EDITORIAL

No gene to predict the future?

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All powerful technology has the potential to cause harm. Genomic testing is no exception. How, you might reasonably ask, can such a seemingly innocuous procedure cause harm? Misinterpretation of the clinical significance of genetic variants, and excessive belief in the ability of genomic variants to predict phenotypes is one route to harm. In rare diseases, a variant in a single gene can (in)directly lead to a full set of clinical manifestations, such as a syndrome. For the common, complex diseases - such as ischaemic heart disease, depression or diabetes - the role of genetic variants in causation is much less clearly defined. A current vogue is to combine single nucleotide polymorphisms, which have been identified as associated with increased disease risk in genome-wide association studies (GWAS), into "polygenic risk scores", that predict liability to a physical trait (intelligence, height) or a multifactorial disease. Repeatedly, such polygenic risk scores have been shown to have low utility and predictive power. It is thus caused for concern that some reproductive medicine providers propose to use polygenic risk scores to identify embryos which have a genetic liability, and potentially select against not only risk of complex diseases but phenotypes which may be perceived as undesirable. Both the historical, and science fiction literature contains strident warnings against such interventions, which carry enormous potential for discrimination and cataclysmic societal harm. Forzano et al. document the European Society of Human Genetics position in this month's issue [1].

Gerring and colleagues provide an interesting modification on the traditional GWAS [2]. They examined the influence of GWAS risk loci on gene expression (mRNA levels) in the human cortex. Transcriptomic correlations with phenotypes were often greater than genomic correlates. Providing further evidence that GWAS-derived polygenic risk scores may have limitations in predicting phenotypes. Majumdar et al.'s paper highlights that GWAS cannot detect all the genome variations, which might predict phenotypes —in this case a tandem repeat polymorphism in the serotonin receptor [3]. Conversely, He et al.'s study on the health impacts of obesity demonstrates the power of combining genomic and phenotypic data together in biomedical research: confirming the health impacts of raised body mass index [4]. Restuadi et al. analyse GWAS data from motor neuron disease to show overlap of genetic risk with educational attainment and risk of schizophrenia [5]. Demonstrating the non-specific nature of some GWAS loci and limitations in their predictive use.

But enough gloom. Let us focus on the power of genomics to help patients and families. Firstly, genomics can identify the causes of disease, when all other diagnostic approaches have been exhausted. Rahikkala et al. report a new series of patients with bi-allelic SMG9 variants [6]. Interestingly, they provide evidence that SMG9 may regulate transcription but not have a role in nonsense-mediated decay. Reuter et al. report a multiple congenital anomaly syndrome associated with bi-allelic PAN2 variants [7]. This implicates the deadenylation complex in neurodevelopmental disorders.

It is clear that many clinicians view exome and genome sequencing as immensely valuable diagnostic tools. But what do patients and families think of them? A mixed-methods study of participants in the 100,000 genomes project identified little evidence of regret at participating, but some potential for negative psychological consequences [8].

Research on families' perspectives on genetic testing has mainly been conducted in populations of Western European descent. Verberne et al. report a qualitative interview study of the experience of parents in the Caribbean who receive a diagnosis of a rare disease in their child [9]. Some of the findings overlapped with those of previous work, while certain themes were identified that were specific to the Caribbean population.

Potentially all clinicians may have to manage a patient with a secondary finding from exome or genome sequencing. But how do primary care practitioners (General Practitioners) feel about managing secondary findings? This Canadian study highlights that primary care practitioners would prioritise management of secondary findings by focussing on those which are actionable (i.e. require instigation of treatments or tests) [10]. Care must be taken when communicating genetic results to families, both by specialist and non-specialist clinicians. In a systematic review Johnson et al. identify that individuals who receive genetic results of "uncertain significance" (e.g. a VUS) often experience negative psychological impact just as if they had a genetic diagnosis [11].

Clinicians, patients and families clearly recognise the value of genomic testing. But what is the health economic perspective? An Australian study estimates that genomic sequencing for mitochondrial disease (as opposed to traditional diagnostics including muscle biopsy) could save 700,000 Australian dollars per year [12]. It may also have benefits in reducing invasive testing.

Precision medicine requires correct management of genetic conditions. This month we publish a meeting report on the management of Alport syndrome, including how to increase the molecular diagnostic rate [13]. Last, but not least, Cabrera-Alarcon et al. propose a new technique to classify pathogenic variants based upon locus variability [14] while Denommé-Pichon et al. describe the French experience of rapid genome sequencing for ill neonates [15].

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AUTHOR CONTRIBUTIONS

Alisdair McNeill conceived and wrote.

Competing interests

The author declares no competing interests.

ADDITIONAL INFORMATION

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