Published in final edited form as:

Nat Genet. 2024 February ; 56(2): 189–193. doi:10.1038/s41588-023-01642-1.

Advancing diagnosis and research for rare genetic diseases in Indigenous peoples

Gareth Baynam[1,2,3,4,5,6,7], **Daria Julkowska**[8], **Sarah Bowdin**[9], **Azure Hermes**[10], **Christopher R. McMaster**[11,12], **Elissa Prichep**[13], **Étienne Richer**[12], **Francois H. van der Westhuizen**[14], **Gabriela M. Repetto**[15], **Helen Malherbe**[16,17], **Juergen K. V. Reichardt**[18], **Laura Arbour**[19], **Maui Hudson**[20], **Kelly du Plessis**[17], **Melissa Haendel**[21], **Phillip Wilcox**[22], **Sally Ann Lynch**[23,24], **Shamir Rind**[25], **Simon Easteal**[10], **Xavier Estivill**[26], **Nadine Caron**[27,28], **Meck Chongo**[27], **Yarlalu Thomas**[25], **Mary Catherine V. Letinturier**[8], **Barend Christiaan Vorster**[29]

[1]Rare Care Centre and Genetic Services of Western Australia, Department of Health, Government of Western Australia, Perth, Western Australia, Australia.

[2]Faculty of Health and Medicine, Division of Pediatrics, University of Western Australia, Perth, Western Australia, Australia.

[3]Telethon Kids Institute, University of Western Australia, Perth, Western Australia, Australia.

[4]Faculty of Medicine, University of Notre Dame, Fremantle, Western Australia, Australia.

[5]Faculty of Science and Engineering, Spatial Sciences, Curtin University, Perth, Western Australia, Australia.

[6]Faculty of Medicine, Notre Dame University, Perth, Western Australia, Australia.

[7]School of Population and Global Health, University of Melbourne, Melbourne, Victoria, Australia.

[8]IRDiRC Scientific Secretariat, French National Institute of Health and Medical Research (Inserm), Paris, France.

[9]Department of Clinical Genetics, Addenbrooke's Hospital, Cambridge, UK.

[10]National Centre for Indigenous Genomics, Australian National University, Canberra, Australian Capital Territory, Australia.

[11]Department of Pharmacology, Dalhousie University, Halifax, Nova Scotia, Canada.

[12]Institute of Genetics, Canadian Institutes of Health Research, Halifax, Nova Scotia, Canada.

[13]Platform on Shaping the Future of Health and Healthcare, World Economic Forum, New York, NY, USA.

✉ gareth.baynam@health.wa.gov.au .

Author contributions

G.B. proposed, developed, and chaired the related IRDiRC Task Force, wrote multiple sections of this article, and coordinated the writing and review of the manuscript. D.J., S.B., A.H., C.R.M., E.P., E.R., F.v.d.W., G.M.R., H.M., J.K.V.R, L.A., Ma.H., K.d.P., Me.H., P.W., S.L., S.R., S.E., X.E., N.C., M.C., Y.T. and B.C.V. participated in the related IRDiRC Task Force, co-conceived the framework of the paper and contributed to writing and review. J.K.V.R. contributed to the section on engagement and edited the entire manuscript. M.C.V.L. revised and edited the entire manuscript.

Competing interests

The authors declare no competing interests.

[14]Human Metabolomics, North-West University, Potchefstroom, South Africa.

[15]Facultad de Medicina, Center for Genetics and Genomics, Clinica Alemana Universidad del Desarrollo, Santiago, Chile.

[16]Department of Biochemistry, Genetics and Microbiology, University of Pretoria, Pretoria, South Africa.

[17]Rare Diseases South Africa, Johannesburg, South Africa.

[18]Australian Institute of Tropical Health and Medicine, James Cook University, Smithfield, Queensland, Australia.

[19]Department of Medical Genetics, University of British Columbia, Victoria, British Columbia, Canada.

[20]Faculty of Maori and Indigenous Studies, University of Waikato, Hamilton, New Zealand.

[21]Oregon Clinical and Translational Research Institute, Oregon Health and Science University, Portland, OR, USA.

[22]Department of Mathematics and Statistics, University of Otago, Dunedin, New Zealand.

[23]National Rare Disease Office, Mater Misericordiae University Hospital, Dublin, Ireland.

[24]Academic Centre on Rare Diseases, University College Dublin, Dublin, Ireland.

[25]Western Australian Register of Developmental Anomalies, Perth, Western Australia, Australia.

[26]Quantitative Genomics Medicine Laboratories (qgenomics), Esplugues de Llobregat, Barcelona, Spain.

[27]UBC Centre for Excellence in Indigenous Health, Vancouver, British Columbia, Canada.

[28]UBC Northern Medical Program and Department of Surgery, Prince George, British Columbia, Canada.

[29]Centre for Human Metabolomics, North-West University, Capetown, South Africa.

Abstract

Achieving a diagnosis for Indigenous people living with a rare, often genetic, disease is crucial for equitable healthcare. The International Rare Disease Research Consortium convened a global Task Force to bridge the gap in diagnosing Indigenous rare diseases, and identify solutions to tackle the health inequity faced by Indigenous people.

In Nelson Mandela's words, "Without language, one cannot talk to people and understand them; one cannot share their hopes and aspirations, grasp their [for example, medical] history, appreciate their poetry, or savour their songs"[1]. To advance the diagnosis of diseases that affect Indigenous people, it is necessary to listen to their voices.

Although there is no universally accepted definition of 'Indigenous', among the common themes reflected in some definitions are self-identification, acceptance as a member by the community, historical continuity, connection to country, and distinct cultures and

languages. Indigenous peoples collectively number an estimated 370 to 500 million across 90 countries (https://en.unesco.org/indigenous-peoples), amounting to less than 5% of the global population, but 15% of the world's poorest (https://stories.undp.org/10-things-we-all-should-know-about-indigenous-people). Groups of Indigenous peoples are recognized in some low- and middle-income countries (LMICs), including, for instance, the Khoi-Khoi and San people in South Africa. However, these groups face complex and multifaceted challenges to basic healthcare access, and the dialogue around these challenges is in its infancy by comparison with the situation in high-income countries (HICs). Indigenous peoples often live in remote areas where there is limited access to basic social and medical services. Moreover, in many LMICs, there are further barriers that may vary in quality and quantity when compared with HICs, including lack of recognition by governments, discrimination, barriers to land access, and transport issues. Worldwide, Indigenous peoples' health often varies substantially from that of non-Indigenous people, particularly in HICs, where optimized services are available for many majority populations[2].

'Rare disease' is defined as affecting 86 per 100,000 people in the USA or fewer than 50 per 100,000 people in the European Union (EU). They are uncommon when considered individually, but with as many as 6,000–10,000 rare diseases, they are collectively common. A conservative, evidence-based estimate for the population prevalence of rare diseases is 3.5–5.9%, which equates to 263–446 million people affected globally[3]. Although many diseases are uniformly rare across the globe, some that are rare in one jurisdiction are common in others: for instance, sickle cell disease is rare in Australia but more prevalent in sub-Saharan Africa.

There are roughly 12 to 20 million Indigenous people living with a rare disease, and they face additional challenges compared with non-Indigenous people[4]. A variety of factors mean that rare diseases may or may not be more prevalent in Indigenous groups: for example, founder effects, endogamy and the introduction of adult-onset disorders from external communities (such as Machado–Joseph disease in Northern Australia) may increase relative prevalence[5], while sociocultural constructs (such as skin groups in Australian Aboriginals; https://go.nature.com/3NXIv2a) reduce consanguinity and hence the prevalence of recessive diseases. Some rare diseases may not be rare to Indigenous peoples, but are 'rare' as a function of being compared with larger, majority population groups (as with Machado–Joseph disease in some Indigenous Australian communities).

Globally, awareness is the first step towards accelerating the diagnosis of rare diseases, and is particularly crucial for many Indigenous people, where there has been little focus on rare diseases by the community or primary care providers. Identifying emerging health challenges such as the diagnosis of rare disease in LMICs is complex and compounded by competing health priorities (for example, infectious diseases), which may contribute less to the burden of disease as the epidemiological transition continues with an accompanying increase in the relative burden of non-communicable diseases, but due to greater awareness, receive a greater proportion of commitment and resources[6]. This is exacerbated by difficulties in recognizing rare diseases in underserved/understudied populations, from both the clinical phenotypic and the genomic perspective[7]. Furthermore, living remotely can be an additional challenge for Indigenous people with rare diseases.

Nevertheless, substantial initiatives have improved the diagnostic pathway for people living with a rare disease (https://www.globalrare-diseasecommission.com/). These initiatives include the Undiagnosed Diseases Network International (UDNI; http://www.udninternational.org), the US National Institutes of Health (NIH) Undiagnosed Diseases Network (UND; https://undiagnosed.hms.harvard.edu/), and the US NIH Genetic and Rare Diseases Information Center (GARD; http://rarediseases.info.nih.gov). These and other programs have improved the diagnosis of rare diseases and are crucial in advancing toward the diagnostic goal of the International Rare Diseases Research Consortium (IRDiRC; https://irdirc.org/) — specifically, that, "All patients coming to medical attention with a suspected rare disease will be diagnosed within one year if their disorder is known in the medical literature; all currently undiagnosable individuals will enter a globally coordinated diagnostic and research pipeline". Despite all this progress, however, much of the global Indigenous population has very limited access to rare disease diagnostics, especially those that are tailored to address specific scientific challenges and are culturally appropriate. As a consequence, IRDiRC — an international initiative founded in 2011 by the US National Institutes of Health and the European Commission — decided to launch a Task Force to tackle the health inequity faced by Indigenous people, and to improve access to rare disease diagnosis and research by Indigenous people.

IRDiRC serves as a unifying global platform for rare disease stakeholders, facilitating discussion and knowledge exchange regarding gaps and opportunities in rare disease research to advance diagnosis and therapy development. Task Forces and Working Groups are strategic tools that IRDiRC implements to address actionable topics identified by the Consortium in achieving its vision and goals. In line with its global commitment to advancing rare disease research, IRDiRC annually solicits Task Force proposals from its Consortium members, which are instrumental in driving the progress of research. The Consortium Assembly — composed of representatives from major national and international rare disease funding bodies, companies, patient advocacy groups, and research institutions — formulates and submits several Task Force proposals. The evaluation process entails a rigorous review, followed by an anonymous online vote by Consortium members to reach a quorum, and to agree on the high-priority topics that should be included in the Consortium's annual research pipeline. In 2019, the Indigenous Population Task Force was recognized as a topic of priority and consequently integrated as part of the IRDiRC Roadmap 2019–2020 to bring awareness to the current state and to the need for improvement in global health equity for the Indigenous population. Composed of global rare disease stakeholders (funders, researchers, clinicians, and patient advocates) and Indigenous individuals, the Task Force convened virtually every two months for a year to identify topics of priority, with the goal of progressing rare disease diagnosis and research for Indigenous populations. Ultimately, elements that unlock advances for the diagnosis of Indigenous rare diseases will benefit both Indigenous and non-Indigenous people and therefore will contribute to the IRDiRC vision and goals.

Indigenous populations are spread out worldwide, living in metropolitan, rural, and remote areas, and often experience health disparities, particularly in rare disease diagnostics. These disparities will be magnified unless concerted and coordinated initiatives are taken to address the obstacles that hinder equitable access to diagnostic innovation. In

this Commentary, we focus predominantly on diagnostic and screening options, disease phenotyping, building data and resources, and co-designing research with Indigenous people.

Key findings of the Task Force

Improving screening to support rare disease diagnosis for Indigenous peoples.

There is a range of diagnostic and screening options for rare diseases, and ultimately, they should be applied in a coordinated, integrated, inclusive, and equitable way across the relevant time points in a human lifespan. Screening approaches include, for example, newborn screening and population carrier screening.

The scope and coverage of newborn screening is expanding globally, supporting early diagnosis. However, the implementation of newborn screening is variable within and between countries. For instance, sickle cell disease and congenital hypothyroidism are newborn screening conditions in Africa that are arguably the most prevalent and most manageable in the African healthcare context, resulting in a substantial burden to healthcare provision if not diagnosed and managed correctly[8]. Numerous pilot projects have been conducted, but upscaling coverage or national implementation to address these and other conditions has thus far been unsuccessful[9]. Local and Indigenous knowledge, as well as some practical considerations, are important additional considerations in creating a cohesive and equitable system in which screening is followed up with formal diagnosis and research, which drives further improvement and implementation. Acknowledging logistical difficulties in maintaining sample integrity when faced with poor infrastructure, intermittent electricity supply, and extreme weather conditions is essential in ensuring downstream clinician and patient satisfaction. Culturally appropriate post-screening diagnosis, counselling, and treatment services must be established with locally relevant guidelines[10]. Establishing and maintaining registries and biobanks is necessary to improving diagnosis, long-term disease characterization, clinical care, and access to treatments. Initiatives to promote the export of samples and patient registration are often well meaning, but are not always compatible with the sovereignty of Indigenous data, and thus are not always in the best interests of Indigenous people with rare diseases.

Given that identity by descent is more common in some Indigenous populations, to facilitate early diagnosis, one could also develop testing of genetic variants using a molecular approach targeted to the population-specific allelic and genomic architecture. This approach — developed and used successfully in some populations with a high rate of autosomal recessive conditions[11] — could be rapid and cost-effective, as well as reducing the complexity of pre-test and post-test genetic counselling by reducing the identification of incidental findings and variants of uncertain significance. These might be particularly challenging to address in the combined context of a lack of reference data (resulting in a greater pre-test probability of a false positive), limited resources for clarifying the pathogenicity or otherwise of variants (for example, by imaging), and a lack of the genetic counselling capacities required for managing pyschosocial nuances. With community engagement and cultural endorsement that promotes the maintenance of trust and sensitively addresses stigmatization, targeted screening could be used as a foundation

for subsequent expanded population carrier screening[12], for instance for primary prevention. This paradigm could also deliver a way to progress — with greater clarity and a more secure and trusted foundation — towards the increased use of technologies that are less targeted to variants of known pathogenicity and more towards new informatics approaches.

A holistic 'whole-of-life' approach to disease phenotype.

Moving from a medical view of disease phenotype — which may restrictively see an individual through a biomedical disease lens — to using an Indigenous 'whole-of-life' lens provides an opportunity for a broader and potentially less pejorative ('disordered') view of phenotype. For example, the Aboriginal Community Controlled Health Services Model of Care is underpinned by eight determinants: family, community, culture, emotional, spiritual, country, physical, and language (https://go.nature.com/47vRP4c). These align with the Indigenous understanding of wellbeing as an encompassing concept that incorporates other species. These underpinnings are thematically reflected in other embracing paradigms such as Ubuntu (South Africa), toda la vida (Latin America; https://www.todaunavida.gob.ec), and whakapapa and hauora (Maori).

Developing approaches to phenotyping that are holistically inclusive of these aspects may yield new data elements, expanded ontologies, new processes, and insights to advance diagnosis and treatment. For instance, ontologies (representations of knowledge in a domain) and their interconnections underpin cross-species comparisons. Accordingly, the Monarch Initiative connects phenotypes to genotypes across species, bridging basic and applied research with semantics-based analysis. Monarch supports the correlation of phenotypes and disease with genetic variation and environmental factors, and develops and maintains an ontology — the Mondo Disease Ontology (Mondo). This semi-automatically constructed ontology merges multiple disease resources such as human phenotype ontology terms to yield a coherent merged ontology (http://mondo.monarchinitiative.org). In addition, Indigenous ways of knowing and being could be incorporated into ontologies and standards. For example, ontologies that better incorporate elements of family and community structures, Indigenous languages and concepts, and elements of the country (environment) could be combined with existing ontologies such as Mondo. Similarly, these elements could be tailored for inclusion in standards for phenotypic exchange, such as phenopackets. Phenopackets provide a schema for sharing clinical (phenotypic) data that is computer readable, as well as understandable by people (http://phenopacket.org). Furthermore, to enable ontologies for Indigenous applications, Lyfe Languages is translating medical ontology terms—such as human phenotype ontology terms — into Indigenous languages (http://www.lyfelanguages.com).

Building on Indigenous rare disease data and resources.

The infrequency of individual rare diseases mandates interoperability and sharing. Interoperability is the ability to exchange and use information. Like sharing, it can occur at the level of people and partnerships; policy and frameworks; platforms and ecosystems; algorithms, such as those for artificial intelligence and analysis of facial imaging (Cliniface, for example; https://www.cliniface.org); and data. Indigenous engagement, governance and leadership in the generation, sovereignty, use, interoperability, and sharing of Indigenous

data is crucial at all levels and from the outset. Challenges to data sharing include regulations (such as privacy protection and community knowledge control), data complexity, and volume. One approach to these challenges is to supplement data sharing with data visiting. This is where the algorithms are applied under the regulatory conditions of the local resource and then return analysis results but not primary data, which remain under the control of a community-appointed governing body. This could support federated machine learning, for example.

Like data sharing, data visiting is enabled by FAIR (findable, accessible, interoperable, reusable) principles, and data visiting is one mechanism to reconcile FAIR principles[13] with Indigenous CARE (collective benefit, authority to control, responsibility, ethics) requirements (https://www.gida-global.org/care). The CARE principles were specifically created to address potential exploitation and build trusted ways to use Indigenous data and knowledge for collective benefit, in the context of a recognition that the movement towards open data and open science does not always fully engage with Indigenous people's rights and interests[14]. Notably, data visiting has been implemented for African COVID-19 research through machine-based querying of FAIR data points (https://go.nature.com/41WmPJp).

For some Indigenous communities, data are owned by multiple members, and permissions for use may be hierarchical and/or collective. New methods that track data and make overt their culturally appropriate regulatory requirements will support trusted data use. Additionally, systems may need to incorporate core data elements specific to Indigenous needs, such as relationship to place and culture. Benefits will include new knowledge and tools that are applicable to all.

Similarly, medical coding and classification systems are generally used to monitor disease burden and to plan and assess health interventions. It is crucial that these comprehensively accommodate Indigenous people living with rare diseases. Of the estimated 6,000–10,000 rare diseases, only approximately 500 are listed in the most commonly used medical classification system, ICD-10, and only half of these have a specific code. Even in prevalent diseases such as cancer, Indigenous identifiers are lacking, potentially undermining the relevance and efficacy of policies, guidelines, and treatment approaches. This issue is likely magnified within the context of rare diseases. Failure to accurately document Indigenous status and data could result in inadequate representation of Indigenous people, greatly influencing disease rates and subsequent research and clinical outcomes.

Finally, there are few specific tools — and none all in one place — that facilitate connection from diagnosis through to resources in the practical care domains of drug treatment, care pathways, information provision, and psychosocial and integrated care, including clinical trials and research participation. The Treatabolome initiative (https://solve-rd.eu/the-treatabolome/) represents a key step towards this[15]. It creates a database of evidence for rare disease treatments linked to the precise genetic variant. Multiple rare diseases do have treatments available; however, frequently, there is a substantial delay before individuals receive them. The Treatabolome addresses this need by making this information readily accessible at the point of diagnosis. Ultimately, this should account for Indigenous rare disease demographics and potential differences in phenotypic expression (such as treatment

response) of the same disorder or variant in Indigenous versus non-Indigenous populations. The equitable utility of this resource will be supported by expanded studies of genomic architecture and phenotypic expression in Indigenous populations.

Co-designing rare disease research with Indigenous peoples.

Indigenous peoples are often marginalized from research opportunities and less visible to ethically approved and culturally relevant research, decision-makers, and funders. It is important to note that across many health domains, conducting research with Indigenous peoples has been challenged by a legacy of mistrust in response to previous and ongoing exploitative research that: first, is culturally insensitive 'helicopter research' with no knowledge translation or sharing; second, benefits mainstream science and commercialization with minimal to no consideration for a primary benefit to the community; third, stigmatizes and disempowers Indigenous communities and ancestors; and fourth, negatively stereotypes or perpetuates systemic racism and discrimination[16]. Other challenges encountered by Indigenous peoples (and researchers wishing to engage) stem from multiple factors, including: geographic remoteness, which adds cost and travel time to and from a community; low population density, which has implications for privacy and confidentiality; and inclement weather conditions, which can limit windows for travel. All these factors have ripple effects on planning, executing, and disseminating research that if not addressed, cumulatively have an effect on (re) building and maintaining trust.

Going forward, this calls for processes of engagement that, from the outset, incorporate pathways towards Indigenous self-governance, promote the role of ceremony, consider the benefit to the community as paramount based on the community and its leaders' perspectives, and incorporate appropriate models for outcome sustainability. An example with a substantial rare disease focus, is the Silent Genomes Project by the British Columbia Children's Hospital Research Institute (https://www.bcchr.ca/silent-genomes-project) and the associated Voicing the Silent Genome initiative (https://www.youtube.com/watch?v=MoMyNYPDBbI).

Several jurisdictions have introduced approaches to support community co-designed Indigenous biomedical and socio-cultural research. As one example of increasing and close partnership with Indigenous communities, the Canadian Institutes of Health Research (CIHR) has committed to funding for Indigenous research that is at least proportionate to the percentage of the population that is Indigenous, and with a major thrust of Indigenous capacity building, training, and mentoring (https://cihr-irsc.gc.ca/e/50372.html). Since 2019, Indigenous-led organizations can apply for and directly hold and administer funds. CIHR also established a dedicated peer-review process that includes Indigenous Elders, community members, and researchers to carry out ethically and culturally appropriate research that truly involves Indigenous peoples in line with Indigenous values and embracing the wellness and resilience of Indigenous peoples.

Other examples of projects focused on community-led and co-designed research with a strong rare disease focus include the work of the National Centre for Indigenous Genomics (https://ncig.anu.edu.au/), the Better Indigenous Genetic Health Services Achieving Equity in Genomic Healthcare projects in Australia, and the Rakeiora project

(https://www.genomics-aotearoa.org.nz/projects/rakeiora-pathfinder-genomic-medicine) and Aotearoa Variome project in New Zealand. Although these projects confirm the above challenges, which cross-cut health domains, they also identify areas that are particularly relevant to rare disease research, such as how to incorporate cultural and familial considerations into consent and data-sharing processes, the need for explanations of genomic and rare disease concepts that are resonant with Indigenous narratives (see, for example, https://www.youtube.com/watch?v=wftujBV2LPs), and better methods to address the stigma that can be associated with rare diseases.

Summary of recommendations by the Task Force

Addressing the challenges and opportunities in advancing rare disease diagnosis for Indigenous people requires a holistic approach that encompasses recognizing and redressing transgressions, addressing health inequities, embracing Indigenous peoples' strengths and resilience, and generating new culturally safe and responsive solutions that will benefit Indigenous (and ultimately also non-Indigenous) people living with rare diseases. Combining Indigenous worldviews, whole-of-person, and cross-species initiatives may provide unique pathways for new diagnostic approaches (Fig. 1).

Diagnostic approaches need to be culturally appropriate and informed by local healthcare professionals familiar with the specific rare disease demography, and can benefit enormously from the characterization of Indigenous genomic architecture. This requires a whole-of-community and whole-of-health systems-level design and response.

Moreover, research that is co-designed with Indigenous peoples must benefit from adaptive funding designs with fewer time limitations. The pressure to conduct research with a Western-style timeline can erode trust, as it disrespects the priorities of Indigenous engagement. There is a need for better consultation prior to and throughout the research. The funding model also needs to support research participation, including related costs (such as travel and lodging expenses, childcare, and translators), and involvement of multilingual patient advocates and caregivers in research design to educate and help participants navigate the risks and benefits. The role of Elders, Knowledge Keepers, Indigenous leaders, and their corresponding institutions (such as Trusts) must be respected and budgeted for[17].

Further research, advocacy, and training are urgently needed to address the challenges that limit the equitable receipt of rare disease diagnosis for Indigenous peoples. Ultimately, this will benefit all people.

Acknowledgements

This manuscript was prepared by the authors in their personal capacity. The views and opinions expressed here are those of the authors and do not necessarily reflect the views, opinions, or position of their employers or organizations. The IRDiRC Indigenous Population Task Force was supported by the Scientific Secretariat of IRDiRC, funded by the European Union through the European Joint Programme on Rare Disease (EJP RD) under the European Union's Horizon 2020 Research and Innovation Programme (grant agreement 825575). The Scientific Secretariat is hosted at the French National Institute of Health and Medical Research (INSERM) in Paris, France.

References

1. Mandela M Long Walk to Freedom: The Autobiography of Nelson Mandela (Little, Brown & Company, 1994).
2. D'Angelo CS et al. Front. Pediatr 8, 579924 (2020). [PubMed: 33381478]
3. Richter T et al. Value Health J. Int. Soc. Pharmacoeconomics Outcomes Res 18, 906–914 (2015).
4. Nguengang Wakap S et al. Eur. J. Hum. Genet 28, 165–173 (2020). [PubMed: 31527858]
5. Carr JJ et al. PLoS One 14, e0212953 (2019).
6. Malherbe HL, Christianson AL & Aldous C South Afr. Med. J. Suid-Afr. Tydskr. Vir Geneeskd 105, 186–188 (2015).
7. Fraiman YS & Wojcik MH Pediatr. Res 89, 295–300 (2021). [PubMed: 32932427]
8. Piel FB, Hay SI, Gupta S, Weatherall DJ & Williams TN PLoS Med. 10, e1001484 (2013). [PubMed: 23874164]
9. Therrell BL et al. Semin. Perinatol 39, 171–187 (2015). [PubMed: 25979780]
10. Port RV, Arnold J, Kerr D, Glavish N & Winship I Clin. Genet 73, 132–138 (2008). [PubMed: 18177468]
11. Triggs-Raine B et al. Mol. Genet. Genomic Med 4, 312–321 (2016). [PubMed: 27247959]
12. Easteal S et al. Am. J. Hum. Genet 107, 175–182 (2020). [PubMed: 32763188]
13. Wilkinson MD et al. Sci. Data 3, 160018 (2016). [PubMed: 26978244]
14. Hudson M et al. Nat. Rev. Genet 21, 377–384 (2020). [PubMed: 32251390]
15. Bonne GJ Neuromuscul. Dis 8, 337–339 (2021).
16. Caron NR et al. Front. Public Health 8, 111 (2020). [PubMed: 32391301]
17. Curtis E et al. Int. J. Equity Health 18, 174 (2019). [PubMed: 31727076]

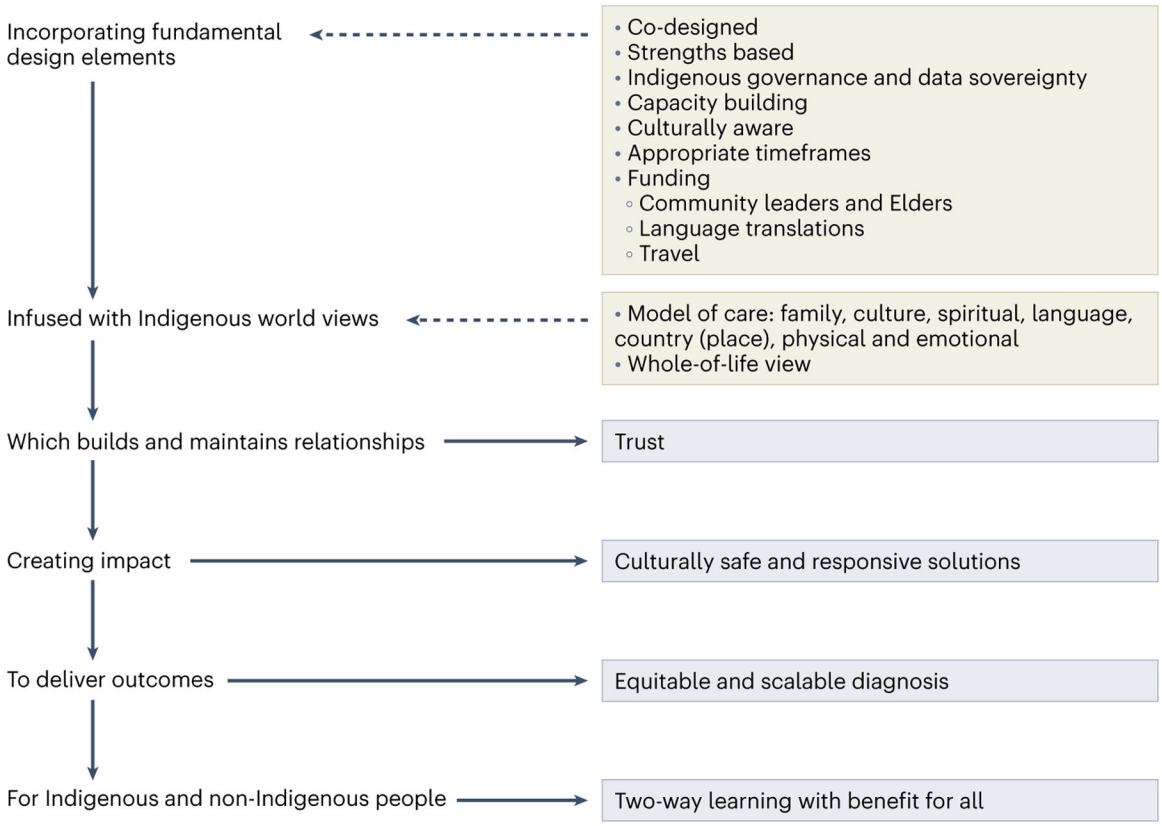

Fig. 1 |. A model for advancing the diagnosis of rare diseases in Indigenous people.
The figure summarizes key themes (such as incorporating Indigenous world views) as well as core elements (such as co-design, strengths-based approaches, and the sovereignty and governance of Indigenous data), and resulting outputs (such as trust, and culturally safe and responsive solutions) for both Indigenous and non-Indigenous people (two-way learning).