EDITORIAL

The future of rare autonomic disease research

Casey M. Rand[1,2] · Debra E. Weese-Mayer[1,2]

There are more than 10,000 known rare diseases, defined as affecting < 200,000 people in the US or fewer than 1 in 2000 in the EU, collectively affecting ~ 350 million people worldwide [1]. According to the U.S. Food & Drug Administration, less than 10% of these rare diseases currently have an approved treatment or therapy [2]. Most rare diseases also lack diagnostic biomarkers, leading to often extended diagnostic journeys for patients and families [3]. Taken together, hundreds of millions of people are still living with rare conditions lacking treatment or biomarkers. Without an understanding of what causes a specific rare disease, and a consistent biomarker to diagnose and follow the clinical course, the outlook for treatment is often bleak.

Small patient populations, often scattered around the globe and distant from centers with specialized expertise and research capacity, have historically made research progress painfully slow. Amongst rare diseases, those of autonomic origin are some of the most complex, severe, and difficult to diagnose given the multi-system and life-sustaining role of the autonomic nervous system (ANS). Despite the multitude of challenges, this is an unprecedented time to be researching rare autonomic disorders, and rare diseases in general. Though the global COVID-19 health emergency shattered the health care balance and trajectories of progress, its aftermath offers the serendipitous convergence of several developments that hold high potential to hasten progress in the discipline of rare diseases and pediatric autonomic medicine. Some of these are highlighted in the paragraphs that follow.

First, the pandemic forced rapid development of several tools that are immediately transferrable to rare disease research. Among these are wireless, wearable devices (referred to as "wearables"), both consumer and research, that are rapidly approaching clinical-grade data quality. Such wearables could allow rapid amplification of real-world (non-clinical) data capture in geographically dispersed rare disease patient populations [4]. These data can be used to identify biomarkers and potentially to monitor such biomarkers during trials of new therapeutics in the home environment and other natural settings, with the aim to objectively ensure representative conditions of study. Such developments could move rare diseases more rapidly toward decentralized clinical trials, reducing trial costs, burden of participation, and challenges of enrollment. Another important tool is addressed in the Ramirez et al. [5] big data article in this issue of *Clinical Autonomic Research*. It demonstrates, for instance, the power of capturing respiratory measures using in-home multimodal wearables in several rare diseases. In addition, yet another pandemic-expedited development is telemedicine and other telehealth tools. Such tools could allow centers with expertise in a particular rare disease to expand their reach, allowing larger cohorts to be identified, evaluated, and followed in natural history studies and intervention trials, across multiple sites, without recurrent in-person evaluations and study.

Second, recent development of new genetic technologies appears primed to aid in both diagnosis and treatment of rare diseases. Advances in gene sequencing and single-cell RNA techniques, for example, have aided investigators in identifying genetic mutations and pathways that cause or contribute to rare diseases [6]. Such findings can empower the development of diagnostic testing and investigation of

✉ Debra E. Weese-Mayer
D-Weese-Mayer@Northwestern.edu

1   Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

2   Division of Autonomic Medicine, Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital of Chicago and Stanley Manne Children's Research Institute, 225 East Chicago Avenue, Box 165, Chicago, IL 60611-2605, USA

new therapies. As the genetic basis of more rare diseases is identified, newborn genetic screening programs can be designed or enhanced to allow earlier diagnosis, expedited intervention, sustained disease-specific treatment, and a better understanding of disease natural history. Once the genetic underpinning of a rare disease is understood, new techniques such as gene therapy or gene editing have demonstrated success in treating or even curing certain rare disorders [7–9]. While not all rare diseases are genetic, it is estimated that over 80% have a genetic component[9]. Advances in these genetic technology fields hold high promise for these rare disorders with a genetic component.

Third, advances in data availability and consistent terminology will be critical to further advancing rare disease research. At no time in history has it been more apparent that powerful tools and consequent advances can be made if adequate data exist. Continued improvement in interoperability of electronic healthcare data and virtual disease registry data (e.g., international CCHS Registry: https://clinicaltrials.gov/show/NCT03088020; international ROHHAD Registry: https://clinicaltrials.gov/show/NCT03 135730) can make this a reality, even in rare diseases. Registries can now utilize tools such as REDCap and global unique identifiers (GUID) to support collaborative data collection and knowledge sharing. Use of data standards for rare diseases, such as Boris et al.'s data dictionary [10] described in this issue, will allow data to be shared between rare diseases that have overlapping phenotypes. Such methods will allow advanced analytic tools to be applied in rare diseases, improving diagnosis, early detection, biomarker development, and clinical trial optimization.

Fourth, and perhaps most importantly, the future of rare disease research hinges on patients and their families. Their growing advocacy efforts have played a critical role in founding rare disease-focused organizations such as NORD, changing national policies, and driving recent advances in rare disease research. Their continued efforts to raise awareness and research funding while simultaneously advocating for policy to support rare disease research and treatment will continue to be crucial. Furthermore, research and clinical trial participation are at an all-time high in the rare disease population [11]. Continued collaboration between patients, their families, and the research community will enhance participation, expedite progress and ensure involvement of all rare diseases, not just a select few.

The future of rare disease research is exciting. Advocacy efforts, policy change, scientific advances, and new technologies are coalescing to drive advances in a field long overdue for major progress. Approval for rare disease drugs has seen a significant increase in recent years as shared in the articles by Gonzalez-Duarte et al. [12] and Ramirez et al. [5]. Optimism is high that diagnostic tools and treatments will soon be available for many more rare diseases and that the innovations spawned by the COVID-19 pandemic will usher in a new era for rare disease medicine and the millions of affected families.

Data availability Not applicable.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

References

1. NIH NCATS genetic and rare disease center (2023) FAQs about rare diseases. Accessed 22 May 2023. https://rarediseases.info.nih.gov/about
2. U.S. food and drug administration (2022) Rare disease cures accelerator. Accessed 22 May 2023. https://www.fda.gov/drugs/regulatory-science-research-and-education/rare-disease-cures-accelerator
3. Zanello G, Chan CH, Pearce DA, Group IRW (2022) Recommendations from the IRDiRC Working Group on methodologies to assess the impact of diagnoses and therapies on rare disease patients. Orphanet J Rare Dis 17:181
4. Rwei AY, Lu W, Wu C, Human K, Suen E, Franklin D, Fabiani M, Gratton G, Xie Z, Deng Y, Kwak SS, Li L, Gu C, Liu A, Rand CM, Stewart TM, Huang Y, Weese-Mayer DE, Rogers JA (2020) A wireless, skin-interfaced biosensor for cerebral hemodynamic monitoring in pediatric care. Proc Natl Acad Sci USA 117:31674–31684
5. Ramirez J-M, Carroll MS, Burgraff N, Rand CM, Weese-Mayer DE (2023) A narrative review of the mechanisms and consequences of intermittent hypoxia and the role of advanced analytic techniques in pediatric autonomic disorders. Clinical Autonomic Research (Special edition on Pediatric Autonomic Disorders) https://doi.org/10.1007/s10286-023-00958-6
6. Montgomery SB, Bernstein JA, Wheeler MT (2022) Toward transcriptomics as a primary tool for rare disease investigation. Cold Spring Harb Mol Case Stud. https://doi.org/10.1101/mcs.a006198
7. Nance ME, Hakim CH, Yang NN, Duan D (2018) Nanotherapy for Duchenne muscular dystrophy. Wiley Interdiscip Rev Nanomed Nanobiotechnol. https://doi.org/10.1002/wnan.1472
8. Pearson TS, Gupta N, San Sebastian W, Imamura-Ching J, Viehoever A, Grijalvo-Perez A, Fay AJ, Seth N, Lundy SM, Seo Y, Pampaloni M, Hyland K, Smith E, de Oliveira BG, Heathcock JC, Minnema A, Lonser R, Elder JB, Leonard J, Larson P, Bankiewicz KS (2021) Gene therapy for aromatic L-amino acid decarboxylase deficiency by MR-guided direct delivery of AAV2-AADC to midbrain dopaminergic neurons. Nat Commun 12:4251
9. National center for advancing translational sciences (2023) Gene therapy platform for rare diseases. Accessed 22 May 2023. https://ncats.nih.gov/trnd/projects/gene-therapy
10. Boris JR, Abdallah H, Ahrens S, Chelimsky G, Chelimsky TC, Fischer PR, Fortunato JE, Gavin R, Gilden JL, Gonik R,

Grubb BP, Klaas KM, Marriott E, Marsillio LE, Medow MS, Norcliffe-Kaufmann L, Numan MT, Olufs E, Pace LA, Pianosi PT, Simpson P, Stewart JM, Tarbell S, Van Waning NR, Weese-Mayer DE (2023) Creating a data dictionary for pediatric autonomic disorders. Clinical Autonomic Research (Special edition on Pediatric Autonomic Disorders) https://doi.org/10.1007/s10286-023-00923-3

11. National organization for rare disorders (2020) Barriers to rare disease diagnosis, care, and treatment in the US: a 30-year comparative analysis. Accessed: 22 May 2023. https://rarediseases.org/wp-content/uploads/2020/11/NRD-2088-Barriers-30-Yr-Survey-Report_FNL-2.pdf

12. Gonzalez-Duarte A, Cotrina-Vidal M, Kaufmann H, Norcliffe-Kaufmann L (2023) Familial Dysautonomia. Clinical Autonomic Research (Special edition on Pediatric Autonomic Disorders) https://doi.org/10.1007/s10286-023-00941-1