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.\(^1\)\(^2\) 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.\(^3\)\(^4\) 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.\(^5\)\(^6\) The latter provides some novel insights into the speculative correlation between the p.T36del mutation and the associated clinical presentation.\(^7\) In other studies of mitochondrial disease, unique myopathic and hepatocerebral phenotypes, and various novel mutations, were identified.\(^8\)\(^9\) 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.\(^10\) 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.\(^11\)\(^12\) Similarly, a high prevalence of the p.A293T mutation corroborated previous reports that low 3-hydroxyglutaric acid excreters are independent of genotype.\(^13\)\(^14\) As an additional example, owing to a founder effect in a white, isovaleric acidemia patient cohort, it was proven that the p.G123R mutation decreases the structural integrity of the isovaleryl-CoA dehydrogenase protein, rendering it unstable.\(^15\) These studies are just some of the unique IMDS observed in SA. Krause et al.\(^16\) have elegantly summarised prevalent founder mutations resulting in monogenic 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.\(^16\) 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.\(^17\)

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.\(^18\)\(^19\) 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.\(^18\) 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.\(^21\) 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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