The advantages of rare disease biobanking: A localised source of genetic knowledge to benefit the South African rare disease community and related stakeholders worldwide

Established rare disease (RD) biobanks in high-income countries have shown great benefits through their contribution to biomarker discovery, new diagnostic assays and drug development, as well as through facilitating clinical trial participation.[1] Research findings from several South African (SA) studies of inherited metabolic disease (IMD) (a group of diseases within the larger RD group) cohorts, discussed below, exemplify how country-specific genetic diversity can contribute to global knowledge of clinical, biochemical and genetic complexity. Globally, precision treatment is migrating from targeting gene function towards drug refurbishment or pharmacological development with specific mutations in mind.[2,3] Although the latter is not yet a reality for most RD patients in SA, opportunities for the development of competitive treatment options become a possibility, since patients receiving treatment may be less inclined to consider alternatives. We provide evidence of why a RD biobank is relevant not only for affected patients, but also for the collective medical community.

The richness of scientific information that is still to be discovered is illustrated in two studies on Gaucher disease, the first focused on SA Ashkenazi Jewish Gaucher patients and the second on a cohort of black SA Gaucher patients.[4,5] The latter provides some novel insights into the speculative correlation between the p.T36del mutation and the associated clinical presentation.[4] In other studies of mitochondrial disease, unique myopathic and hepatocerebral phenotypes, and various novel mutations, were identified.[6-8] In ultra-rare IMDs, such as ALG6-CDG, data on phenotype-genotype correlation are scarce, and even small cohort descriptions contribute substantially to the existing literature.[9] Founder effects offer unique opportunities to study genetically homogenous cohorts. Black galactosaemia patients in the Cape Town region of SA have contributed significantly to the current understanding of the clinical phenotype and prevalence of the p.S135L mutation.[10,11] Similarly, a high prevalence of the p.A293T mutation corroborated previous reports that low 3-hydroxyglutaric acid excretors are independent of genotype.[12] As an additional example, owing to a founder effect in a white, isovaleric acidaemia patient cohort, it was proven that the p.G123R mutation decreases the structural integrity of the isovaleryl-CoA dehydrogenase protein, rendering it unstable.[13] These studies are just some of the unique IMDs observed in SA. Krause *et al.*[2] have elegantly summarised prevalent founder mutations resulting in monogenetic disorders observed in sub-Saharan Africa. Founder populations are likely to become increasingly attractive for drug development, as illustrated for cystic fibrosis in particular.[2]

The current limitation in RD therapeutics in SA may offer an appealing opportunity to industry partners. RD patients in the developed world who already receive the standard of care may not be receptive to new treatment options.[14] Access to treatment-naive patients will likely be a significant attraction for those companies able to develop competitive RD treatments where therapeutics already exist. A 2023 study showed that up to 15% of RDs have at least one approved drug for prevention, diagnosis and/or treatment since the Orphan Drug Act was implemented in the USA 40 years ago.[15]

The benefits of RD research may extend far beyond those patients affected by it, and be of value to other more common conditions. While there is an abundance of literature on the contribution of RDs to the burden of disease globally, the scientific value they represent is all too frequently forgotten. RD can unlock some of the complex biomedical answers required to help advance common disease research.[16,17] A considerable amount of preclinical research uses animal models that, while a valuable research component, do not fully represent human tissues. RD biobank samples, including tissue, may be valuable in improving understanding of common diseases such as dementia, diabetes and stroke, as control samples are required to test for newly discovered conditions, and in the exploration of effective new therapies. Rather than using an animal model for dementia research, samples from Niemann-Pick type C patients may be used as a preferred alternative, since this RD also presents with early and rapid dementia.[18] The niches of this RD have been described, as well as the potential contribution to wider populations.[19] The overlap of RDs with more common conditions is apparent when reviewing networks based on human interactome modelling.[20] RD research has already contributed to some of the most threatening communicable diseases present in the world today, as in the case of the Ebola epidemics.[21,22]

The fairly recent discovery of PCSK9 mutations as a cause of autosomal dominant hypercholesterolaemia provides a typical example of how a discovery in one RD patient can lead to insight into the mechanisms that underlie important health concerns globally, and impact a whole pipeline of drugs currently in development.[23,24] While it may take time to deliver such breakthroughs to patients, attractive medium-term benefits, including significant research outputs, international collaboration, sharing of expertise and the promotion of high standards of care, make for a convincing argument in favour of RD biobanks.[20] Within this context, the SA bio-economy strategy collectively aims to establish infrastructure and research to drive employment and access to international markets.[25]

This editorial highlights some benefits of research on RDs and its important role in various research and innovative applications. RD biobank samples find applications in biomarker discovery, new diagnostic assay development, drug development and clinical trials for both rare and common disorders.[1] Together with an accompanying registry and deep phenotyping, RD biobanking advances basic science and may lead to multiple drug discoveries and academic publications, both now and via the retrospective use of samples. As knowledge and technology develop, building a robust, locally relevant evidence base able to respond to the ever-changing RD landscape remains a priority.[26,27]

Within this context, an ethically approved RD biobank on the African continent to promote contribution to universal knowledge of genetic variation and disease was established at North-West University, which houses one of the historical IMD diagnostic units in SA. We believe this initiative will promote global contributions in IMD '-omics', precision medicine and bio-innovation. Our ultimate vision is that the RD biobank may receive support worldwide as it contributes to discoveries in genomic diversity and potentially affordable care for all IMD patients.

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1. Garcia M, Downs J, Russell A, Wang W. Impact of biobanks on research outcomes in rare diseases: A systematic review. Orphanet J Rare Dis 2018;13(1):202.
2. Krause A, Seymour H, Ramsey M. Common and founder mutations for monogenic traits in sub-Saharan African populations. Annu Rev Genomics Hum Genet 2018;19:149-175. https://doi.org/10.1146/annurev-genom-083117-021256
3. Tesi B, Boileau C, Boycott KM, Canaud G, Caulfield M, Choukair, D et al. Precision medicine in rare diseases: What is next? J Intern Med 2023(epub ahead of print). https://doi.org/10.1111/joim.13655
4. Morar B, Lane AB. The molecular characterisation of Gaucher disease in South Africa. Clin Genet 1996;50(2):78-84.
5. Arendt S, Heitner R, Lane AB, Ramsay M. Glucocerebrosidase gene mutations in black South Africans with Gaucher disease. Blood Cells Mol Dis 2009;43(1):129-133. https://doi.org/10.1016/j.bcmd.2009.02.008
6. Smuts I, Louw R, du Toit H, et al. An overview of a cohort of South African patients with mitochondrial disorders. J Inherit Metab Dis 2010;33(Suppl 3):S95-S104. https://doi.org/10.1007/s10545-009-9031-8
7. Van der Walt EM, Smuts I, Taylor RW, et al. Characterisation of mtDNA variation in a cohort of South African paediatric patients with mitochondrial disease. Eur J Hum Genet 2012;20(6):650-656. https://doi.org/10.1038/ejhg.2011.262
8. Meldau S, de Lacy RJ, Riordan GTM, et al. Identification of a single MPV17 nonsense-associated altered splice variant in 24 South African infants with mitochondrial neurohepatopathy. Clin Genet 2018;93(5):1093-1096. https://doi.org/10.1111/cge.13208
9. Dercksen M, Crutchley A, Honey E, et al. ALG6-CDG in South Africa: Genotype-phenotype description of five novel patients. J Inher Metab Dis 2012;8:17-23. https://doi.org/10.1007%2F8904_2012_150
10. Henderson H, Leisegang F, Brown R, et al. The clinical and molecular spectrum of galactosemia in patients from the Cape Town region of South Africa. BMC Pediatr 2002;2(1):7.
11. Berry GT. Classic galactosemia and clinical variant galactosemia. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. GeneReviews. Seattle: University of Washington, 1993 - 2023. https://www.ncbi.nlm.nih.gov/books/NBK1518/ (accessed 14 November 2023).
12. Van der Watt G, Owen EP, Berman P, et al. Glutaric aciduria type 1 in South Africa – high incidence of glutaryl-CoA dehydrogenase deficiency in black South Africans. Mol Genet Metab 2010;101(2-3):178-182. https://doi.org/10.1016/j.ymgme.2010.07.018
13. Dercksen M, Duran M, Ijlst MLJ, et al. Clinical variability of isovaleric acidemia in a genetically homogeneous population. J Inher Metab Dis 2012;25(6):1021-1029. https://doi.org/10.1007/s10545-012-9457-2
14. Kesselheim AS, McGraw S, Thompson L, et al. Development and use of new therapeutics for rare diseases: Views from patients, caregivers, and advocates. Patient 2014;8(1):75-84. https://doi.org/10.1007/s40271-014-0096-6
15. Fermaglich LJ, Miller KL. A comprehensive study of the rare diseases and conditions targeted by orphan drug designations and approvals over the forty years of the Orphan Drug Act. Orphanet J Rare Dis 2023;18(1):163.
16. Sudlow C, Gallacher J, Allen N, et al. UK biobank: An open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015;12(3):e1001779. https://doi.org/10.1371/journal.pmed.1001779
17. Mora M, Angelini C, Bignami F, et al. The EuroBioBank Network: 10 years of hands-on experience of collaborative, transnational biobanking for rare diseases. Eur J Hum Genet 2015;23(9):1116-1123. https://doi.org/10.1038%2Fejhg.2014.272
18. Malnar M, Hecimovic S, Mattsson N, Zetterberg H. Bidirectional links between Alzheimer's disease and Niemann-Pick type C disease. Neurobiol Dis 2014;72(A):37-47. https://doi.org/10.1016/j.nbd.2014.05.033
19. Hendriksz CJ, Anheim M, Bauer P, et al. The hidden Niemann-Pick type C patient: Clinical niches for a rare inherited metabolic disease. Curr Med Res Opin 2017;33(5):877-890. https://doi.org/10.1080/03007995.2017.1294054
20. Woidy M, Muntau AC, Gersting SW. Inborn errors of metabolism and the human interactome: a systems medicine approach. J Inherit Metab Dis 2018;41(3):285-296. https://doi.org/10.1007/s10545-018-0140-0
21. Herbert AS, Davidson C, Kuehne AI, et al. Niemann-Pick C1 is essential for Ebolavirus replication and pathogenesis in vivo. MBio 2015;6(3):e00565-15.
22. Hoenen T, Groseth A, Falzarano D, et al. Ebola virus: Unravelling pathogenesis to combat a deadly disease. Trends Mol Med 2006;12(5):206-215. https://doi.org/10.1016/j.molmed.2006.03.006
23. Abifadel M, Varret M, Rabès JP, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nature Genetics 2003;34(2):154-156. https://doi.org/10.1038/ng1161
24. Wang Y, Liu Z-P. PCSK9 inhibitors: Novel therapeutic strategies for lowering LDL cholesterol. Mini Rev Med Chem 2019;19(2):165-176. https://doi.org/10.2174/1389557518666180423111442
25. Bracco S, Calicioglu O, Gomez San Juan M, et al. Assessing the contribution of bioeconomy to the total economy: A review of national frameworks. Sustainability 2018;10(6):1698. https://doi.org/10.3390/su10061698
26. Kakkis ED, O'Donovan M, Cox G, et al. Recommendations for the development of rare disease drugs using the accelerated approval pathway and for qualifying biomarkers as primary endpoints. Orphanet J Rare Dis 2015;10(10):16. https://doi.org/10.1186/s13023-014-0195-4
27. Pariser AR, Gahl WA. Important role of translational science in rare disease innovation, discovery, and drug development. J Gen Intern Med 2014;29(3):804-807. https://doi.org/10.1007/s11606-014-2881-2

S Afr Med J 2023;113(12):e1507. https://doi.org/10.7196/SAMJ.2023.v113i12.1507