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[*1], Christopher A. Lamb[*2,3], Kelsey D. J. Jones[4,5], Carl A. Anderson[6], Emma Baple[7], Chrissy Bolton[8], Helen Braggins[9,10], Tanya Coulter[11], Kimberly C. Gilmour[12], Vicki Gregory[13], Sophie Hambleton[2,14], David Hartley[15], A. Barney Hawthorne[16], Sarah Hearn[17], Arian Laurence[18,19], Miles Parkes[20], Richard Russell,[21] R. Alexander Speight[2,3], Simon Travis[17], David C. Wilson[21], Holm H. Uhlig[**17,22]

[*]Joint 1st authors

[**]Correspondence to:

Professor Holm H. Uhlig, Translational Gastroenterology Unit, Department of Paediatrics and Biomedical Research Centre, University of Oxford, Oxford, OX3 9DU, UK.

Email: holm.uhlig@ndm.ox.ac.uk

Author ORCID iDs

Jochen Kammermeier: https://orcid.org/0000-0002-6046-8727
Christopher A. Lamb: https://orcid.org/0000-0002-7271-4956
Kelsey Jones: https://orcid.org/0000-0002-1237-0127
Carl Anderson: https://orcid.org/0000-0003-1719-7009
Emma Baple: https://orcid.org/0000-0002-6637-3411
Chrissy Bolton: https://orcid.org/0000-0003-0240-3244
Helen Braggins: https://orcid.org/0000-0002-4006-8638
Tanya Coulter: https://orcid.org/0000-0001-8182-9854
Kimberly Gilmour: https://orcid.org/0000-0003-0285-3958
Vicki Gregory: https://orcid.org/0000-0002-9391-843X
Sophie Hambleton: https://orcid.org/0000-0001-7954-3267
David Hartley: https://orcid.org/0000-0001-5763-9794
A. Barney Hawthorne: https://orcid.org/0000-0002-8768-4550
Sarah Hearn: https://orcid.org/0000-0003-0418-6036
Arian Laurence: https://orcid.org/0000-0003-0942-8292
Miles Parkes https://orcid.org/0000-0002-6467-0631
Richard Russell https://orcid.org/0000-0001-7398-4926
R. Alexander Speight https://orcid.org/0000-0003-3184-9181

Simon Travis https://orcid.org/0000-0002-2690-4361
David Wilson https://orcid.org/0000-0003-0879-1129
Holm H. Uhlig https://orcid.org/0000-0002-6111-7355

Author affiliations

1. Department of Paediatric Gastroenterology, Evelina London Children's Hospital, Guy's and St Thomas' NHS Foundation Trust, London, SE1 7EH, UK.
2. Translational & Clinical Research Institute, Newcastle University, Newcastle upon Tyne, NE2 4HH, UK.
3. Department of Gastroenterology, Newcastle upon Tyne Hospitals NHS Foundation Trust, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP, UK.
4. Department of Gastroenterology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, WC1N 3JH, UK.
5. Kennedy Institute of Rheumatology, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, OX3 7LD, UK.
6. Wellcome Sanger Institute, Wellcome Genome Campus, Hinxton, Cambridgeshire, CB10 1SA, UK.
7. University of Exeter Medical School, Royal Devon & Exeter Hospital, Exeter, EX2 5DW, UK.
8. Department of Infection, Immunity and Inflammation, UCL Great Ormond Street Institute for Child Health, London, WC1N 1EH, UK.
9. Department of Immunology, Great Ormond Street Hospital for Children NHS Foundation Trust and NIHR Great Ormond Street Hospital Biomedical Research Centre, London, WC1N 1DZ, UK.
10. Chronic Granulomatous Disorder Society, PO Box 454, Dartford, DA1 9PE, UK.
11. Regional Immunology Service for Northern Ireland, Belfast Health and Social Care Trust, Belfast, BT12 6BA, UK.
12. Clinical Immunology Laboratory, NIHR Great Ormond Street Hospital Biomedical Research Centre, Great Ormond Street Hospital for Children NHS Foundation Trust, London, WC1N 3JH, UK.
13. Crohn's & Colitis UK, 1 Bishops Square, Hatfield, AL10 9NE, UK.
14. Department of Paediatric Immunology, Great North Children's Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, NE1 4LP, UK.
15. XLP Research Trust, 60 Winchester Road, Romsey, Hampshire, SO51 8JA, UK.
16. Department of Gastroenterology, Cardiff & Vale University Health Board, Heath Park, Cardiff, CF14 4XW, UK.
17. Translational Gastroenterology Unit, and Biomedical Research Centre, University of Oxford, Oxford, OX39DU, UK.
18. Department of Clinical Immunology, Royal Free Hospital, Royal Free London NHS Foundation Trust, London, NW3 2QG, UK.

19. Department of Haematology and Bone Marrow Transplantation, University College London Hospitals NHS Trust, London, NW1 2BU, UK.
20. Department of Gastroenterology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, CB2 0QQ, UK.
21. Child Life and Health, University of Edinburgh; Department of Paediatric Gastroenterology, The Royal Hospital for Sick Children, Edinburgh, UK.
22. Department of Paediatrics, University of Oxford, Oxford, OX39DU, UK.

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Abbreviations:

BSG: British Society of Gastroenterology; BSPGHAN: British Society of Paediatric Gastroenterology Hepatology and Nutrition; CD: Crohn's disease; CGD: Chronic Granulomatous Disease; ESPGHAN: European Society of Paediatric Gastroenterology, Hepatology and Nutrition; GDG: Guideline Development Group; GIM: Genomic inflammatory bowel disease multidisciplinary team; HSCT: haematopoietic stem cell transplantation; IBD: inflammatory bowel disease; MDT: multidisciplinary team; NASPGHAN: North American Society for Paediatric Gastroenterology Hepatology and Nutrition; NHS: National Health Service; PEO, Population, Exposure, Outcome; PICO: Population, Intervention, Comparator, Outcome; RCPCH: Royal College of Paediatrics and Child Health; RCT: randomised controlled trial; TNF: tumour necrosis factor; UC: ulcerative colitis; UK: United Kingdom; XLP: X-linked Lymphoproliferative Syndrome.

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Conflicts of interest for authors and contributors are presented in *Supplementary Table 1*.

1 Abstracts

1.1 Scientific abstract

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 suffer from extremely early onset of treatment-refractory disease, with complex extra-intestinal disease such as immunodeficiency. Since over 100 monogenic disorders can present with IBD, new genetic disorders and variants are being discovered every year and phenotypic expression of the gene defects is variable, adaptive genomic technologies are required. Monogenic IBD has become an area to establish the concept of precision medicine. Clear guidance as well as standardised and affordable applications of genomic technologies are needed to implement exome or genome sequencing as standard-of-care in a health care system. This joint British Society of Gastroenterology (BSG) and the British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) guideline aims to ensure that testing resources are appropriately applied to maximise the benefit to patients on a national scale, minimise healthcare disparities in accessing genomic technologies, and optimise resource utilisation. 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, as well as potential implications for future therapies. We outline the diagnostic care pathway for paediatric and adult patients. This guideline considers how to handle potentially 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 gastroenterology physicians, immunologists, transplant specialists, clinical geneticists, scientists and research leads of UK genetic programs, in partnership with patient representatives of several IBD and rare disease charities.

1.2 Graphical abstract

Overview of BSG/BSPGHAN guideline for monogenic inflammatory bowel disease genomic medicine - the diagnostic genomic medicine pathway initiated by the IBD MDT and supported by the Genomic IBD MDT (GIM) supports genomic screening and implementation of actionable results into clinical practice.

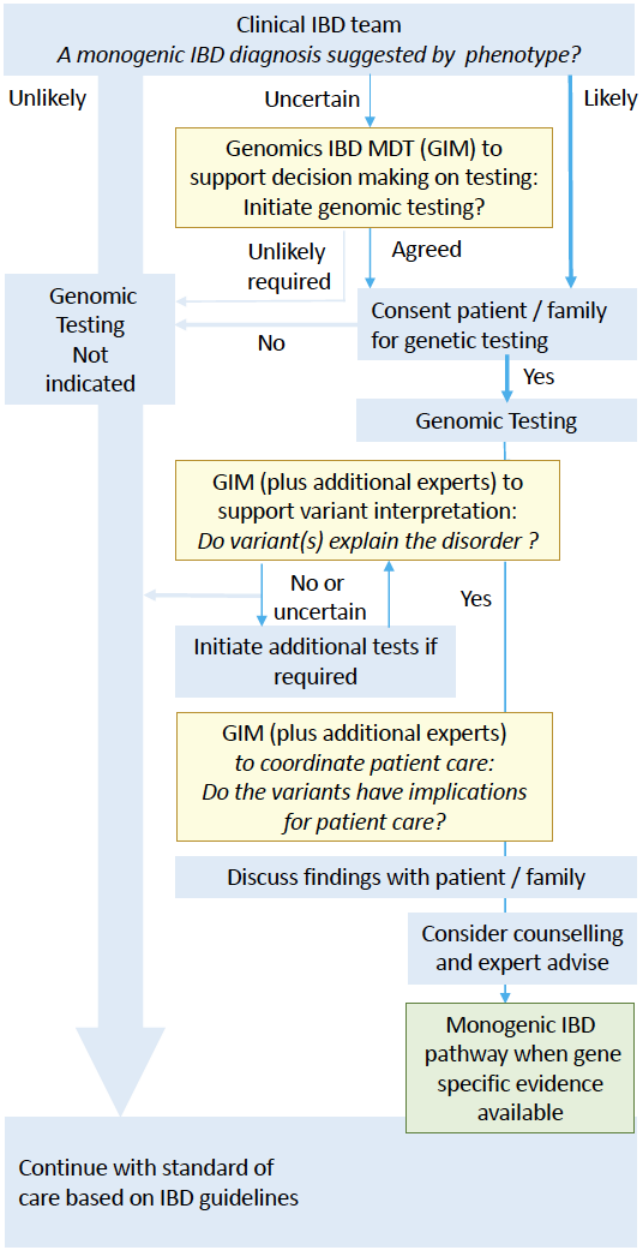

Figure 1: Overview genomic medicine for monogenic IBD

1.3 Patient facing written and graphical summary

1.3.1 Genomic testing for single gene inflammatory bowel disease

Crohn's disease and ulcerative colitis are the two main forms of inflammatory bowel disease (IBD). Crohn's and Colitis can develop when immune cells enter your gut and react in an abnormal way. We do not know exactly why this happens in most people. Many things are probably involved. This includes lifestyle factors, such as the food you eat, whether you smoke, and your stress levels. It also includes changes in your genes. Together, these things affect how your immune system reacts to the world around it.

Rarely, some people have a type of Crohn's or Colitis that is caused by a damaging change in a single gene that stops it working properly. This is called 'monogenic inflammatory bowel disease' or monogenic IBD.

Monogenic IBD usually shows up at a young age – often in babies or toddlers. They may become very ill as a result. People with monogenic IBD might also get unusual symptoms outside the gut, like repeated severe infections or inflammation in other parts of their body. Other family members might also be affected. Monogenic IBD often does not respond well to the medicines usually used to treat Crohn's and Colitis.

Knowing that someone has monogenic IBD, and exactly what changes they have in their genes, could help their hospital team to work out the best treatment to use. To do this, a blood sample can be tested to look for changes in their genes. This is called genomic testing.

Genomic testing is expensive and it can take weeks or even months to get the results. Most people with Crohn's and Colitis do not need this testing because they are very unlikely to have monogenic IBD. But some signs and symptoms make monogenic IBD more likely. So it is important to set out guidelines for who needs genomic testing and the support these people should have.

The British Society of Gastroenterology (BSG) and the British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) have put together these guidelines. They help work out who should have genomic testing for monogenic IBD. They also set out how the process should work, and who should be involved.

Nearly all people with monogenic IBD get symptoms when they are children. But some people might not have had genomic tests when they were children. They might now be adults with ongoing symptoms that started during childhood. The guidelines are relevant for paediatric and adult medicine.

1.3.2 Who should be offered genomic testing?

Consultants should consider genomic testing for:

- People who developed Crohn's or Colitis before they were 2 years old.
- People who developed Crohn's or Colitis before they were 6 years old, especially if they have:
    - Other immune system problems.
    - Frequent infections.
    - Diarrhoea since birth.
    - Cancer as a child or young adult.
    - A close family members with suspected monogenic IBD.
- People with Crohn's or Colitis who are so severely affected that they might need a stem cell transplant.

People who developed Crohn's or Colitis after they were 6 years old rarely need genomic testing. It should mainly be offered to people with specific immune problems or other inherited problems.

1.3.3 How should the system work?

Consultants in gastroenterology or immunology can request genomic testing.

- If a consultant thinks someone might have monogenic IBD, they should discuss it with a team of experts. The team should include the lead consultant, an expert in monogenic IBD and a clinical genetics specialist. It might include other specialists too.
- The team of experts should discuss the person's medical history and test results. Based on these, they should judge whether genomic testing would be helpful.

- The lead consultant should tell the person or their parent(s) what the team of experts has discussed. They should talk about the benefits of having genomic testing, as well as the things that can be difficult or uncertain.
- If the person or their parent(s) choose to go ahead with genomic testing, the expert team should look at the results and work out what they mean.
- The person's consultant should tell them or their parent(s) the results. They should explain what the results mean and if they affect the recommended treatment. If the results might affect other family members, the consultant might refer the person and/or their parent(s) for genetic counselling.
- To help scientists find out more about the genetic changes in Crohn's and Colitis, people who have genomic testing should be invited to take part in research studies. Research is important for everybody with Crohn's and Colitis but it is especially important in people with rare types. Research could help scientists find out what causes Crohn's or Colitis, and help find new, targeted treatments.

1.3.4 What might the results of genomic testing mean?

- In many cases, testing might not find the cause of the condition. This can still be important because it helps rule out monogenic IBD.
- Testing might find a genetic change that is the probable cause of the condition. Doctors might then suggest extra tests and different treatment options. The genetic changes might also be present in other family members and could affect their health too.
- Testing might find a change that scientists do not fully understand. The person may then be asked to participate in research to help scientists understand the change and whether it causes disease or not. Scientific knowledge may become clearer in the future. This might mean that some people who do not get a diagnosis of monogenic IBD at first might get one in the future.
- Rarely, genomic testing might find a change that is not related to gut inflammation but could have other health implications for the person or their family members. If people want to be told about these unexpected genetic findings, the clinical team will discuss them and what they might mean.

1.3.5 Patient visual summary of guideline

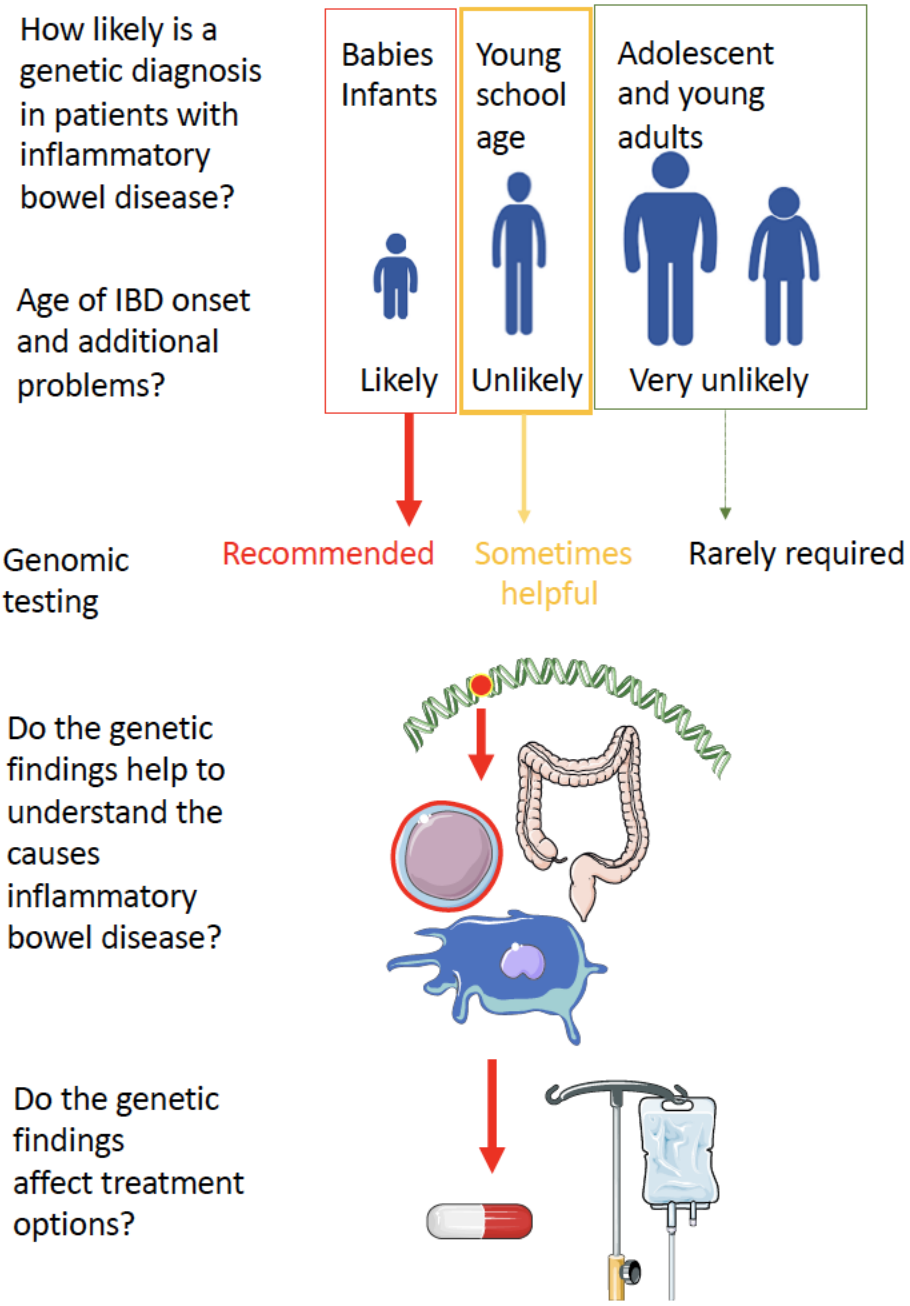

Figure for patient summary

2 Introduction

Translational genomic research has had a transformative impact 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 very severe forms of inflammatory bowel disease harbour highly-penetrant pathogenic variants in a single gene that explain their disease; monogenic IBD.[1,3] In these cases, identification of the precise genetic cause explains the disease and can provide prognostic information (for example, on infection susceptibility, on disease progression, or on malignancy risk). A molecular diagnosis may enable prediction of response to conventional therapy (such as anti-TNF therapy or surgery), and may suggest highly-specific mechanistically-guided therapies, for example allogeneic haematopoietic stem cell transplantation (HSCT) [4,5] or gene therapy.[6]

On surveying ~2,500 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 not only generated via the clinical healthcare sector (in the UK the National Health Service, in particular); but also via clinical research (such as the 100,000 Genomes Project and numerous IBD research studies and consortia); and through consumer genomics.[8-14]

Preconditions for pragmatic implementation of genomic technologies aiming to maximise the benefit to patients and to consider the costs to the healthcare system overall, is to identify

patient groups that benefit the most from testing, to provide appropriate genetic counselling before testing but also when a diagnosis is established (or not), and to manage the expectations of patients or clinicians (*Box 1*). This guideline provides a tool for clinicians who care for patients with suspected monogenic IBD, in particular paediatric and adult gastroenterologists and immunologists, 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.

Box 1: Why is a monogenic IBD guideline required?

- 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 may offer patients mechanistically informed, or even curative treatment options, and the potential for genetic counselling.
- Monogenic forms of IBD are a very heterogenous group of disorders; coordinated multidisciplinary care is essential.
- Compared to other groups of genetic disorders (such as 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.
- Paediatric gastroenterologists, adult gastroenterologists, and immunologists are eligible to request genomic testing; education and guidance on how to interpret and act upon genetic results is lacking.
- Clear consensus guidance will reduce regional, age-dependent (paediatrics versus adult medicine), and ethnic disparities in accessing genomic testing.
- Input from patients is critical for implementing personalised genomic medicine pathways effectively; consulting multiple patient organisations and charities is essential.

3 Methodology

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 NICE-accredited British Society of Gastroenterology (BSG) guideline development process.[17]

3.1 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 haematopoietic stem cell transplantation (HSCT). The group was recruited via the British Society of Paediatric Gastroenterology Hepatology and Nutrition (BSPGHAN) IBD Working Group, 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 specialities, the group included representation from key IBD research consortia, including UK adult and paediatric IBD BioResource,[9] 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, as well as early career stage clinician contribution and non-clinical representation.

3.2 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 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.

3.3 Conflicts of interest

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 prior to

manuscript submission. The submitted conflicts of interest for each member are shown in *Supplementary Table 1*. 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.

3.4 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 (*Box 2*). Clinical questions structured by Population, Intervention, Comparator and Outcome (PICO) or Population, Exposure, Outcome (PEO) were designed, including consideration of patient populations impacted, in order to assimilate evidence and draft statements (*Supplementary Box 1*). Health economic implications were not formally assessed. Due to limited evidence arising largely from small case series or case reports,[5,18,19] an assessment of treatment for individual gene defects was not considered a key topic for these guidelines.

Box 2: Scope and purpose of monogenic IBD guideline

- Outline the setting of genomic medicine for monogenic 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 6 years of age and in adult patients
- Define the patient diagnostic pathway in paediatric and adult medicine (UK National Health Service clinical genomics pathway as an exemplar); Which patients should be offered genomic analysis to investigate for monogenic IBD?
- Determine the role of the MDT in co-ordinating genomic diagnostics and subsequent care in those 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

3.5 Literature review

Definitions of relevance to this guideline are presented in *Supplementary Box 2*. Literature searches were designed using Medline in January 2022. No date or study design limits were incorporated into searches. It was agreed that where up-to-date systematic reviews exist (diagnostic yield of genomic studies, age of onset in different genetic defects, treatment of patients with monogenic IBD),[3,5,18] extensive systematic reviews would not be performed, but data would be summarised. Where prior guidance existed with respect to monogenic IBD, this would be highlighted to encourage best practice.[3] GDG members were able to add papers or electronic documents (e.g. NICE guidance) for inclusion in the literature dataset throughout the guideline development process.

3.6 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, based on 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 by JK, CAL and HHU. 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 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 based on 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 feasibility of intervention implementation. The strength of each recommendation was then recorded as 'strong' (meaning that benefits clearly outweigh risks and burdens or vice versa) and use of terminology 'we recommend' within statements; whereas weak recommendations recorded as 'conditional' (where benefits, risks, and burdens are conditional, closely balanced or uncertain) and use of terminology 'we suggest' within statements.

Following this, two rounds of anonymous online eDelphi voting with commenting 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/PEO, (such as 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 of Practice Point. Final numbers of votes and abstentions are shown in *Supplementary Tables 2 & 3*.

4 Implementation of genomic medicine in a health care system

Statement 1. Although exceptionally rare, monogenic IBD should be considered in patients with IBD since optimal treatment may differ significantly from that of classical IBD (GRADE: high quality, SOR: strong, Agreement: 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 (GRADE: low quality, SOR: strong, Agreement: 95%).

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 time frame and ethical and legal frameworks. The clinical care for patients with suspected monogenic IBD is challenging, depending on experience of the physician(s), extensive interdisciplinary support, and requiring sufficient resources to enable the complex genomic diagnostic process and subsequent individualised therapies to be provided by institutions and the health care system.

In monogenic IBD, the individual rarity of the disorders, the heterogeneity of extra-intestinal 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 increased to over 100.[5,34] Targeted panel sequencing reaches its limits in such an environment since gene panels must be re-designed and undiagnosed patients re-sequenced each time new gene discoveries are made. This 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 upper and middle-income economies.[35]

Several solutions to provide genomic services for patients with potentially monogenic IBD were proposed as part of VEOIBD clinics or genomic medicine clinics on an institutional level.[36,37] In England an NHS Genomic Medicine Service has been established that supports scalable and equitable diagnostic genomic testing (*Box 3).* The health-care system in England takes this strategy into account by commissioning whole genome and exome sequencing[38] where diagnostic grade gene panels are publicly accessible and reviewed at regular intervals. This allows input and critical review by the specialist community, aiming for coordinated efforts to ensure standardised analysis and reporting of genomic testing.

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 (*Box 3*). This is important information for patients, parents and clinicians in order to manage expectations. If, in exceptional cases, a more rapid turn-around is required, 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 hours.[40]

Box 3: Overview of the NHS Genomic Medicine Service (NHS GMS) and the monogenic IBD genomics setup

- The NHS GMS offers a standardised genomic testing directory (the National Genomic Test Directory), sometimes delivered via whole genome sequencing, including informatics and data storage aligned with ethical and legal frameworks in the UK. Funding of clinical genomics is covered by the NHS.
- The national genomic testing service is delivered to a population of 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 program is embedded.[41]
- 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 https://www.england.nhs.uk/publication/national-genomic-test-directories/ [42].
- Eligibility criteria for monogenic IBD testing are: Suspected monogenic IBD diagnosed by a consultant paediatric gastroenterologist, gastroenterologist or immunologist: Infantile onset IBD <2 years onset; very early onset IBD (<6 years of onset) with severe course (requiring biologics or surgery) or relevant comorbidities and extra-intestinal manifestations. Testing may occasionally be appropriate outside these criteria following discussion in a specialist MDT, (for example paediatric or young adult IBD with documented severity criteria e.g. relevant family history, comorbidities and extra-intestinal manifestations such as infection susceptibility).
- The NHS Genomic Medicine Service (GMS) signed off virtual gene panel resource (https://nhsgms-panelapp.genomicsengland.co.uk/) is curated and regularly updated.
- Since about a fifth of over 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 acknowledges that some monogenic IBD disorders are not considered as inborn errors of immunity (such as 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.
- VEOIBD 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 panel is now queried against trio whole genome sequencing data (current turnaround weeks to months; R15 panel).
- 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 exome sequencing for acutely unwell children is available in exceptional instances (such as a child on intensive care with syndromic presentation median turnaround time 10 days, R14 panel; https://www.exeterlaboratory.com/test/exome-sequencing-services/).
- 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.[43]
- Functional screening assays such as lymphocyte subsets or dihydrorhodamin oxidative burst assay or XIAP FACS assay are available through clinical standard immunology laboratories. Specialised validation tests such as IL10 stimulation assays (IL10 signalling defects), soluble IL2Receptor (hemophagocytic lymphohistiocytosis), oligoclonal expansion (hypomorphic SCID defects), telomer length (RTEL defects) are available via centralised NHS laboratories.
- Additional/incidental findings are reported to patients and families according to national standards.
- The NHS GMS offers potential intersection with research programs such as Genomics England 100,000 Genome Project, the NIHR IBD BioResource or research projects with focus on monogenic IBD such as COLORS in 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 (CICRA, Crohn's and Colitis UK) and provide support for patients and families with specific monogenic conditions (such as the CGD society, the XLP Research Trust, the Primary Immune-deficiency Patient Support Charity UKPIPS or Immunodeficiency UK).

4.1 Genomic medicine - A multidisciplinary team approach

Statement 3. We suggest genomic testing for patients with suspected monogenic IBD is best co-ordinated by a Genomics IBD MDT (GIM) which should include at least one specialist in the diagnosis and treatment of monogenic IBD (GRADE: low quality, SOR: conditional, Agreement: 95%)

Statement 4. When genetic results suggest a monogenic IBD diagnosis, we recommend that communication of results to patients (or parents/guardians), functional validation of plausible variants and setup of personalised care plans should be co-ordinated with support from the GIM (GRADE: low quality, SOR: strong, Agreement: 100%)

All patients with IBD benefit from care as part of an IBD multidisciplinary team (IBD MDT).[7] This is particularly relevant for patients with exceptional presentations, such as very early onset of inflammation, infection susceptibility or autoimmunity, multi-organ involvement, 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 patients 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: i) the decision to investigate for monogenic aetiology in more complex or ambiguous cases and the most appropriate technologies, ii) variant interpretation and clinico-genetic correlation, and iii) the clinical care strategy of patients with established monogenic-IBD (*Figure 1*).

The heterogeneity of underlying genetic conditions and clinical presentations means that the GIM should have a core structure with adaptive contribution from local clinicians including the patient's lead consultant and external specialists depending on the patient's presentation and genetic findings (*Figure 1 & Box 4*). Organisation will vary, but the GIM will typically co-opt internal and external representatives to specific case discussions from clinical genetics, immunology, haematology and microbiology/infectious diseases, as appropriate. 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 (national and regional) 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, may generate interest in the genetic and immunological basis of monogenic IBD and the opportunities of precision medicine, thereby ultimately serving the interests of patients.

Box 4: Genomic IBD MDT (GIM) to evaluate patients with suspected or potential monogenic-IBD

GIM team structure

- The patients' lead consultant (typically a paediatric or adult gastroenterologist or immunologist of the patient 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 (see *Figure 1*); specialty trainees; external experts with experience in the disease and gene function (maintaining patient confidentiality); 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 aetiology

- IBD phenotype (current age, main diagnosis, type and location, including age of IBD onset and history of complications, surgery and medication)
- Extra-intestinal manifestations and comorbidities
- Presence of features listed in the 'Genomics testing criteria' (see *Box 5*)
- List of suspected candidate genes prior to genetic analysis
- Identification of who is discussing the diagnostics and potential findings with the family?
- Initiate patients' consent to the diagnostic process, information on genetic counselling, information returned and incidental findings
- Available funding

Variant interpretation stage

- Genetic sequencing technology and analysis strategy (including the panel of genes investigated)
- Are pathogenic, likely pathogenic variant(s), and/or variant(s) of uncertain significance identified in monogenic IBD associated genes and what is the evidence that these variants are causative?
- Are additional confirmatory genetic, clinical or functional tests required?
- What is the likely patho-mechanism and what are the potential implications?
- Are there unexpected findings?

Clinical care of patients with established monogenic IBD

- What are the implications for therapy and prevention of complications?
- Iterative update on implications for therapy and prevention of complications
- Is additional specialist input required (locally, nationally or internationally)?
- Is genetic counselling required?

4.2 Which patients should be offered genomic testing?

4.2.1 Clinical genomics in the paediatric setting

Statement 5. We recommend clinicians should consider genomic testing in all patients with infantile (age <two years) onset IBD (GRADE: high quality, SOR: strong, Agreement: 100%)

Statement 6. We recommend clinicians should consider genomic testing in patients with very early-onset (age <six years) IBD particularly in the presence of one or more additional testing criteria* (GRADE: high quality, SOR: strong, Agreement: 100%)

**See Box 5*

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, a further third tend to present as very early onset (under 6 years of age) and the remaining third present beyond 6 years of age (*Figure 2*). Due to the variable phenotype and course of different genetic conditions, some patients will present directly to paediatric gastroenterologists while those with extra-intestinal features (see below) may first present to other services including paediatric immunology. For patients originally presenting with IBD, a careful history of intestinal and extra-intestinal manifestations and comorbidities, the family history and a limited set of laboratory tests (FBC, inflammatory markers, lymphocyte subsets, immunoglobulin levels) should be undertaken at baseline since these can provide a clear steer towards an 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 but has limited predictive power to identify monogenic IBD.[5,18,44,45]

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 hematopoietic stem cell transplantation, 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.

A large group of monogenic IBD patients present with extra-intestinal 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 may present with (atypical) infection, immune activation syndromes (e.g. hemophagocytic lymphohistiocytosis) or systemic autoimmunity.[3,5] Extra-intestinal disease comprise diverse and sometimes pathognomonic features that suggest a particular potential monogenic IBD cause. These include infantile enterocolitis with perianal disease (*IL10RA, IL10RB, IL10*), abscesses with bacterial or fungal infections (Chronic Granulomatous Disease, CGD: *CYBB, CYBA, NCF1, NCF2, NCF4, PRKCD, CYBC1*), eczema and thrombocytopenia (Wiskott Aldrich syndrome-like features *WAS, WIPF1, ARPC1B*), congenital neutropenia in the presence or absence of metabolic or syndromic features (*G6PC3*, *SLC37A4*), small and large bowel endocrinopathies and dermatitis (IPEX-like syndrome *FOXP3*, and *IL2RA, IL2RB*, *STAT1, STAT3*) or brittle hair and chronic liver disease/cirrhosis as well as immunodeficiency (trichohepatoenteric syndrome; *TTC37, SKIV2L*). Laboratory features based on the recommended limited number of functional screening assays (*Box 3*) include numeric cellular abnormalities such as primary lymphopenia and neutropenia (*G6PC3, SLC37A4*), agammaglobulinemia (*BTK*) or defective neutrophil function test (dihydrorhodamine assay to test for CGD; *CYBB, CYBA, NCF1, NCF2, NCF4, PRKCD, 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, SKIV2L*).[5] Several monogenic IBD conditions are associated with increased risk of malignancy such as lymphoma (IL-10 signalling defects, *CTLA4, SYK*).[46-48] Additional laboratory test are relevant to characterise different organ involvement (i.e. hepatitis or pancreatitis), autoinflammatory disease, or hemophagocytic lymphohistiocytosis.

Very young age of onset, specific symptoms and laboratory features that suggest an 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 (see *Box 5*). Other features such as a family history of other family members with classical IBD, linear/ponderal growth

retardation, severe and/or multiply treatment-refractory disease (i.e. failure to respond to multiple biologic therapies) are less specific and are therefore regarded supportive features (*Box 5*).

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 (complete blood count, serum immunoglobulin levels, lymphocyte subsets and neutrophil oxidative burst assay) to assess for a set of inborn errors of immunity (Agreement: 100%)

For paediatric IBD patients, it is important to discuss the opportunities of genomic medicine with their parents (or guardians), while also highlighting the relatively low chance that a monogenic diagnosis will be made. 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 discussion about genetic testing and results. The views of adolescents regarding predictive gene variants for adult-onset disease and unexpected (incidental) findings should be carefully considered and respected in the decision-making process related to genomic medicine.[49] Patient views may differ from those of their physicians, or, indeed, their parents. 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 a next generation sequencing such as genome sequencing include sample preparation, sequencing, bioinformatic processing, analysis and reporting.[50,51] Multiple studies in different rare disease areas suggest that exome and genome sequencing can be more cost effective compared to targeted approaches.[52] There are major cost saving opportunities if exome and genome sequencing are performed in a standardised manner and on a national scale.[53] Two published cases of monogenic IBD in the UK provide an estimate of potential cost effectiveness: A patient diagnosed at 11 years of age developed a therapy refractory Crohn's disease. During a 3-decade diagnostic odyssey until a XIAP defect was identified, there were annual costs, likely enough to fund a genetic screening program in this tertiary referral cohort.[20] Another patient with infantile onset of IBD who was considered for HSCT was diagnosed with EPCAM defect.[11] The genetic diagnosis of this epithelial defect prevented progression with the HSCT and saved more than £220,000.

Box 5: Genomic testing criteria for monogenic IBD

Genomic testing criteria:

1. Age of IBD onset in particular under 2 years of age or under 6 years of age
2. Infection susceptibility (recurrent sinopulmonary infections, systemic infections meningitis and/or sepsis, gastrointestinal infections, cutaneous infections) in the presence of abnormal laboratory tests (for instance congenital lymphopenia or neutropenia, or combined immunoglobulin level abnormalities) meeting diagnostic criteria of an inborn error of immunity (primary immunodeficiency)*
3. Inflammatory features indicative for an inborn error of immunity such as complex autoimmune features (especially features of Immunodysregulation Polyendocrinopathy Enteropathy X-linked (IPEX) syndrome in the paediatric population or severe multi-organ autoimmune disease in the adult population) or haemophagocytic lymphohistiocytosis**
4. Congenital multiple intestinal atresias or congenital diarrhoea
5. Early-onset malignancy (< 25 years of age)
6. Family history of suspected monogenic IBD (criteria 1-5)
7. In advance of interventions and/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, i.e. context of consanguinity, or multi generation 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 as the prevalence of monogenic IBD and the impact/benefit of clinical genomics in this cohort are unknown

4.2.2 Clinical genomics in the adult setting

Statement 7. We recommend that genomic testing should only be offered in exceptional circumstances to patients with IBD-onset after six years of age. These patients should meet at least one of the genomic testing criteria* (GRADE: moderate quality, SOR: conditional, Agreement: 100%)

**See Box 5*

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 may 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 (e.g. as testing was not available, or genomic testing was incomplete in light of the increasing number of novel monogenic IBD genes over time or suspected 'false negative' in light of the more sensitive technologies available) (*Box 6*). In both such 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 aetiologies (*Figure 2*). For example, patients with congenital diarrhoea due to *SLC26A3* or *GUCY2C* gain of function defects typically develop diarrhoea during 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 (*Box 6*).

Box 6: Case examples of monogenic IBD defects diagnosed in late adolescence and adulthood

Case examples:

- A panel of monogenic IBD genes was investigated by exome sequencing performed in 503 patients of 7-40 years of age who had a history of surgery and biologic prescription.[20] A diagnosis of XIAP deficiency was made in one patient, 30 years after IBD onset (at 11 years of age) who had undergone numerous operations and spent more than 1,000 days in hospital [20]

- A diagnosis of X-linked CGD was made in 16-year-old after he presented with a liver abscess. He had suffered from difficult-to-treat Crohn's disease since 3 years of age and had previously developed neck abscesses and pneumonia. He underwent an allogeneic HSCT after the CGD diagnosis was established (case included in Cole T et al.[54] and personal communication Dr Tanya Coulter).
- A diagnosis of XIAP deficiency was detected for a patient at the age of 17 years, who had suffered from recurrent infections (particularly skin infections) and severe Crohn's disease since the age of 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 18 years of age. A subsequent allogeneic HSCT completely resolved intestinal symptoms of Crohn's disease [56]
- In a 15-year-old patient 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. [47] Non-EBV–related diffuse large B-cell lymphoma as well as EBV-associated lymphoma have been reported in patients with IL-10 receptor signalling defects between 5.3 to 16.5 years of age [47,57,58]
- Identification of novel genes allows to test patient with years of ongoing intestinal inflammation. Gain-of-function *SYK* variants were identified in adult patients after the molecular defect was functionally characterised [46]
- An essential loss-of-function variant in the *LRBA* gene was identified by exome sequencing in a 37-year-old patient with a history of diarrhoea and duodenitis with villous atrophy as well as colonic abnormalities, arthritis, hepatitis and a relevant family history [59]

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

Statement 8. In order 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 (GRADE: low quality, SOR: strong, Agreement: 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 (Agreement: 100%)

Results of genetic testing can help the therapeutic decision-making process. This is particularly relevant for those therapeutic interventions that come with a high-risk of therapy associated morbidity and mortality. An example is HSCT. Autologous HSCT has been proposed as a therapeutic option in adult patients with severe and therapy-refractory IBD.[60-62] 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 hematopoietic 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 secondary to ignorance of a relevant monogenic defect should be a key consideration in pre-transplant planning.

Some monogenic conditions, in particular XIAP deficiency or chronic granulomatous disease, can present with severe Crohn's disease including severe therapy-refractory perianal disease, collections and exceptional wound healing problems after surgery in the absence of additional signs of immunodeficiency. 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 or adult onset therapy-refractory ulcerative colitis or perianal Crohn's disease are not uncommon (e.g. about 60% of patients with perianal Crohn's disease relapse during one year of anti-TNF therapy)[63]. This means that the number of patients needed to test is probably very high; hundreds of patients may need to be screened in order to identify one patient with XIAP or CGD.[20,64] 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.[65,66] 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 versus small targeted genetic panels or more comprehensive genomic testing as default option).

4.4 Which genes should be investigated?

Statement 9. We suggest that genomic testing to investigate monogenic IBD utilises a curated adaptable gene panel approach, best facilitated by whole genome sequencing to allow an updated analysis when new evidence becomes available (GRADE: moderate quality, SOR: conditional, Agreement: 100%)

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

In a position statement of ESPGHAN, 75 genes were selected based on expert consensus (*ADA, ADAM17, AICDA, ALPI, ARPC1B, BTK, CASP8, CD3G, CD40LG, CD55, COL7A1, CTLA4, CYBA, CYBB, DCLRE1C, DKC1, DOCK8, FERMT1, FOXP3, G6PC3, GUCY2C, HPS1, HPS4, HPS6, ICOS, IKBKG, IL10, IL10RA, IL10RB, IL21, IL2RA, IL2RB, IL2RG, ITCH, ITGB2, LIG4, LRBA, MALT1, MASP2, MVK, NCF1, NCF2, NCF4, NLRC4, NPC1, PIK3CD, PIK3R1, PLCG2, POLA1, RAG1, RAG2, RIPK1, RTEL1, SH2D1A, SKIV2L, SLC37A4, SLC9A3, SLCO2A1, STAT1, STAT3, STIM1, STXBP2, STXBP3, TGFB1, TGFBR1, TGFBR2, TNFAIP3, TRIM22, TRNT1, TTC37, TTC7A, WAS, XIAP, ZAP70, ZBTB24*).[3] Since then, additional genes have been described and quantitative parameters for gene-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 adoption of increasing numbers of genes over time and the collective evidence (*Box 3*).

4.5 How should genetic results be interpreted?

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 (ACMG) and the Association for Clinical Genomic Science (ACGS). This variant classification framework includes assessing the prior evidence in variant/mutation databases, conducting literature searches, quantifying the variant frequency in disease cohorts and population data sets (e.g. gnomAD) and using of *in silico* tools to predict variant pathogenicity.[67,68] This allows classification of sequence variants into one of 5 classes (*Supplementary Box 2*).[67]

The clinical diagnostic genomic report will reflect the indication for sequencing and samples sequenced (e.g. proband only, parent-child trio), the panel of genes investigated, the classification of any reportable variants, and may also summarise the evidence that was available to classify the variant and any additional testing/evidence (genetic, clinical, functional) that may aid variant reclassification to likely pathogenic/pathogenic. The report will typically comment upon 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.

4.6 How should results be actioned for the management of patients?

Practice Point 3. Prior to genomic analysis, clinicians should discuss the potential impact of a genetic diagnosis with the patient, or the patient's parent(s)/guardian(s) depending on age. Genetic counselling should be offered in particular if pathogenic variants have been established (Agreement: 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, as well as the patients' age, phenotype and prognostic factors (Agreement: 100%)

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 may enable the individual to receive

information for patient support groups that specifically focus on individual monogenic conditions (*Box 3*).

A genetic diagnosis may 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 may benefit from off-label treatment with IL-1 targeting treatments.[69] Patients with XIAP deficiency may be informed of the risk of fistulising disease and wound healing problems after surgery.[70] For patients with CGD, the increased risk of infection during anti-TNF therapy may influence treatment choice.[71]

Patients may be enrolled into clinical research trials that include personalised therapeutics or may consider off-licence treatment strategies under expert-advice based on molecular rationale (e.g. IL-1 blockade in mevalonate kinase deficiency, or treatment with abatacept in patients with CTLA4 and LRBA deficiency, or IL18BP in XIAP deficiency).[72-74]

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 may best be provided with the support of national and international clinical networks involving paediatric and adult gastroenterologists and clinical immunology specialists. Overall, the evidence for therapeutic efficacy of most medications and interventions is limited. Consequently, no formal recommendations for treatment can be made and an individualised approach is required, based on the disease gene, the genetic variant(s) identified, age of the patient, intestinal and extra-intestinal manifestations, history of previous medications, organ damage and the perspective of the patient or family.

The availability of genetic counselling is paramount. Genetic counsellors are highly skilled in discussing genetic information with patients and their families whilst maintaining confidentiality and adherence to legal standards. The prediction of recurrence risk for a monogenic disorder can be highly relevant to parents with affected children. Genetic findings might also be relevant to the wider family (adult siblings or distant relatives).

In some instances, parents may wish to consider prenatal testing or preimplantation diagnosis for a fully penetrant form of monogenic-IBD (such as IL-10 signalling defects), which are services that are available in the UK and several other countries.[75]

For patients in whom no genetic diagnosis can be established a pragmatic approach is required i) to follow the established paediatric and adult IBD guidelines, ii) to consider immunomodulatory or immunosuppressive therapies based on clinical and immunological similarities with known monogenic defects, while iii) carefully consider potential benefit and risks of the therapies, and iv) be guided by the quality of life of the patient.

4.7 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, NASPGHAN, or national organisations such as the RCPCH recognise the need to establish a genetic diagnosis, but scarcely cover the underlying principles of genomic medicine in the training curriculum.[76] Adult gastroenterology curricula are even less specific.[77] 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 program did not adequately cover the field of genomic medicine.[78]

4.8 Identification of potential actionable monogenic IBD variants in the research setting

Practice Point 5. Patients with suspected or confirmed monogenic IBD should be offered the opportunity to participate in research studies (Agreement: 100%)

Practice Point 6. Research studies in patients with IBD which 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 those patients and their clinical team who wish to receive genetic information. The clinical team should facilitate confirmatory clinical genetics testing and consider Genomics IBD MDT input to ensure patient benefit (Agreement: 100%)

In the last 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 gene-gene interactions, facilitate population-based studies, and develop novel therapies.

Nevertheless, potentially 'actionable genetic variants' may emerge from research studies that are potentially relevant to the care of a specific patient. Clear pathways need to be in place to confirm how research-derived genetic variants are prioritised and validated within the research setting via a steering group to assess potentially clinically relevant variants and 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] Whereas the research team may provide the patients' 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. A suggested pathway to integrate research findings in clinical care is depicted in *Supplementary Figure 1*.

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 fed back into the NHS to inform clinical practice.

4.9 Establishing a genomic diagnosis in a resource limited setting

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 may be complemented by access to national and international specialist networks and research studies (Agreement: 95%)

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, limited coverage of genomic medicine by some health care insurers, or limited access of some individuals to health care insurance. In these settings, access to research studies that investigate monogenic IBD causes, and access to virtual centralised national and international monogenic IBD clinics can help provide access to diagnostics.[3] Even in settings where HSCT, for example, is not feasible, a positive genetic diagnosis might be partially clinically actionable – for example via the provision of targeted antimicrobial chemoprophylaxis or the consideration of use of off-label and repurposed drugs with some plausible mechanistic specificity e.g. thalidomide in IL-10 receptor defects.[79]

4.10 Consumer-initiated genomics

Practice Point 8. Consumer-based genetics is not recommended in a care setting where clinical genomic resources are available (Agreement: 90%)

Outside the healthcare system not only ‘recreational genetics’, but also whole exome and genome sequencing are becoming available to consumers via direct-to-consumer testing. There is a growing market in the UK [8] and worldwide. In an international market, major challenges relate to informed consent, testing of children, as well as difficulties in interpreting

the complex data by consumers (potentially patients), lack of genetic counselling, commercialisation of data, genetic privacy, dealing with unexpected genetic results and, once relevant clinical questions arise, lack of clinical guidance or MDT involvement.[80-82] The majority of tests offered as direct-to-consumer testing do not aim to detect rare genetic conditions, but exome and genome sequencing is offered by some companies. Since the reported analysis frequently fails to provide established quality control parameters required to interpret the data, clinical geneticists in healthcare systems are typically not commissioned to interpret results from "direct-to-consumer" testing.

4.11 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 healthcare utilisation because of geographical differences, limited awareness of monogenic IBD in the adult care setting and ethnic variations.[83] Importantly, this reduces ancestry-related bias when using genomic databases, since information on genetic variants is biased.[84] Variable resources for genomic medicine and variable healthcare insurer policies worldwide create additional disparities in access to genomic medicine for patients.[85] There are differences in national strategies for implementing genomic medicine among different countries, despite similar challenges.[86] Applying genomic medicine in immune-mediated disorders is particularly difficult because the expressed phenotype from the same genetic defect may vary, based on the surrounding genetic and environmental context (for example, variation in diet, the microbiome, or lifestyle factors).

Cost-effectiveness of interventions is a key consideration: the high cost of genomic programs 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 or very early onset IBD, those data might be biased by 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 healthcare system will cope with increasing numbers of variants of unknown significance that emerge from increased screening. Nor is it clear how functional

validation of genetic results needing highly specialised assays can be implemented in routine clinical or research settings. It is equally unclear how clinical genomic data will be re-analysed and results updated over time. Furthermore, there is no strategy in place 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 evidence and consensus opinion presented in this guideline, we propose an exemplar clinical genomics pathway for monogenic IBD diagnosis and management co-ordination in *Figure 3*.

5 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 how potentially actionable genetic variants identified through research studies can be transitioned into clinical care.

Figures

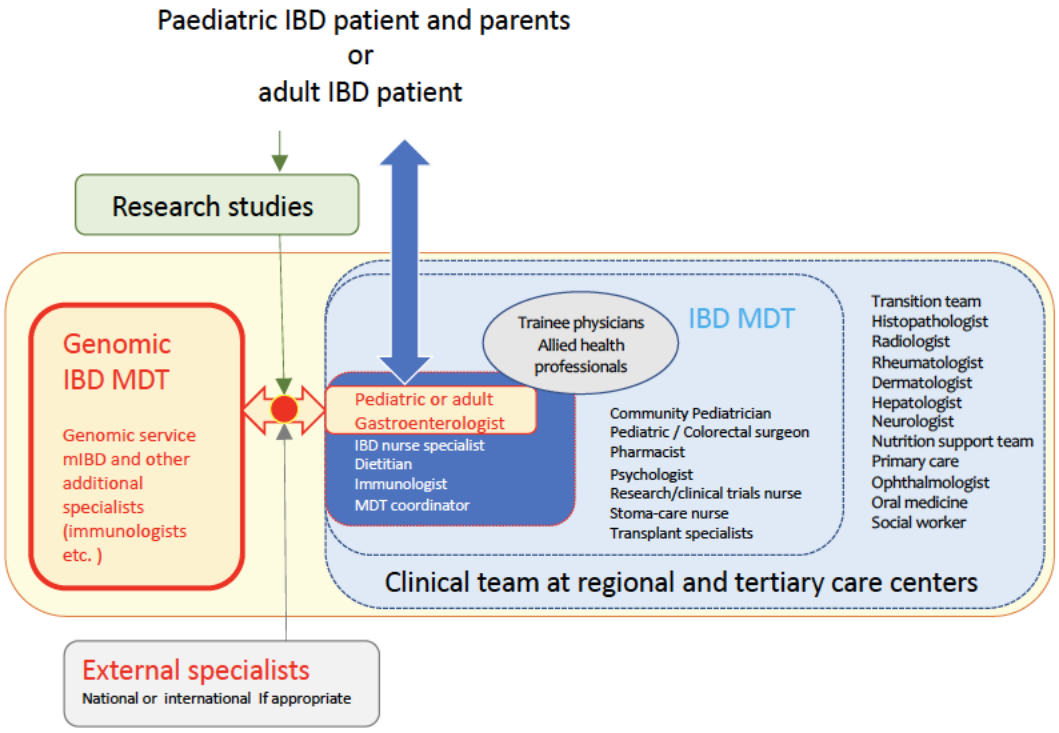

Figure 1: The Genomic Inflammatory bowel disease Multidisciplinary team (GIM)

Each IBD patient is supported by a number of specialities depending on age and course of the disease (core IBD MDT support 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 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 HSCT) (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.

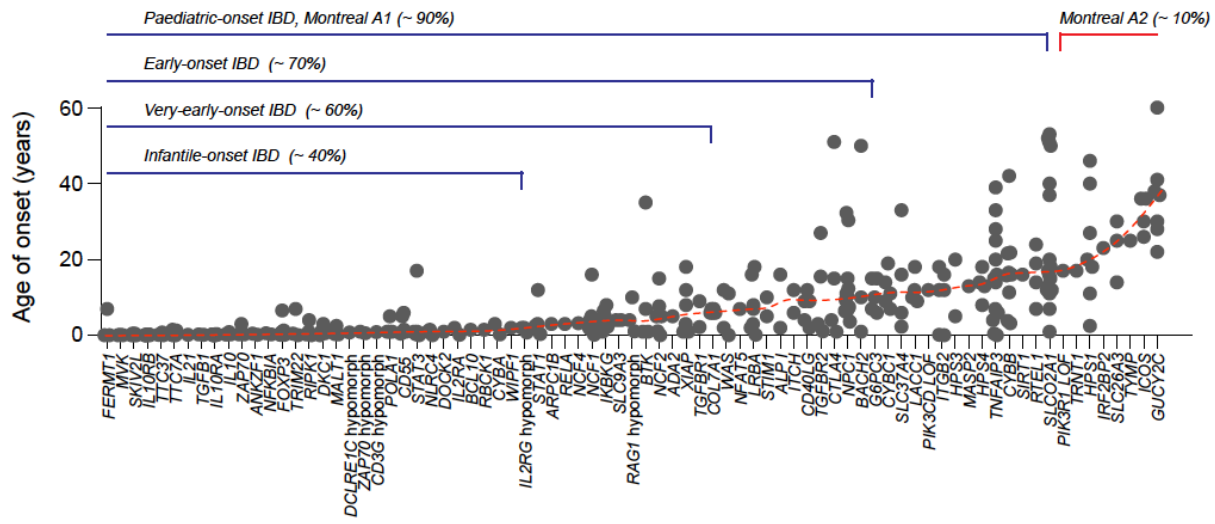

Figure 2: Age of onset of IBD in patients with monogenic IBD.

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]

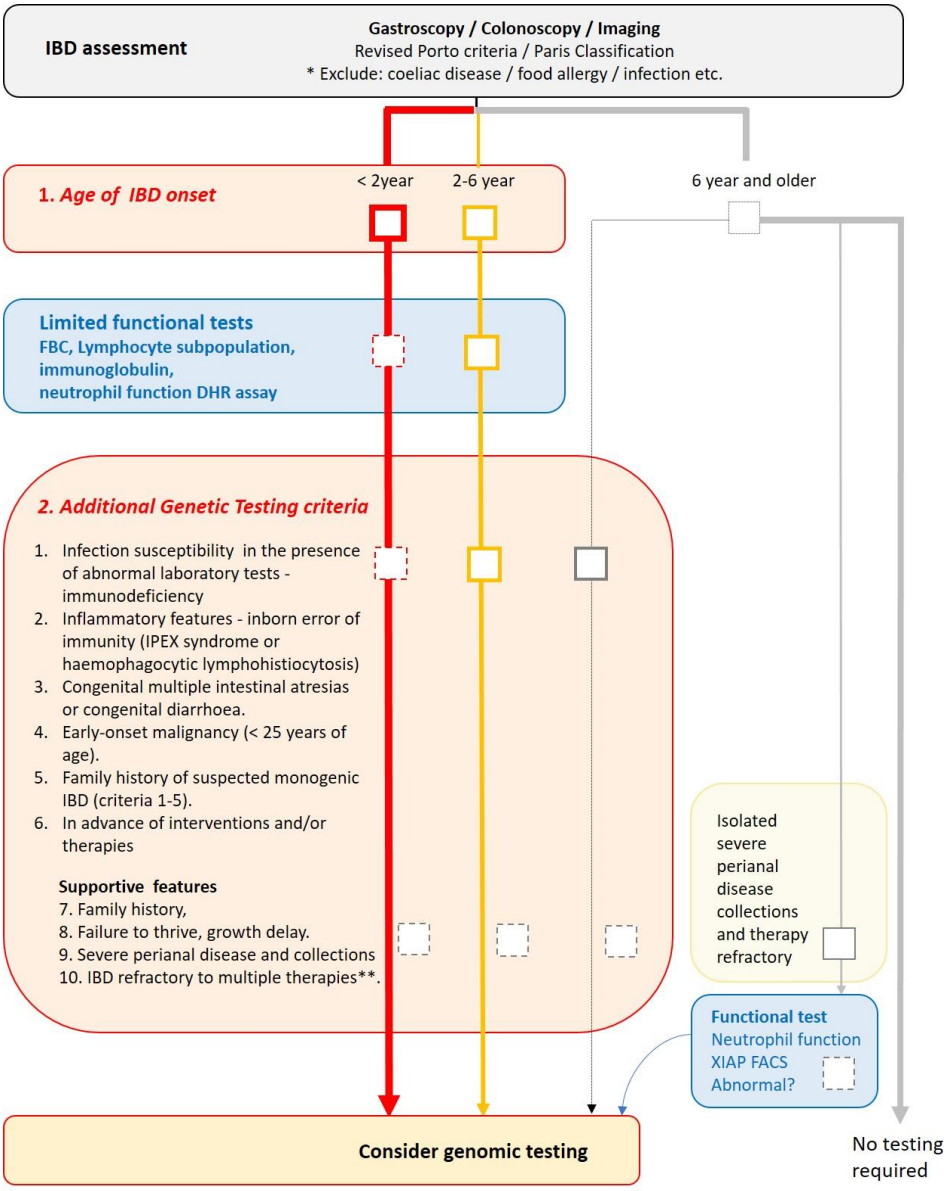

Figure 3: Monogenic IBD testing criteria and risk stratification

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]

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