

# Catalyzing change: Implementing standardised reporting in monogenic inflammatory bowel disease research

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Modern medicine is aiming to merge two concepts in clinical practice: providing highly personalised precision medicine on the one hand (individualised), and implementing evidence-based medicine for decision making that depends on large-high-quality studies (population characteristics). For common disorders, high-quality studies or meta-analysis may allow prognostication of therapeutic outcomes and risk stratification, while patients with rare conditions or extreme phenotypes (such as at the extremes of age) are often excluded from study protocols. Furthermore, some patient populations are underrepresented in studies due to geography, socioeconomic state or genetics, limiting fast access to evidence-based medicine for them.

The concept of personalised precision medicine is receiving significant attention in the field of rare genetic conditions, where patients can benefit from a molecular understanding of their genetic defects and receive targeted therapies. One example is the spectrum of monogenic inflammatory bowel diseases (mIBD), representing a very small subgroup of patients with inflammatory bowel disease (IBD) with single gene

mono- or biallelic pathogenic variants.<sup>1,2</sup> Over a hundred genes that regulate processes of intestinal mucosal barrier integrity and immune homeostasis have been associated with mIBD. Considering the therapeutic and prognostic consequences of a genetic diagnosis for patients, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and the IBD Porto group of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) have formulated position papers for the diagnosis of mIBD.<sup>2,3</sup> To support clinical care pathways for patients with suspected mIBD, a recent expert consensus guideline formalised the stratified use of clinical genomics for select paediatric and adult IBD patients within the UK healthcare system as part of a multidisciplinary team approach.<sup>4</sup>

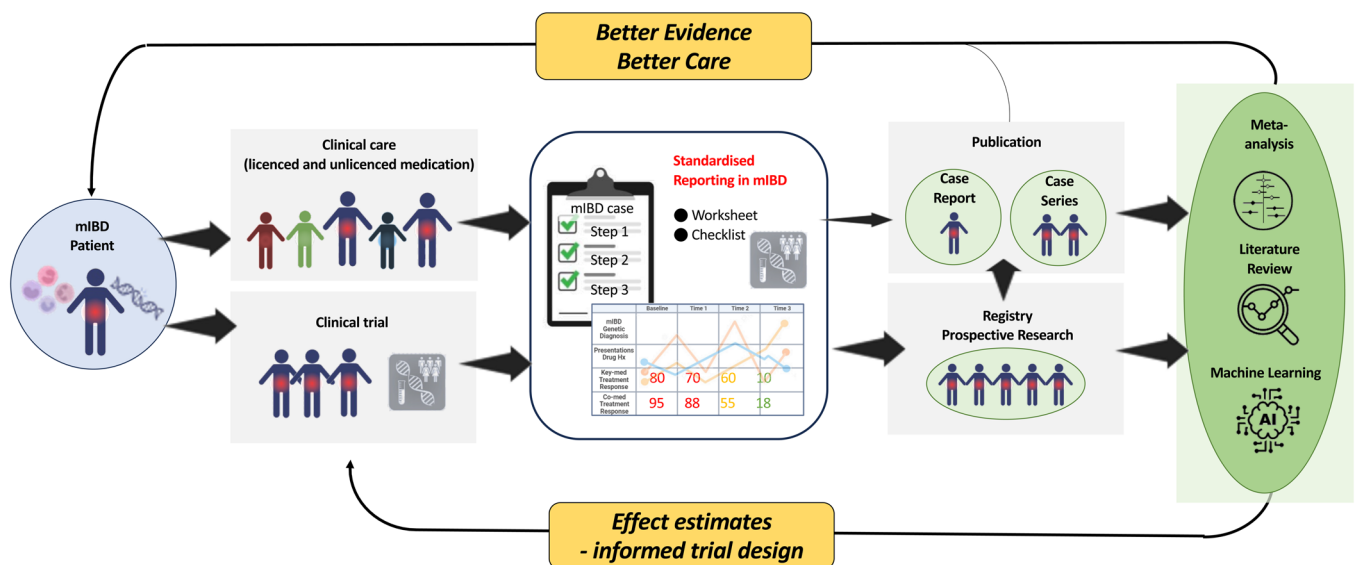
The increased application of those genomic technologies over the last decade has identified novel variants underlying mIBD, helped the understanding of IBD mechanisms and produce a large number of clinical observations in those patients (medicine response, complications). Due to its focus on paediatric

gastroenterology, the Journal of Paediatric Gastroenterology and Nutrition (JPGN) and its online counterpart JPGN reports have published a number of case reports and case series on mIBD patients and therapies. Examples include case reports of a patient with glycogen storage disease type 1b (GSD-1b) treated with the sodium-glucose co-transporter 2 inhibitor empagliflozin<sup>5</sup>; immunological findings and responses to thalidomide and intravenous immunoglobulin in an adolescent patient with interleukin-10 receptor signalling defect<sup>6</sup>; the gastrointestinal and immunological findings in patients with Trichohepatoenteric syndrome<sup>7</sup>; or dual biological therapy with infliximab and ustekinumab in a patient with Niemann-Pick type C and Crohn's disease.<sup>8</sup> These case reports illustrate the genetic and phenotypic diversity of patients with a mIBD diagnosis, the impact of extra-intestinal problems, and the need for better treatments in clinical care. Indeed, while hematopoietic stem cell transplantation has emerged as standard of care in some conditions such as interleukin 10 (IL10) signalling defects, the pharmacological treatment of intestinal inflammation in those disorders such as IL10 signalling defects, Trichohepatoenteric syndrome or Niemann-Pick type C remains challenging. Evidence-based precision medicine for patients with mIBD is delayed due to the rarity of mIBD conditions (limited patient numbers), publication bias, a lack of systematic reporting on short-term and long-term therapeutic responses (limited comparability), and difficulties in conducting high quality trials progress (fragmented populations).<sup>9</sup> Acknowledging those limitations, recommendations for mIBD REPORT standards (**m**onogenic **I**nflammatory **B**owel **D**isease **R**eport **E**xtended **P**henotype and **O**utcome of **t**ReaTments) were established.<sup>9</sup>

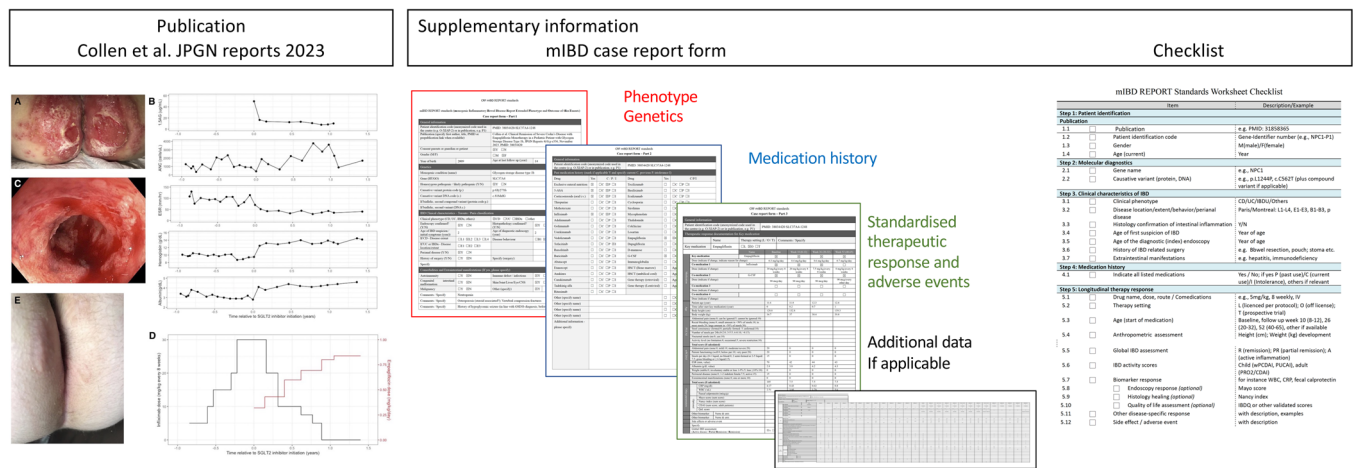
Based on these recommendations, we propose a reporting algorithm including a reporting checklist and a Case Report Form template with supportive information on relevant disease classification and activity scores (Figure 1, Supporting Information S1: File 1 and 2). The Case Report Form comprised relevant parameters in the categories of molecular genetic diagnosis, clinical intestinal and extraintestinal phenotype characteristics, and exposure to IBD treatment(s) including unsuccessful treatment approaches and adverse events. The mIBD REPORT standards focus on single key treatment while pragmatically reporting on concomitant therapies. Longitudinal therapeutic outcome, based on clinical parameters (disease activity index, laboratory markers, quality of life score, etc.) is measured preferentially over at least a 1-year period including a longitudinal series of at least four intervals (baseline, and approximately 10, 26, and 52 weeks) that can provide a realistic insight into the response. This enables the assessment of short-term and long-term therapeutic goals according to STRIDE-II recommendations.<sup>10</sup>

To illustrate this concept, we provide a demonstration file of a patient with glycogen storage disease type 1b (GSD-1b) treated with empagliflozin based on previously published data (Figure 2, Supporting Information S1: File 3).<sup>5</sup>

Overall, this standardised reporting aims to improve the quality and comparability of published case studies and case series, registries and databases, which is key to systematic literature review, meta-analysis, or data-driven Machine learning (artificial intelligence) assisted research; all areas that rely on accurate data extraction and pattern recognition. Furthermore, standardised documentation could refine patient care by providing



**FIGURE 1** Standardised reporting in monogenic inflammatory bowel disease—translating fragmented observations into systematic data and better care in clinical practice.



**FIGURE 2** Monogenic inflammatory bowel disease report standards as a complement to published data. The example illustrates a case report and its corresponding supplemental information with machine-readable structured reporting and a checklist for completion.

a reference framework for clinicians to benchmark their patient's response in comparison to patients with published treatment outcome (Figure 1).

Advances in metadata processing, systems biology analysis, bioinformatics, artificial intelligence and machine learning (ML) have significant impact across several domains in healthcare.<sup>11</sup> Patients with mIBD may benefit from these tools especially in diagnosis (endoscopic and pathologic reading), therapeutic monitoring, personalised medicine, predictive analysis on disease course, and drug development. However, any advanced analysis or modelling, is based on reliable data. The implementation of a pragmatic reporting form and supplementary checklist for publication, will make prospective data aggregation more effective and dynamic.

Nevertheless, there are limitations for standardised mIBD reporting. The data form is designed for a single case and a key medication, meaning that case series or cohorts will require multiple separate tables and longitudinal exposure to multiple subsequent medications needs adjustment; some outcome parameters may not be relevant or applicable for all mIBD conditions and treatments, due to the pharmacokinetics and disease mechanisms.

The power of standardisation is of great importance in the field of rare diseases. Large randomised trials (evidence level I or II) are lacking, requiring clinical decision making on the basis of published case series (evidence level IV), case reports (evidence level V), or—not uncommonly—expert experience (evidence level VI). JPGN already requests in its author instructions to follow reporting standards for specific study types including Consolidated Standards of Reporting Trials (CONSORT); STANDards for the Reporting of Diagnostic accuracy studies (STARD checklist); STrengthening the Reporting of OBservational studies in Epidemiology (STROBE Statement); Standards for Quality

Improvement Reporting Excellence (SQUIRE statement) (see JPGN website instructions for authors). Those initiatives have shown that standardisation improves the quality of individual research and subsequent meta-analysis. The mIBD REPORT standards have a similar aim. A limited effort of authors in future articles reporting on mIBD will be transformative for patients with mIBD. Individual case descriptions will have enhanced educational and clinical impact by ensuring minimum reporting of therapeutic outcomes. Furthermore, adoption of mIBD REPORT standards will allow effective collation, comparison, and comprehensive analysis of genetically, phenotypically or immunologically similar patients to support or refute specific therapeutic strategies.


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**CONFLICTS OF INTEREST STATEMENT**

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## REFERENCES

1. Bolton C, Smillie CS, Pandey S, et al. An integrated taxonomy for monogenic inflammatory bowel disease. *Gastroenterology*. 2022;162(3):859-876.
2. 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(3):456-473.
3. 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(3):389-403.
4. Kammermeier J, Lamb CA, Jones KDJ, et al. Genomic diagnosis and care co-ordination for monogenic inflammatory bowel disease in children and adults: consensus guideline on behalf of the British Society of Gastroenterology and British Society of Paediatric Gastroenterology, Hepatology and Nutrition. *Lancet Gastroenterol Hepatol*. 2023;8(3):271-286.
5. Collen LV, Newburger PE, Snapper SB. Clinical remission of severe Crohn's disease with empagliflozin monotherapy in a pediatric patient with glycogen storage disease type 1b. *JPGN Reports*. 2023;4(4):e356.
6. Veenbergen S, van Leeuwen MA, Driessen GJ, et al. Development and function of immune cells in an adolescent patient with a deficiency in the interleukin-10 receptor. *J Pediatr Gastroenterol Nutr*. 2017;65(1):e5-e15.
7. Busoni VB, Lemale J, Dubern B, et al. IBD-like features in syndromic diarrhea/trichohepatoenteric syndrome. *J Pediatr Gastroenterol Nutr*. 2017;64(1):37-41.
8. Hudson AS, Almeida P, Huynh HQ. Dual biologic therapy in a patient with Niemann-Pick type C and crohn disease: a case report and literature review. *JPGN Rep*. 2022;3(3):e225.
9. Uhlig HH, Booth C, Cho J, et al. Precision medicine in monogenic inflammatory bowel disease: proposed mIBD REPORT standards. *Nat Rev Gastroenterol Hepatol*. 2023;20(12):810-828.
10. Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: an update on the selecting therapeutic targets in inflammatory bowel disease (STRIDE) initiative of the International Organization for the study of IBD (IOIBD): determining therapeutic goals for Treat-to-Target strategies in IBD. *Gastroenterology*. 2021;160(5):1570-1583.
11. Rajpurkar P, Chen E, Banerjee O, Topol EJ. AI in health and Medicine. *Nat Med*. 2022;28(1):31-38.

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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