EDITORIAL

2022: the year that was in the *European Journal of Human Genetics*

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We started in January 2022 with a special issue on the genetics of hearing loss. Bharadwaj et al. reported four potential new genes for recessive deafness (ADAMTS1, MPDZ, MVD and SEZ6) [1]. Adeyemo et al. describe the genetic heterogeneity of hearing loss in the Ibadan region of Nigeria, with important clinical implications [2]. Comprehensive genomic diagnosis of hearing loss relies on exome or genome sequencing; Klau et al. confirm the cost and time savings associated with exome-based testing [3].

For me, as a clinician, the stand out article from February 2022 was the review by Stark and Ellard arguing for rapid genome sequencing to be the standard of care for critically ill children [4]. In many centres, copy number variants are not routinely diagnosed on genome-based testing; if they could be it would further increase diagnostic yield. Coutelier et al. describe a method to improve the detection of copy number variants from genome sequencing [5].

More clinically informative papers were published in March 2022. Forde and colleagues confirmed that the Met992del NF1 variant is associated with very low risk for NF1-associated neoplasia [6]. Understanding genetic test results and acting on them in clinical practice is challenging. Pasquier et al. reported a qualitative study indicating that non-genetic specialists may require additional training and support [7]. This is reinforced by a paper demonstrating lack of consistency between labs in reporting the significance of variants from hereditary cancer gene panels [8].

There were no April fools in EJHG in April 2022. The first paper asks: Is there any evidence of benefit to patients from support groups? Bertonazzi et al. report a systematic review of evidence for BRCA support groups [9]. When a cancer risk gene variant is found in a proband testing may be appropriate in relatives. Woodward et al. describe a 30 year experience of cascade testing for cancer genes; with an average of 3.05 cascade tests per positive index case [10]. Genotype-phenotype correlations can help guide management. Moualed et al. describe the influence of genetic variants on natural history of schwannomas in neurofibromatosis type 2 [11].

In May Forzano and colleagues outlined the problematic issues with using polygenic risk scores in preimplantation genetic testing [12]. Polygenic risk scores are not the sole determinant of disease onset or physical characteristics. For example, Restuadi et al. describe a novel polygenic risk score for motor neuron disease [13]; but the genetic risk does not explain all of the causation of motor neuron disease indicating other important factors such as environmental exposure. Moreover, polygenic risk scores do not capture all classes of genetic variant; for example the serotonin transporter tandem repeat polymorphism [14]. In contrast there is abundant evidence for the role of high impact single gene variants in rare disease. Wu et al. report the cost effectiveness of genome sequencing to diagnosis childhood mitochondrial disease [15]. The issues around genome sequencing in clinical practice are complex; however the study of Peter et al. suggests that few families regret opting to have such testing [16].

The month of June saw Best and colleagues report a systematic review summarising the geographical factors that might lead to inequity of access to genomic medicine [17]. Telemedicine to access clinical genomics advice is one route to overcome geographical barriers. Rouxel et al. report a facial recognition method to aid the differential diagnosis of Kabuki syndrome [18]. Technological advances continue to improve genomic diagnostics. Awamleh et al. report a DNA methylation signature to help classify ASXL gene variants [19]. Nicolle utilised optical genome mapping to describe a novel 16p13.11 triplication syndrome [20].

What happened in July? Increasingly, genomic testing is undertaken in mainstream (ie non genetics) clinics. Slomp et al. report a framework for integrating a genetic counsellor into primary care to assist with mainstream testing [21]. Ormondroyd et al. described where genomic health data is generated in the UK, with relevance to considering how best to mainstream genomic testing [22]. The family perspective on the impact of genetic disease is also important. Douzgou et al. describe the impact of Rubinstein-Taybi syndrome as reported by families [23].

In August, EJHG published a special issue on COVID-19. Papers explored the ethics of vaccine prioritisation in COVID-19, the Corona virus host genetics South Africa database, and genomic determinants of COVID-19 susceptibility [24–26].

Two valuable guidelines papers were published in September 2022. Deans et al. provided an update to the ESHG 2014 guidelines on reporting genomic tests [27]. Souche et al. report recommendations for whole genome sequencing in rare diseases [28]. Both papers help guide clinical practice. One area in which, in my opinion, more detailed guidance is needed is rapid genome and exome sequencing in acutely unwell children [29].

Several valuable systematic reviews were published in EJHG in 2022. Gereis et al. synthesised the literature to show that parents may find exome/genome sequencing and the potential complexity of secondary findings etc difficult to understand during pre-test counselling [30]. Martins et al. reported a systematic review of healthcare professionals understanding of and concerns around direct to consumer genetic testing [31].

Publishing EJHG would not be possible without the dedicated work of our Section Editors and Editorial Board, and I would like to share with you their highlight papers from 2022.

Zoltán Kutalik picked a paper on gene-lifestyle interactions (Laville et al. [32]), commenting:

"This study was one of the largest efforts (including up to 610,475 individuals) across four ancestry groups that analysed SNP-environment (drinking and smoking) interaction effects for three lipids and four blood pressure traits. They have made both

methodological advances and pushed the limits of our knowledge of how genetic effects are modified by key lifestyle factors."

Peter Robinson chose Almeida et al.'s paper describing multi-omic diagnosis of inherited metabolic disease [33]. Commenting that it confirmed the value of using large study cohorts and orthogonal diagnostic techniques to diagnose rare diseases.

Magda Mroczek chose a paper by Moreno-Ruiz et al. examining digenic inheritance in rare disease [34], commenting:

"The authors propose an innovative approach to assess the possibility of digenic inheritance in unsolved rare diseases through statistical power, detected as a deficit of observed co-carrier individuals compared to the expected number in a healthy cohort. This paper is trying to solve the problem of lack of diagnosis in a significant number of rare diseases by using the existing population data and, instead of focusing on pairs of candidate genes that require functional knowledge, building alternative scenarios to reveal novel gene combinations. Although a similar approach exists in common diseases, it has not been applied to rare diseases so far."

Patrick Benusiglio selected the paper by Vibert and colleagues describing predictive testing for von Hippel Lindau syndrome in minors [35]. Those who underwent predictive genetic testing benefited from screening and treatment of neoplasms.

Angus Clarke selected two papers on rapid genomic diagnostics in the neonatal unit (Bowman-Smart [36] and Lynch [37]) commenting:

"These papers are important in alerting us to both the practical and the emotional difficulties that can arise when an infant on NICU is given an unanticipated genetic diagnosis. Both aspects of practice are immensely important and must 'be got right' in the way emotional tone is managed."

Katta Girisha selected the paper by Kariyawasam and colleagues on the incidence of Duchenne muscular dystrophy [38]:

"I liked this article as it revisits the incidence of Duchenne muscular dystrophy freshly and confirms it is close to 1 in 5000 male births. Kariyawasam et al. performed this study in Australia examining the statistics and practices over a decade and reflect on clinical genetics practice (cascade testing, preconception counselling and prenatal testing)."

Andrew Walley selected the paper on PSCK9 in the UK Biobank [39]:

"I would highlight a paper from 2nd May 2022 using UK Biobank data that demonstrates overlap of common obesity-associated loci with other traits. They analysed variants at the PCSK9 locus, a known obesity-associated locus, and looked at associations with a wide range of traits available for analysis. Given PCSK9 is already a drug target, it is possible that such drugs can be re-purposed and used for treatment."

Louise Bicknell selected two clinical papers (Zhao et al. [40] and Vaché et al. [41]):

"I consider both of these papers to be important because of the additional effort required, whether bioinformatic or functional, that lead to a confirmed genetic diagnosis. As more and more disease genes are identified, for those patients in whom an obvious diagnosis is not reached, we are going to need to spend more time, effort and creative thinking to identify the genetic alteration(s) that underlie their condition."

Mridul Johari selected a paper describing a novel form of cardiomyopathy (Koopmann et al. [42]):

"Biallelic variants in LDB3 in five unrelated families with an early-onset severe cardiomyopathy and myopathy phenotype open up a new chapter in LDB3 associated diseases. Similar to the severe LDB3 knockout mouse phenotype, these recessive variants in LDB3 show a loss of function mechanism."

I would like to conclude by thanking all of our peer reviewers, section editors, editorial board members and editorial staff for their hard work and contributions to the running of the *European Journal of Human Genetics*. All the best for 2023.

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