EDITORIAL

Guidelines, guidelines everywhere—and still I'm not sure what to do

European Journal of Human Genetics (2022) 30:989–990; https://doi.org/10.1038/s41431-022-01167-x

Alisdair McNeill [1,2]✉

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

In this month's EJHG, Deans et al. summarise ESHG recommendations for how to write reports of diagnostic genetic testing [1]. This encompasses genetic, biochemical and cytogenetic tests. Key components of a report include description of limitations of the test, use of standardised nomenclature and recommendations for further testing. Of more focussed relevance is guidance on how to report splicing studies of MMR gene variants [2]. It is suggested that two complementary splicing assays be used to confirm results. This is vital for correct classification of variants of uncertain significance. Guidelines from EuroGenTest on whole genome sequencing in rare diseases are also in September's issue [3]. Recommendations are made on selection of the most appropriate test, informatics pipelines, ethical issues and reporting.

These guidelines do not refer to specific clinical settings, and further work may be needed to consider the evidence (or lack thereof) for testing scenarios other than the outpatient department. For example, Almeida et al. report the use of multiple technologies to diagnose inherited metabolic diseases—future guidelines might consider more how to integrate such technologies and what scenarios this should be used in [4]. Increasingly, genomic techniques are being used in the diagnosis of acutely unwell children. Wells et al. report on a single-centre French experience [5]. Forty percent of neonates who had rapid exome sequencing were diagnosed by the technique. An Australian study found evidence of 'diagnostic shock' and possible problems with family functioning associated with diagnoses being made by rapid exome sequencing [6]. As ever, unintended consequences can occur when introducing novel technologies.

Several papers in this month's EJHG again highlight the value of exome or genome sequencing to increase our understanding of rare diseases. A novel HRAS variant associated with a milder Costello syndrome phenotype is described [7]. Aiding clinical interpretation of HRAS variants. Zhao et al. describe a novel SRCAP variant with unusual clinical features [8]. Liu et al. identify novel genotype-phenotype correlations in central conducting lymphatic anomalies [9].

Of course genomic technologies have relevance beyond rare diseases. Saule considers different radiological monitoring strategies for breast cancer in women with BRCA1/2 variants [10]. It is recognised that women at increased risk of breast cancer, with or without genetic predisposition variants, have increased psychological distress. Geneticists may not recognise women in distress [11]. Tschigg et al review the ethical issues in recall by genotype study designs in biobanks [12]. A key issue identified was appropriate consent procedures for biobank participants.

REFERENCES

1. Deans ZC, Ahn JW, Carreira IM, Dequeker E, Henderson M, Lovrecic L, et al. Recommendations for reporting results of diagnostic genomic testing. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-022-01091-0
2. Morak M, Pineda M, Martins A, Gaildrat P, Tubeuf H, Drouet A, et al. Splicing analyses for variants in MMR genes: best practice recommendations from the European Mismatch Repair Working Group. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-022-01106-w
3. Souche E, Beltran S, Brosens E, Belmont JW, Fossum M, Riess O, et al. Recommendations for whole genome sequencing in diagnostics for rare diseases. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-022-01113-x
4. Almeida LS, Pereira C, Aanicai R, Schröder S, Bochinski T, Kaune A, et al. An integrated multiomic approach as an excellent tool for the diagnosis of metabolic diseases: our first 3720 patients. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-022-01119-5
5. Wells CF, Boursier G, Yauy K, Ruiz-Pallares N, Mechin D, Ruault V, et al. Rapid exome sequencing in critically ill infants: implementation in routine care from French regional hospital's perspective. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-022-01133-7
6. Bowman-Smart H, Vears DF, Brett GR, Martyn M, Stark Z, Gyngell C. 'Diagnostic shock': the impact of results from ultrarapid genomic sequencing of critically unwell children on aspects of family functioning. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-022-01140-8
7. Lindsey-Temple S, Edwards M, Rickassel V, Nauth T, Rosenberger G. A novel HRAS c.466C>T p.(Phe156Leu) variant in two patients with attenuated features of Costello syndrome. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-022-01139-1
8. Zhao B, Madden JA, Lin J, Berry GT, Wojcik MH, Zhao X, et al. A neurodevelopmental disorder caused by a novel de novo SVA insertion in exon 13 of the SRCAP gene. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-022-01137-3
9. Liu M, Smith CL, Biko DM, Li D, Pinto E, O'Connor N, et al. Genetics etiologies and genotype phenotype correlations in a cohort of individuals with central conducting lymphatic anomaly. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-022-01123-9
10. Saule C, Menu-Hespel S, Carton M, Malhaire C, Cherel P, Reyal F, et al. Prevalent versus incident breast cancers: benefits of clinical and radiological monitoring in women with pathogenic BRCA1/2 variants. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-022-01049-2
11. Brédart A, Kop JL, Tüchler A, De Pauw A, Cano A, Dick J, et al. Assessment of psychosocial difficulties by genetic clinicians and distress in women at high risk of breast cancer: a prospective study. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-022-01096-9
12. Tschigg K, Consoli L, Biasiotto R, Mascalzoni D. Ethical, legal and social/societal implications (ELSI) of recall-by-genotype (RbG) and genotype-driven-research (GDR) approaches: a scoping review. Eur J Hum Genet. 2022. https://doi.org/10.1038/s41431-022-01120-y

AUTHOR CONTRIBUTIONS

AM conceived, wrote and edited this article.

COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Alisdair McNeill.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.