptor defects).[77]

Consumer-initiated genomics

Outside the health-care system, whole exome and genome sequencing are becoming available to consumers via direct-to-consumer testing, with growing markets in the UK and worldwide.[8] In an international market major challenges relate to informed consent, testing of children, difficulties in interpreting the complex data by consumers (potentially patients), absence of genetic counselling, commercialisation of data, genetic privacy, dealing with unexpected genetic results, and scarcity of clinical guidance or MDT involvement once relevant clinical questions arise.[78–80] Since the reported analysis for rare variants frequently fails to provide established quality control parameters required to interpret the data, clinical geneticists in health-care systems are typically not commissioned to interpret results from direct-to-consumer testing. Consequently, consumer-based genetics is not recommended for diagnosis in a care setting where clinical genomic resources are available (table 2).

Challenges and future needs

When genomic testing is established at a national level, there is an opportunity to achieve a more standardised approach, aiming to reduce disparities in genomic health-care use because of geographical differences, limited awareness of monogenic IBD in the adult care setting, and variations due to ethnicity.[81] Population-based application of genomics in research and standardisation of variant reporting could reduce ancestry-related bias when using genomic databases, since information on genetic variants is biased.[82] Worldwide, variable resources for genomic medicine and variable health-care insurer policies create additional disparities in access to genomic medicine for patients.[83] Despite similar national challenges, there are countries that differ in their strategies for implementing genomic medicine.[84] Applying genomic medicine in immune-mediated disorders is particularly difficult because the expressed phenotype from the same genetic defect can vary based on the surrounding genetic and environmental context (eg, variation in diet, the microbiome, or lifestyle factors).

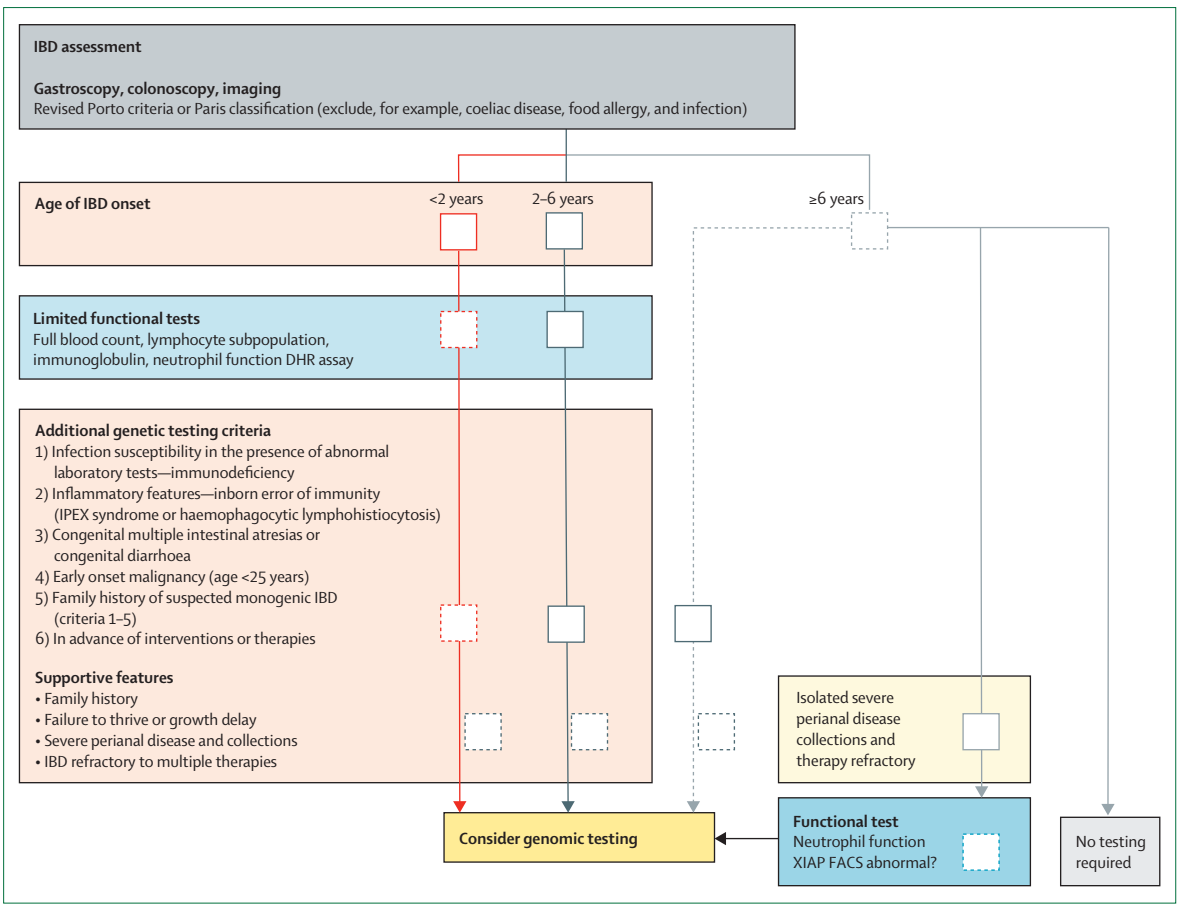

Figure 3: **Monogenic IBD testing criteria and risk stratification**
Initiating genomic testing based on risk stratification according to age of IBD onset and additional genetic testing criteria and supportive features. The pathway is adapted from the Porto ESPGHAN guidelines to clarify integration of adolescents and adults.[3] IBD=inflammatory bowel disease. DHR=dihydrorhodamine. IPEX=immune dysregulation polyendocrinopathy enteropathy X-linked syndrome. XIAP FACS=X-linked inhibitor of apoptosis protein fluorescence-activated cell sorting.

Cost-effectiveness of interventions is a key consideration: the high cost of genomic programmes must be balanced against the reduction in diagnostic delay and the benefit to individual patients of preventing decades of failed clinical interventions.[20,56] Whereas there are reasonable estimates on the number-needed-to-screen in infantile-onset or very-early-onset IBD, the data might include selection or referral bias, causing an enrichment of patients with more severe phenotype in centres with an interest in genomic medicine. Better estimates in older populations are needed.

It is currently not clear how a health-care system will cope with increasing numbers of variants of unknown significance that emerge from increased screening. How functional validation of genetic results needing highly specialised assays can be implemented in routine clinical or research settings needs further clarification. Guidance is needed as to how clinical genomic data will be re-analysed and results updated over time. Furthermore, informed strategies are required to communicate genetic information to patients with disorders of variable expressivity, or when implications for disease and future health and therapeutic evidence are not certain. These uncertainties merit national and international discussion.

After considering the evidence and consensus opinion presented in this guideline, we propose an exemplar clinical genomics pathway for monogenic IBD diagnosis and management coordination (figure 3).

Conclusions

Genomic medicine is a key service for facilitating personalised medicine in the context of monogenic IBD. This guideline extends the published position statement on clinical genomics by the Porto group of ESPGHAN.[3] It provides practical advice on how to establish clinical genomics in a national health-care system for paediatric and adult patients. It highlights the value of adaptive genomic screening strategies over targeted panel sequencing. This guideline defines the structure of genomic IBD MDTs at the interphase between the clinical care teams and genomic laboratory hubs, examines the role of direct-to-consumer genomics, and

evaluates the process of how potentially actionable genetic variants identified through research studies can transition into clinical care.

Contributors

HHU, JK, and CAL were responsible for conceptualisation of the guideline. The method was developed by CAL, JK, ST, and HHU. JK, CAL, KDJJ, CAA, ELB, CB, HB, TIC, KCG, VG, SHa, DH, ABH, SHe, AL, MP, RKR, RAS, ST, DCW, and HHU undertook data review, analysis, and statement voting. JK, CAL, and HHU were responsible for project supervision. Visualisation was developed by HHU and CB. The original draft was written by HHU, JK, KDJJ, CAL, and ST. The patient-facing summary was written by VG, DH, HB, SHa, ST, CAL, and HHU. Review and editing of the final manuscript was undertaken by JK, CAL, KDJJ, CAA, ELB, CB, HB, TIC, KCG, VG, SHa, DH, ABH, SHe, AL, MP, RKR, RAS, ST, DCW, and HHU.

Declaration of interests

All members of the panel were asked to declare a minimum of 12 months competing personal and non-personal financial or non-financial interests when joining the group and before manuscript submission. eDelphi participants could abstain from voting where they either did not have sufficient knowledge to vote on a particular statement, or where they identified themselves as having a conflict precluding voting. CAA declares directorship of Anderson Genomics Consultancy, and consultancy for Genomics and Bridge Bio. HB is a Clinical Nurse Specialist for the Chronic Granulomatous Disorder Society. KCG is a Trustee for the UK Primary Immunodeficiency Network. VG is an employee of Crohn's & Colitis UK. SHa declares consultancy for Takeda. DH declares an advisory role for The X-linked Lymphoproliferative Syndrome Research Trust. ABH has been an invited speaker for Takeda UK, Ferring, and Janssen-Cilag; is Chair of the Crohn's & Colitis UK Medical Research Awards Committee and clinical representative on the Trustee Board; is Chair of the IBD UK Benchmarking Working Group and member of the IBD UK Steering Committee. CAL declares research support or fees for development and delivery of non-promotional education (or both) from Janssen, Takeda, AbbVie, AstraZeneca, Eli Lilly, Orion, Pfizer, Roche, Sanofi Aventis, Ferring, Union Chimique Belge (UCB), Biogen, and Genentech; is Secretary of the Inflammatory Bowel Disease Section, British Society of Gastroenterology, and a member of the Steering Committee of IBD UK. MP declares speaker fees from Janssen; declares research support for the IBD BioResource from Pfizer and Gilead (and research fellow for Pfizer); and is a member of the Crohn's & Colitis UK Research Advisory Group. RKR declares honoraria from Pharmacosmos and Celltrion; declares research support from Nestle; and is a member of the European Society for Paediatric Gastroenterology Hepatology and Nutrition Porto Group Monogenic IBD Guideline. RAS declares speaker honoraria, consultancy for early phase studies, and conference fees from GlaxoSmithKline, AbbVie, and Janssen. ST declares consultancy from Biogen, Bristol-Myers Squibb, Celgene, ChemoCentryx, Cosmo, Enterome, Ferring, Giuliani, GlaxoSmithKline, Genentech, Immunocore, Immunometabolism, Janssen, Lilly, MSD, Merck, Neovacks, Novonordisk, Novartis, NPS Pharmaceuticals, Pfizer, Proximagen, Receptos, Roche, Shire, Sigmoid Pharma, Takeda, Topivert, UCB, VHsquared, Vifor, Zeria, Sensyne, Satisfai, Bioclinica, Equillium, Mestag, Sorriso, and Protagonist; declares research support from AbbVie, the International Organization for the Study of Inflammatory Bowel Diseases, Lilly, UCB, Vifor, Norman Collisson Foundation, Pfizer, UK–India Education and Research Initiative, ECCO Health Care, and the Helmsley Trust; declares honoraria from AbbVie, Amgen, Biogen, Ferring, Takeda, Lilly; and declares travel expenses covered or reimbursed from AbbVie, Lilly, Johnson & Johnson, Pfizer, Takeda, Ferring, Amgen, and Biogen. HHU declares consultancy from OMass, Mestag, and SAB Novartis; project collaboration with Celgene/Bristol-Myers Squibb, Janssen, UCB, MiroBio, and Regeneron; grant reviewing for Crohn's In Childhood Research Association; and is a member of the Porto Group of ESPGHAN. DCW declares speaker fees from Celltrion and AbbVie; and is a member of the Scientific committee of the Crohn's in Childhood Research Association charity. ELB, CB, TIC, SHe, KDJJ, JK, and AL declare no competing interests. Further details of competing interests of authors are presented in the appendix (p 1).

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References

1 de Lange KM, Moutsianas L, Lee JC, et al. Genome-wide association study implicates immune activation of multiple integrin genes in inflammatory bowel disease. *Nat Genet* 2017; **49:** 256–61.

2 Liu JZ, van Sommeren S, Huang H, et al. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. *Nat Genet* 2015; **47:** 979–86.

3 Uhlig HH, Charbit-Henrion F, Kotlarz D, 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* 2021; **72:** 456–73.

4 Uhlig HH, Schwerd T, Koletzko S, et al. The diagnostic approach to monogenic very early onset inflammatory bowel disease. *Gastroenterology* 2014; **147:** 990–1007.

5 Bolton C, Smillie CS, Pandey S, et al. An integrated taxonomy for monogenic inflammatory bowel disease. *Gastroenterology* 2022; **162:** 859–76.

6 Kohn DB, Booth C, Kang EM, et al. Lentiviral gene therapy for X-linked chronic granulomatous disease. *Nat Med* 2020; **26:** 200–06.

7 Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut* 2019; **68** (suppl 3)**:** s1–s106.

8 Ormondroyd E, Border P, Hayward J, Papanikitas A. Genomic health data generation in the UK: a 360 view. *Eur J Hum Genet* 2021; **30:** 782–89.

9 Parkes M. IBD BioResource: an open-access platform of 25 000 patients to accelerate research in Crohn's and Colitis. *Gut* 2019; **68:** 1537–40.

10 Serra EG, Schwerd T, Moutsianas L, et al. Somatic mosaicism and common genetic variation contribute to the risk of very-early-onset inflammatory bowel disease. *Nat Commun* 2020; **11:** 995.

11 Kammermeier J, Drury S, James CT, et al. Targeted gene panel sequencing in children with very early onset inflammatory bowel disease—evaluation and prospective analysis. *J Med Genet* 2014; **51:** 748–55.

12 Kammermeier J, Dziubak R, Pescarin M, et al. Phenotypic and genotypic characterisation of inflammatory bowel disease presenting before the age of 2 years. *J Crohns Colitis* 2017; **11:** 60–69.

13 Ashton JJ, Andreoletti G, Coelho T, et al. Identification of variants in genes associated with single-gene inflammatory bowel disease by whole-exome sequencing. *Inflamm Bowel Dis* 2016; **22:** 2317–27.

14 Ashton JJ, Mossotto E, Stafford IS, et al. Genetic sequencing of pediatric patients identifies mutations in monogenic inflammatory bowel disease genes that translate to distinct clinical phenotypes. *Clin Transl Gastroenterol* 2020; **11:** e00129.

15 Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; **336:** 924–26.

16 Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ* 2010; **182:** e839–42.

17 British Society of Gastroenterology. British Society of Gastroenterology writing and review process on the production of BSG Guidelines. September, 2021. https://www.bsg.org.uk/wp-content/uploads/2021/09/BSG-Guidelines-Writing-and-Review-Process-Document-Sept-2021.pdf (accessed March 28, 2022).

18 Nambu R, Warner N, Mulder DJ, et al. A systematic review of monogenic inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2022; **20:** e653–e63.

19 Both T, Dalm V, Richardson SA, et al. Inflammatory bowel disease in primary immunodeficiency disorders is a heterogeneous clinical entity requiring an individualized treatment strategy: a systematic review. *Autoimmun Rev* 2021; **20:** 102872.

20 Quaranta M, Wilson R, Goncalves Serra E, et al. Consequences of identifying XIAP deficiency in an adult patient with inflammatory bowel disease. *Gastroenterology* 2018; **155:** 231–34.

21 Taylor JC, Martin HC, Lise S, et al. Factors influencing success of clinical genome sequencing across a broad spectrum of disorders. *Nat Genet* 2015; **47:** 717–26.

22 Kelsen JR, Dawany N, Moran CJ, et al. Exome sequencing analysis reveals variants in primary immunodeficiency genes in patients with very early onset inflammatory bowel disease. *Gastroenterology* 2015; **149:** 1415–24.

23 Ostrowski J, Paziewska A, Lazowska I, et al. Genetic architecture differences between pediatric and adult-onset inflammatory bowel diseases in the Polish population. *Sci Rep* 2016; **6:** 39831.

24 Xiao Y, Wang XQ, Yu Y, et al. Comprehensive mutation screening for 10 genes in Chinese patients suffering very early onset inflammatory bowel disease. *World J Gastroenterol* 2016; **22:** 5578–88.

25 Petersen BS, August D, Abt R, et al. Targeted gene panel sequencing for early-onset inflammatory bowel disease and chronic diarrhea. *Inflamm Bowel Dis* 2017; **23:** 2109–20.

26 Suzuki T, Sasahara Y, Kikuchi A, et al. targeted sequencing and immunological analysis reveal the involvement of primary immunodeficiency genes in pediatric IBD: a Japanese multicenter study. *J Clin Immunol* 2017; **37:** 67–79.

27 Charbit-Henrion F, Parlato M, Hanein S, et al. Diagnostic yield of next-generation sequencing in very early-onset inflammatory bowel diseases: a multicentre study. *J Crohns Colitis* 2018; **12:** 1104–12.

28 Amininejad L, Charloteaux B, Theatre E, et al. Analysis of genes associated with monogenic primary immunodeficiency identifies rare variants in XIAP in patients with Crohn's disease. *Gastroenterology* 2018; **154:** 2165–77.

29 Fang YH, Luo YY, Yu JD, Lou JG, Chen J. Phenotypic and genotypic characterization of inflammatory bowel disease in children under six years of age in China. *World J Gastroenterol* 2018; **24:** 1035–45.

30 Crowley E, Warner N, Pan J, 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* 2020; **158:** 2208–20.

31 Lega S, Pin A, Arrigo S, et al. Diagnostic approach to monogenic inflammatory bowel disease in clinical practice: a ten-year multicentric experience. *Inflamm Bowel Dis* 2020; **26:** 720–27.

32 Uchida T, Suzuki T, Kikuchi A, et al. Comprehensive targeted sequencing identifies monogenic disorders in patients with early-onset refractory diarrhea. *J Pediatr Gastroenterol Nutr* 2020; **71:** 333–39.

33 Rahmani F, Rayzan E, Rahmani MR, et al. Clinical and mutation description of the first Iranian cohort of infantile inflammatory bowel disease: the Iranian Primary Immunodeficiency Registry (IPIDR). *Immunol Invest* 2021; **50:** 445–59.

34 Uhlig HH. Monogenic diseases associated with intestinal inflammation: implications for the understanding of inflammatory bowel disease. *Gut* 2013; **62:** 1795–805.

35 Phillips KA, Douglas MP, Wordsworth S, Buchanan J, Marshall DA. Availability and funding of clinical genomic sequencing globally. *BMJ Glob Health* 2021; **6:** e004415

36 Sullivan KE, Conrad M, Kelsen JR. Very early-onset inflammatory bowel disease: an integrated approach. *Curr Opin Allergy Clin Immunol* 2018; **18:** 459–69.

37 Taylor J, Craft J, Blair E, et al. Implementation of a genomic medicine multi-disciplinary team approach for rare disease in the clinical setting: a prospective exome sequencing case series. *Genome Med* 2019; **11:** 46.

38 National Health Service, England. National Genomic Test Directory. Feb 2, 2022. https://www.england.nhs.uk/publication/national-genomic-test-directories/ (accessed March 29, 2022A).

39 McDermott H, Baple E, Ellard S, Naik S. 1435 Rapid exome sequencing in acutely unwell children—providing new diagnostic options in intensive care settings. *Arch Dis Child* 2021; **106:** A368–69.

40 Gorzynski JE, Goenka SD, Shafin K, et al. Ultrarapid nanopore genome sequencing in a critical care setting. *N Engl J Med* 2022; **386:** 700–02.

41 Barber JL, Shah N, Watson TA. Early onset inflammatory bowel disease—What the radiologist needs to know. *Eur J Radiol* 2018; **106:** 173–82.

42 Conrad MA, Carreon CK, Dawany N, Russo P, Kelsen JR. Distinct histopathological features at diagnosis of very early onset inflammatory bowel disease. *J Crohns Colitis* 2019; **13:** 615–25.

43 Wang L, Aschenbrenner D, Zeng Z, et al. Gain-of-function variants in SYK cause immune dysregulation and systemic inflammation in humans and mice. *Nat Genet* 2021; **53:** 500–10.

44 Shouval DS, Ebens CL, Murchie R, et al. Large B-cell lymphoma in an adolescent patient with interleukin-10 receptor deficiency and history of infantile inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2016; **63:** e15–17.

45 Egg D, Schwab C, Gabrysch A, et al. Increased risk for malignancies in 131 affected CTLA4 mutation carriers. *Front Immunol* 2018; **9:** 2012.

46 Lillie N, Prows CA, McGowan ML, Blumling AA, Myers MF. Experiences of adolescents and their parents after receiving adolescents' genomic screening results. *J Genet Couns* 2022; **31:** 608–19

47 Schwarze K, Buchanan J, Fermont JM, et al. The complete costs of genome sequencing: a microcosting study in cancer and rare diseases from a single center in the United Kingdom. *Genet Med* 2020; **22:** 85–94.

48 Abbott M, McKenzie L, Moran BVG, et al. Continuing the sequence? Towards an economic evaluation of whole genome sequencing for the diagnosis of rare diseases in Scotland. *J Community Genet* 2022; **13:** 487–501.

49 Tan TY, Dillon OJ, Stark Z, et al. Diagnostic impact and cost-effectiveness of whole-exome sequencing for ambulant children with suspected monogenic conditions. *JAMA Pediatr* 2017; **171:** 855–62.

50 Turnbull C, Sud A, Houlston RS. Cancer genetics, precision prevention and a call to action. *Nat Genet* 2018; **50:** 1212–18.

51 Cole T, Pearce MS, Cant AJ, Cale CM, Goldblatt D, Gennery AR. Clinical outcome in children with chronic granulomatous disease managed conservatively or with hematopoietic stem cell transplantation. *J Allergy Clin Immunol* 2013; **132:** 1150–55.

52 Zacharias SA, Seshadri P, Hwang S, et al. Delayed diagnosis of X-linked lymphoproliferative syndrome type 2 in a 17-year-old male with severe Crohn's disease and recurrent skin infections. *JPGN Rep* 2021; **2:** e102.

53 Bolton C, Burch N, Morgan J, et al. Remission of inflammatory bowel disease in glucose-6-phosphatase 3 deficiency by allogeneic haematopoietic stem cell transplantation. *J Crohns Colitis* 2020; **14:** 142–47.

54 Neven B, Mamessier E, Bruneau J, et al. A Mendelian predisposition to B-cell lymphoma caused by IL-10R deficiency. *Blood* 2013; **122:** 3713–22.

55 Engelhardt KR, Shah N, Faizura-Yeop I, et al. Clinical outcome in IL-10- and IL-10 receptor-deficient patients with or without hematopoietic stem cell transplantation. *J Allergy Clin Immunol* 2013; **131:** 825–30.

56 Vardi I, Chermesh I, Werner L, et al. Monogenic Inflammatory Bowel Disease: it's never too late to make a diagnosis. *Front Immunol* 2020; **11:** 1775.

57 Snowden JA, Hawkey C, Hind D, et al. Autologous stem cell transplantation in refractory Crohn's disease - low intensity therapy evaluation (ASTIClite): study protocols for a multicentre, randomised controlled trial and observational follow up study. *BMC Gastroenterol* 2019; **19:** 82.

58 Brierley CK, Castilla-Llorente C, Labopin M, et al. Autologous haematopoietic stem cell transplantation for Crohn's disease: a retrospective survey of long-term outcomes from the European Society for Blood and Marrow Transplantation. *J Crohns Colitis* 2018; **12:** 1097–103.

59 Lindsay JO, Allez M, Clark M, et al. Autologous stem-cell transplantation in treatment-refractory Crohn's disease: an analysis of pooled data from the ASTIC trial. *Lancet Gastroenterol Hepatol* 2017; **2:** 399–406.

60 Jaggi P, Scherzer R, Knieper R, Mousa H, Prasad V. Utility of screening for chronic granulomatous disease in patients with inflammatory bowel disease. *J Clin Immunol* 2012; **32:** 78–81.

61 Marsh RA, Villanueva J, Zhang K, et al. A rapid flow cytometric screening test for X-linked lymphoproliferative disease due to XIAP deficiency. *Cytometry B Clin Cytom* 2009; **76:** 334–44.

62 Kanegane H, Hoshino A, Okano T, et al. Flow cytometry-based diagnosis of primary immunodeficiency diseases. *Allergol Int* 2018; **67:** 43–54.

63 Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015; **17:** 405–24.

64 Ellard S, Baple EL, Callaway A, Berry I. ACGS best practice guidelines for variant classification in rare disease 2020. Feb 4, 2020. https://www.acgs.uk.com/media/11631/uk-practice-guidelines-for-variant-classification-v4-01-2020.pdf (accessed April 20, 2022).

65 Shouval DS, Biswas A, Kang YH, et al. Interleukin 1beta mediates intestinal inflammation in mice and patients with interleukin 10 receptor deficiency. *Gastroenterology* 2016; **151:** 1100–04.

66 Yang L, Booth C, Speckmann C, et al. Phenotype, genotype, treatment, and survival outcomes in patients with X-linked inhibitor of apoptosis deficiency. *J Allergy Clin Immunol* 2022; **150:** 456–66.

67 Conrad A, Neven B, Mahlaoui N, et al. Infections in patients with chronic granulomatous disease treated with tumor necrosis factor alpha blockers for inflammatory complications. *J Clin Immunol* 2021; **41:** 185–93.

68 Levy M, Arion A, Berrebi D, et al. Severe early-onset colitis revealing mevalonate kinase deficiency. *Pediatrics* 2013; **132:** e779–83.

69 Egg D, Rump IC, Mitsuiki N, et al. Therapeutic options for CTLA-4 insufficiency. *J Allergy Clin Immunol* 2022; **149:** 736–46.

70 Geerlinks AV, Dvorak AM, Consortium XDT. A case of XIAP deficiency successfully managed with tadekinig alfa (rhIL-18BP). *J Clin Immunol* 2022; **42:** 901–03.

71 Ouahed J, Spencer E, Kotlarz D, 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* 2020; **26:** 820–42.

72 Kelsen JR, Sullivan KE, Rabizadeh S, et al. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Position Paper on the evaluation and management for patients with very early-onset inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2020; **70:** 389–403.

73 Ye Z, Hu W, Wu B, et al. Predictive prenatal diagnosis for infantile-onset inflammatory bowel disease because of interleukin-10 signalling defects. *J Pediatr Gastroenterol Nutr* 2021; **72:** 276–81.

74 Paediatric Gastroenterology, Hepatology and Nutrition. Level 3: paediatrics sub-specialty syllabus Aug 1, 2018. https://www.rcpch.ac.uk/sites/default/files/2018-03/phgan_syllabus_final.pdf (accessed March 28, 2022).

75 Joint Royal Colleges of Physicians Training Board. Curriculum for gastroenterology training. Implementation August 2022. May 18, 2021. https://www.jrcptb.org.uk/sites/default/files/DRAFT%20Gastroenterology%20curriculum%202022.pdf (accessed March 29, 2022).

76 Al Bakir I, Sebepos-Rogers GM, Burton H, Monahan KJ. Mainstreaming of genomic medicine in gastroenterology, present and future: a nationwide survey of UK gastroenterology trainees. *BMJ Open* 2019; **9:** e030505.

77 Ye Z, Qian L, Hu W, et al. Clinical outcome of infantile-onset inflammatory bowel disease in 102 patients with interleukin-10 signalling deficiency. *Aliment Pharmacol Ther* 2022; **55:** 1414–22.

78 Tandy-Connor S, Guiltinan J, Krempely K, et al. False-positive results released by direct-to-consumer genetic tests highlight the importance of clinical confirmation testing for appropriate patient care. *Genet Med* 2018; **20:** 1515–21.

79 Hsieh V, Braid T, Gordon E, Hercher L. Direct-to-consumer genetic testing companies tell their customers to 'see a genetic counselor'. How do genetic counselors feel about direct-to-consumer genetic testing? *J Genet Couns* 2021; **30:** 191–97.

80 Daemmrich AA. 23andMe: the business and ethics of personal genetics testing. *SSRN* 2015; published online April 2. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2587944 (preprint).

81 Carroll NM, Blum-Barnett E, Madrid SD, et al. Demographic differences in the utilization of clinical and direct-to-consumer genetic testing. *J Genet Couns* 2020; **29:** 634–43.

82 Kessler MD, Yerges-Armstrong L, Taub MA, et al. Challenges and disparities in the application of personalized genomic medicine to populations with African ancestry. *Nat Commun* 2016; **7:** 12521.

83 Beachy SH, Alper J, Addie S. Understanding disparities in access to genomic medicine: proceedings of a workshop. National Academies Press: Washington DC; 2018.

84 Gaille M, Horn R, Consortia U-FG. The ethics of genomic medicine: redefining values and norms in the UK and France. *Eur J Hum Genet* 2021; **29:** 780–8.