Quo vadis now: beyond genomics to an era of personalised medicine

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Seven years ago, we asked the question: "How should we define or redefine inborn metabolic diseases in the era of a genetic diagnostic revolution?" (1). Since then, as expected, exome and genome sequencing strategies have identified several hundred new IMDs. In 2020 a global consortium of metabolic specialists published the new International Classification of Inherited Metabolic Disease (ICIMD), in which an inherited metabolic disease (IMD) is defined as any primary genetic condition in which alteration of a biochemical pathway is intrinsic to specific clinical, biochemical and/or pathophysiological features (2).

As exome and genome sequencing identify new disorders at an unprecedented pace and reveal expanding phenotypes for already known genetic entities, we are reminded that nature is not black and white but a continuum of shades of grey. We now know that one gene defect may cause different diseases. Two examples are *POLG* variants, that may be associated with quite diverse phenotypes ranging from fatal infantile Alpers-Huttenlocher syndrome to late onset progressive external ophthalmoplegia and/or parkinsonism, and pathogenic variants in *ALDH18A1* that may be associated with dominant and recessive forms of cutis laxa and spastic paraplegia, and there are a growing number of other examples. Conversely, a single clinical entity may be caused by many different genes, for example more than 100 genes have now been linked to the disease that Denis Leigh described as subacute necrotising encephalomyelopathy in 1951 (3), and which is now known as Leigh syndrome. Incomplete penetrance is well-recognised for many genetic disorders, and may become the rule rather than the exception, even for rare disorders (4).

As is so often the case with technological advances, the obvious benefits must be balanced against new challenges. In the case of DNA sequencing, the identification of sequence changes *in trans* does not guarantee a diagnosis, unless the functional significance of these changes can be proven. Specifically, the detection of abnormal metabolites in relevant biochemical pathways remains the *sine qua non* of diagnosis. The traditional tools of biochemical investigation have also been enhanced by metabolomics, which permits the simultaneous examination of large numbers of metabolites in multiple pathways to produce biochemical profiles in sickness and in health.

Multi-omics methodologies are now being employed to interrogate the pathomechanisms underlying phenotypic variability in IMDs (5), in addition to clarifying the diagnosis in problematic cases. Understanding the contribution of polygenic or environmental modifiers to the phenotypic expression of "monogenic" disease variants is still in its infancy but will be essential to our ability to predict disease phenotype and prognosticate for patients affected by IMDs (6).

Genomic advances have shortened diagnostic odysseys, improved the accuracy of genetic counselling, and allowed reproductive options for many thousands of families across the globe. Reducing the time to diagnosis is particularly important for IMDs that are currently amenable to treatment, which include 116 IMDs associated with intellectual disability that may be ameliorated by early initiation of therapy (7). Debates about utilising exome or genome sequencing for newborn screening of IMDs continue (8), but the ultimate pot of gold at the end of the rainbow will be the translation of genomic advances into personalised therapies for patients affected by IMDs. An early example of personalised genomic medicine was the rapid development of a customised antisense oligonucleotide for a patient with CLN7 Batten disease. This retrotransposon prevented abnormal splicing of the mutant allele and led to clinical improvement including reduction of seizures (9).

The field of metabolic medicine is increasingly engaged in international collaborative efforts to facilitate the development of global patient registries, management guidelines, and novel therapies. This is exemplified by the European Reference Networks (ERNs) such as MetabERN, which has been active in breaking down geographical boundaries and garnering international consensus for guidelines and protocols (10).

Key stakeholders are, of course, the patients affected by IMDs, and we have heard from them in a series of View from Inside articles published in the *Journal of Inherited Metabolic Disease* since 2018 (11). Patient and public involvement (PPI) is increasingly recognised as essential to the quality, relevance, validity, and credibility of clinical research, as exemplified by the James

Lind Alliance Priority Setting Partnerships in which patients, carers, and healthcare professionals work together to establish research priorities for a particular condition (12). Additionally, one systematic review and meta-analysis revealed that PPI interventions, particularly those involving patients with lived experience of the disease under study, positively impacted patient enrolment and retention in clinical trials (13).

The computational advances that underpinned the omics revolution have also led to other benefits for the practice of medicine. Progress in telemedicine including improvements in electronic patient records, video consultations and remote physical assessments facilitated support for patients with rare disorders, including those with IMDs, during the global SARS-CoV-2 pandemic (14). Post-pandemic and (hopefully) a return to normal face-to-face interactions, care must be taken that the electronic health record does not create barriers that impede patient-clinician relationships. Data security will also be an important issue (15).

It is anticipated that digital transformation will provide a roadmap to data driven agile learning healthcare systems. Artificial intelligence (AI) and machine learning are key players in our current age of e-healthcare and are already facilitating drug discovery – both novel drugs and repurposing already licensed drugs – and improving pattern recognition in medical images to enhance diagnosis and monitor disease progression. AI is also needed to maximise outputs from the mountain of healthcare data now available, ranging from hundreds of thousands of genomes sequenced to a myriad of clinical trial data sets. There is increasing pressure to make these data publicly available, in a FAIR (Findable, Accessible, Interoperable and Reusable) data sharing model (16). A synergy of artificial and human intelligence will be needed to ensure that mankind's benefits from these advances are fully realised (17).

In this exciting era of multi-omic data driven personalised medicine, we aim to maintain the *Journal of Inherited Metabolic Disease* as the go-to journal for the increasingly diverse community of scientists, clinicians, and others with an interest in inherited metabolic disease.

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