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[1,2]. 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[2,3]. 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 apporach[4].

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 Pediatric 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[5]; immunological findings and responses to thalidomide and intravenous immunoglobulin in an adolescent patient with interleukin-10 receptor signalling defect[6]; the gastrointestinal and immunological findings in patients with Trichohepatoenteric syndrome [7]; or dual biological therapy with infliximab and ustekinumab in a patient with Niemann-Pick type C and Crohn's disease[8]. These case reports illustrate the genetic and phenotypic diversity of patients with a mIBD diagnosis, the impact of extraintestinal problems, and the need for better treatments in clinical care. Indeed, while hematopoietic stem cell transplantation has emerges as standard of care in some conditions such as 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) [9]. 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**R**ea**T**ments) were established[9]. Based on these recommendations, we propose a reporting algorithm including a reporting checklist

and a template reporting worksheet (**Figure 1, Supplementary file 1 and 2**). The algorithm is comprised of 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 are also documented. 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 one-year period including a longitudinal series of at four intervals (baseline, and approximately 10 weeks, 26 weeks, and 52 weeks) that can provide a realistic insight into the response. This enables the assessment of short-term and long-term outcomes, and comparison with the expected outcomes in classical IBD.

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, Supplementary file 3**)[5].

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 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[10]. Patients with mIBD may benefit from these tools especially in diagnosis (endoscopic and pathologic reading), therapeutic monitoring, personalized 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.

However, 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 as a whole. 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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Conflict of interest:

Figure 1. Standardised reporting in mIBD – translating fragmented observations into systematic data and better care in clinical practice.

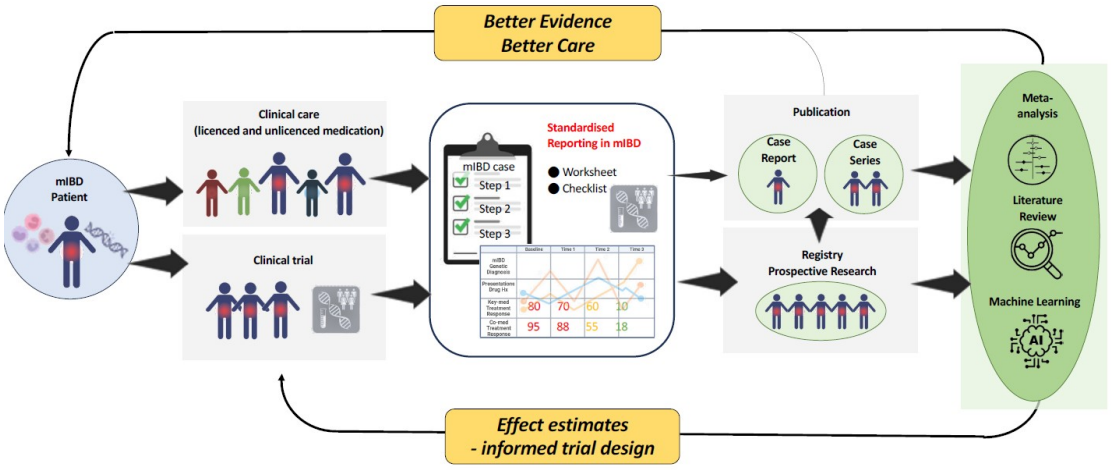
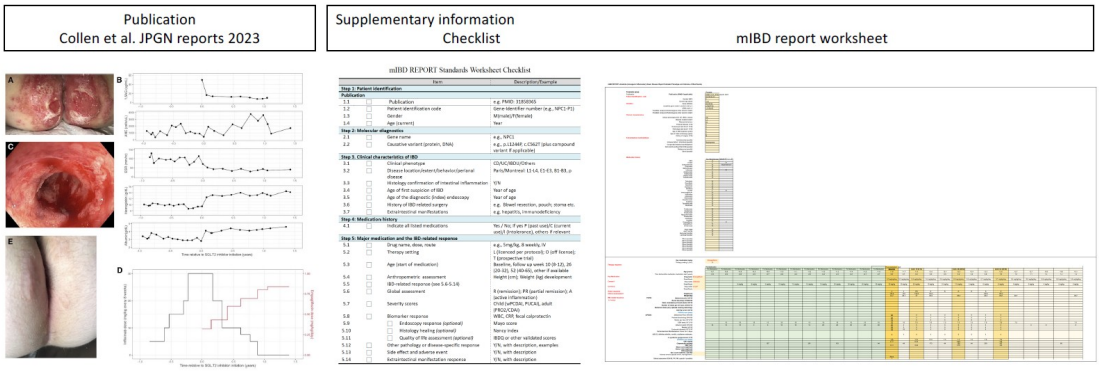


Figure 2. mIBD report standards as a complement to published data.

The example illustrates a case report and its corresponding supplemental information with machine readable structured reporting and a checklist for completion.



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