EDITORIAL

What's new in EJHG in June 2024?

European Journal of Human Genetics (2024) 32:603–604; https://doi.org/10.1038/s41431-024-01630-x

Measuring health related quality of life is important to understand the impact of diseases on peoples' lives. Van Pottelberghe and colleagues report a systematic review of patient reported outcome measures in inherited cardiac conditions [1]. Most studies used generic, non-disease specific measures. A high prevalence of anxiety and depression was identified. The authors argue that disease specific outcome measures should be developed to facilitate patient centred care in inherited cardiac conditions. Remaining on the topic of the genetics of cardiac conditions, Topriceanu et al examine the validity of cardiometabolic polygenic risk scores in diverse populations [2]. Most polygenic risk scores are derived from genome wide association studies performed in European populations.The authors evaluate polygenic risk scores for cardiometabolic traits in diverse populations in UK biobank data. They find that the polygenic risk scores perform better in European populations. They argue that improved polygenic risk scores are required, and this will need genome wide association studies in diverse populations.

People affected by rare conditions represent another underserved, minority population. Pearson et al report a Scottish cohort of people with SMAD4 Juvenile-polyposis hereditary haemorrhagic telangiectasia [3]. Almost 90% had colonic polyps and 42% had pulmonary arterio-venous malformations. It is well recognised that there can be long diagnostic delays for patients with rare conditions. D'Incal and colleagues demonstrate a multi-pronged approach to confirm the pathogenic role of an ADNP variant in an affected person [4]. Mowat-Wilson syndrome is an example of a rare condition where diagnosis can be challenging - due to phenotypic variability. Caraffi et al report an epigenetic signature for Mowat-Wilson syndrome [5]. This blood based DNA methylation analysis will allow accurate interpretation of ZEB2 variants, for example distinguishing benign and pathogenic variants were informatics analysis is inconclusive. Of course, for some rare conditions, a diagnosis is not made because the genetic cause has not been defined. In this issue, the genetic basis of acrokeratoelastoidosis is reported [6]. Further clinical complexity arises when a phenotype can be caused by multiple genotypes. Hearing loss is a prime example of this. Ramzan and colleagues report the presence of more than 1 cause of recessive hearing loss within a family, and identify TOGARAM2 as a candidate gene for deafness [7].

Exome and genome sequencing is undertaken in clinical practice to identify the genomic cause of a disease. But such technologies can also identify pathogenic variants in genes which are unrelated to the person's clinical presentation. This can be referred to as "opportunistic genome screening". Martyn et al report a novel approach - offering analysis of secondary genomic findings after return of the primary report [8]. Take up was low at 42%. The authors suggest that making the consent decision around opportunistic genome screening a separate conversation to the diagnostic exome/genome consent process allows more informed decision making. A key point in the consent conversation around genomic sequencing is how the person's genome data will be stored, and who will have access to it. Brown and colleagues report a framework for reporting incidental genomic findings [9]. They suggest a multi-step approach; with the clinical significance and actionability of incidental findings key factors in deciding to return the result to patients or not. By using this framework, around 5% of participants having whole genome sequencing had a reportable incidental finding. Sharing of genomic data is vital to aid research and variant interpretation. Martyn et al report that most people who have had genome sequencing would consent to data sharing, but want some degree of control over the process [10]. Horn et al report on a workshop that explored ethical issues and approaches to genomic data sharing in public-private partnerships [11].

While the diagnostic utility of genomic tests is beyond doubt, the impact of a genomic diagnosis on a family needs to be remembered. A qualitative study indicates that parents who experience a foetal loss, value the potential answers provided by genome sequencing [12].

Lastly, a piece examines the social value of the human genome in the UNESCO declarations with a thoughtful commentary [13].

Alisdair McNeill[1,2]✉

[1]*Division of Neuroscience and Neuroscience Institute, The University of Sheffield, Sheffield, UK.* [2]*Sheffield Clinical Genetics Service, Sheffield Children's Hospital NHS Foundation Trust, Sheffield, UK.*
✉*email: a.mcneill@sheffield.ac.uk*

REFERENCES

1. Van Pottelberghe S, Kupper N, Scheirlynck E, Amin AS, Wilde AAM, Hofman N, et al. Are disease-specific patient-reported outcomes measures (PROMs) used in cardiogenetics? A systematic review. Eur J Hum Genet. 2023. https://doi.org/10.1038/s41431-023-01510-w.
2. Topriceanu C-C, Chaturvedi N, Mathur R, Garfield V. Validity of European-centric cardiometabolic polygenic scores in multi-ancestry populations. Eur J Hum Genet. 2024. https://doi.org/10.1038/s41431-023-01517-3.
3. Pearson M, Mcgowan R, Greene P, Lam W, Miedzybrodzka Z, Berg J. Outcomes of patients with juvenile polyposis-hereditary haemorrhagic telangiectasia caused by pathogenic SMAD4 variants in a pan-Scotland cohort. Eur J Hum Genet. 2024. https://doi.org/10.1038/s41431-024-01607-w.
4. D'incal CP, Annear DJ, Elinck E, Van Der Smagt JJ, Alders M, Dingemans AJM, et al. Loss-of-function of activity-dependent neuroprotective protein (ADNP) by a splice-acceptor site mutation causes Helsmoortel–Van der Aa syndrome. Eur J Hum Genet. 2024. https://doi.org/10.1038/s41431-024-01556-4.
5. Caraffi SG, Van Der Laan L, Rooney K, Trajkova S, Zuntini R, Relator R, et al. Identification of the DNA methylation signature of Mowat-Wilson syndrome. Eur J Hum Genet. 2024. https://doi.org/10.1038/s41431-024-01548-4.
6. Zhu Y, Bai Y, Yan W, Li M, Wu F, Xu M, et al. A mutation in CCDC91, Homo sapiens coiled-coil domain containing 91 protein, cause autosomal-dominant acrokeratoelastoidosis. Eur J Hum Genet. 2024. https://doi.org/10.1038/s41431-024-01573-3.
7. Ramzan M, Zafeer MF, Abad C, Guo S, Owrang D, Alper O, et al. Genetic heterogeneity in hereditary hearing loss: Potential role of kinociliary protein TOGARAM2. Eur J Hum Genet. 2024. https://doi.org/10.1038/s41431-024-01562-6.

8. Martyn M, Lee L, Jan A, Lynch E, Weerasuriya R, Kanga-Parabia A, et al. Evaluation of a two-step model of opportunistic genomic screening. Eur J Hum Genet. 2024. https://doi.org/10.1038/s41431-024-01592-0.
9. Brown CM, Amendola LM, Chandrasekhar A, Hagelstrom RT, Halter G, Kesari A, et al. A framework for the evaluation and reporting of incidental findings in clinical genomic testing. Eur J Hum Genet. 2024. https://doi.org/10.1038/s41431-024-01575-1.
10. Martyn M, Forbes E, Lee L, Kanga-Parabia A, Weerasuriya R, Lynch E, et al. Secondary use of genomic data: patients' decisions at point of testing and perspectives to inform international data sharing. Eur J Hum Genet. 2024. https://doi.org/10.1038/s41431-023-01531-5.
11. Horn R, Merchant J.The UK-FR+GENE (Genetics and Ethics Network) Consortium Ethical and social implications of public–private partnerships in the context of genomic/big health data collection. Eur J Hum Genet. 2024. https://doi.org/10.1038/s41431-024-01608-9.
12. Slegers I, Keymolen K, Van Berkel K, Dimitrov B, Van Dooren S, Cooreman R, et al. Searching for a sense of closure: parental experiences of recontacting after a terminated pregnancy for congenital malformations. Eur J Hum Genet. 2023. https://doi.org/10.1038/s41431-023-01375-z.
13. Gaydarska H, Takashima K, Shahrier S, Raz A, Minari J. The interplay of ethics and genetic technologies in balancing the social valuation of the human genome in UNESCO declarations. Eur J Hum Genet. 2024. https://doi.org/10.1038/s41431-024-01549-3.

AUTHOR CONTRIBUTIONS

AM conceived, wrote and edited the paper.

FUNDING

No financial assistance was received in support of this study.

COMPETING INTERESTS

The author declares no competing interests.