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ECCO Scientific Workshop Paper

Results of the Seventh Scientific Workshop of ECCO: Precision Medicine in IBD – Challenges and Future Directions

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This edition of the *Journal of Crohns and Colitis* presents three state-of-the-art reviews from the 7th ECCO Scientific Workshop, 'Precision Medicine in Inflammatory Bowel Disease'. These papers describe the need for individual disease stratification by factors including clinical phenotype or molecular signatures [or both] while considering current and required predictive tools, the importance of identifying higher risk populations, the crucial need for academic–industry collaborations, and the process of implementing precision medicine in varying healthcare systems globally [Figure 1]. Although precision medicine primarily describes individualized healthcare, it also aims to limit unnecessary healthcare expenditure, which is particularly challenging in inflammatory bowel disease [IBD] due to the complexity and heterogeneity of the disease.

1. Precision medicine requires a target

Much can be learned from other disciplines in directing therapeutics to specific molecular signatures, such as immunotherapy for colorectal cancer.[1] Whilst cancer may be absent, growing or stable, defining the target of remission in IBD is challenging. Molecular features of remission are incompletely understood, and while clinical trials use mucosal healing as a target, the impact and achievability of histological remission in daily practice remain unclear.[2] Therefore, to develop non-invasive molecular tests as treatment targets, there is an urgent need to comprehensively understand physiological homeostasis and to what degree this needs restoration to sustain clinical, endoscopic or histological remission.

2. Current and ideal precision tools in IBD

Therapeutic drug monitoring [TDM] is an example of routine use of precision medicine in IBD. TDM can help assess immunogenicity, drug metabolism and individual compliance with therapy to individually tailor drug choice and dose.[3] Testing for thiopurine methyltransferase activity is widely used to anticipate adverse effects from thiopurines.[4] Newer innovations have identified genetic variation in *NUDT15* as associated with thiopurine-induced myelosuppression.[5]

What remains elusive is a precision medicine tool that may predict natural history at diagnosis, predict at-risk groups pre-diagnosis or predict efficacy prior to starting therapy. Large genetic studies have identified sub-phenotypes of IBD, specifically with regard to disease location, reinforcing heterogeneity that ultimately may require sub-classification beyond a two-disease model.[6] Despite a wealth of genetic data, there are [somewhat disappointingly] remarkably few genetic associations with prognosis. This may partially be due to the quality of clinical phenotyping within historical cohorts. Thus, development of polygenic risk scores will be dependent on large-scale well-phenotyped cohorts, such as the IBD BioResource,[7] the UK and International IBD Genetics Consortia, UK Biobank, GETAID, and datasets generated as part of industry-led Phase 3 and 4 clinical trials.

3. Translation and challenges for implementation into clinical practice

Several obstacles to translational development and clinical implementation of precision medicine exist. These include:

- Access to existing datasets and ability to generate new data for discovery or replication.
- Practicality and scalability of randomized trials.
- Cost of development and deployment of tests that must be accurate, rapidly and easily performed, and applicable to individuals.
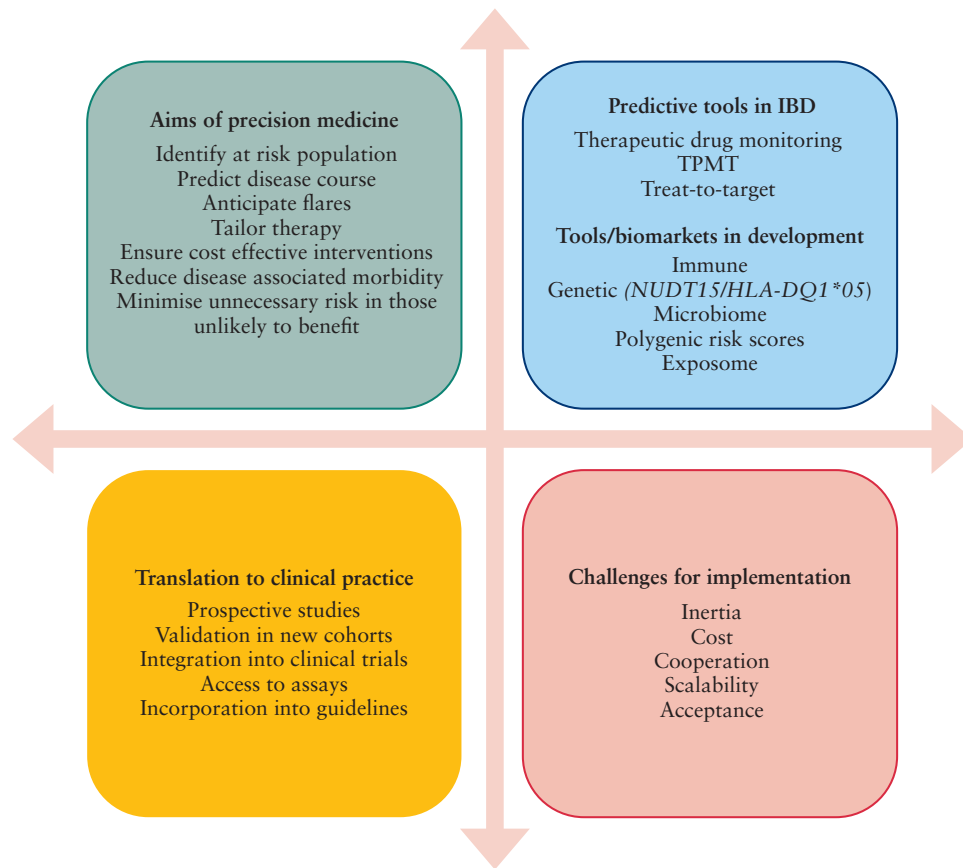
Aims of precision medicine

Identify at risk population
Predict disease course
Anticipate flares
Tailor therapy
Ensure cost effective interventions
Reduce disease associated morbidity
Minimise unnecessary risk in those
unlikely to benefit

Predictive tools in IBD

Therapeutic drug monitoring
TPMT
Treat-to-target

Tools/biomarkets in development

Immune
Genetic (*NUDT15/HLA-DQ1*05*)
Microbiome
Polygenic risk scores
Exposome

Translation to clinical practice

Prospective studies
Validation in new cohorts
Integration into clinical trials
Access to assays
Incorporation into guidelines

Challenges for implementation

Inertia
Cost
Cooperation
Scalability
Acceptance

Figure 1. Challenges and future directions of precision medicine in inflammatory bowel disease.

- Feasibility of tests or interventions in real life, including implementation of outcomes in already busy and financially challenged IBD services.

The cost of development and the implementation of precision medicine assays are perhaps the greatest challenges to academia. Although the development of '-omics' tools is increasing, experimental design is key to ensure appropriate application and judicious use of funds. This is supported by a ground-breaking study of blood-derived T-cell subsets, which revealed a prognostic transcriptomic signature in CD8 cells that may not have been discovered in whole-blood analysis.[8] Subsequent single-cell approaches, though prohibitively expensive for individual use, have revealed granularity hidden in older techniques, such as identifying previously unidentified epithelial-cell subsets.[9] Hence '-omics' studies in IBD are undeniably powerful yet only as good as the clinical phenotyping, material used and study design.

The refinement of -omic and multi-omic technologies into licensed and usable tests requires lengthy, carefully powered, replicated and costly interventional studies. Randomized trials are essential to demonstrate the efficacy and benefit of a precision medicine tool. However, the associated time and complexity means there is often a delay of several years between discovery and clinical implementation of a candidate biomarker or therapy. The pioneering PROFILE trial in Crohn's disease aimed to assess the relative benefit of a 'Top Down' over an 'Accelerated Step-Up' therapy approach, using the CD8 signature discussed above and identified in 2011.[8] This demonstrates the lag and inevitable cost in translating experimental observations into clinical practice.

The cost and clinical utility of individual tests may limit integration in clinical practice. For example, the HLA-DQA1*02:01-HLA-DRB1*07:01 haplotype has been identified as predictive of thiopurine-induced pancreatitis with a number needed to test of 76 to prevent one case of pancreatitis.[10] Whilst screening is not routinely available, this may change with reduced-cost genotyping or if broader screening panels are developed in the future.

Academic–industry collaboration can provide the much-needed infrastructure, bio-statisticians, finance, governance and opportunity to translate results from the laboratory to pivotal human studies, or to translate results from clinical trials into routine healthcare practice. Repositories of large-scale datasets are now widely and freely available and provide an exciting opportunity for data discovery, hypothesis generation or proof-of-concept development. Future consideration should be given to facilitating ethical access to existing widescale clinical datasets within healthcare systems, and how standardization of clinical data collection and recording can be achieved. Opportunities and challenges are provided by the digitization of healthcare globally. Efforts should be made to ensure that datasets generated in private industry as part of therapeutic development are made available for academic discovery. Maintenance of patient confidentiality in the information era is of paramount importance.

Consideration must also be given to the scalability and practicality of precision tools. This is important from an individual patient perspective, including the frequency of benefit or harm and the accuracy of the test or intervention. Scalability and practicality are also important at the healthcare system level, as organizations throughout the world are under financial strain. The development

of molecular diagnostics must consider sustainability according to local resources and the ability of these systems to implement and fund innovation.

4. Beyond biomarkers

The future of research in precision medicine will include trials stratified by or including populations of patients with identifiable biological factors. Identifying those most likely to respond to existing or novel therapies is a vital step in precision medicine, and discoveries in this area will inform future mechanistic studies and drug development. Through an understanding of disease biology, there is an exciting opportunity to reverse-translate understanding of disease pathogenesis from clinical observations.

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Conflict of Interest

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