Chapter 27
Indigenous Genetics and Rare Diseases: Harmony, Diversity and Equity

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Abstract Advances in our understanding of genetic and rare diseases are changing the face of healthcare. Crucially, the global community must implement these advances equitably to reduce health disparities, including between Indigenous and non-Indigenous peoples. We take an Australian perspective to illustrate some key areas that are fundamental to the equitable translation of new knowledge for the improved diagnosis of genetic and rare diseases for Indigenous people. Specifically, we focus on inequalities in access to clinical genetics services and the lack of genetic and phenomic reference data to inform diagnoses. We provide examples of ways in which these inequities are being addressed through Australian partnerships to support a harmonious and inclusive approach to ensure that benefits from traditional wisdom, community knowledge and shared experiences are interwoven to support and inform implementation of new knowledge from genomics and precision public health. This will serve to deliver benefits to all of our diverse citizens, including Indigenous populations.

Keywords Indigenous • Aboriginal • Genomics • Genetics • Phenotyping • Phenomics • Equity • Innovation • Facial

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Advances in our understanding of genetic and rare diseases, precision medicine [12, 29, 31, 32, 38] and precision public health [18, 39] are changing the face of healthcare. Crucially, the global community must implement these advances equitably to reduce existing and potential health disparities, including between Indigenous and non-Indigenous peoples [5, 25, 35, 36]. In this chapter we take an Australian perspective to illustrate some key areas that will be fundamental to the equitable translation of new knowledge for the improved diagnosis of genetic and rare diseases for Indigenous Australians. Specifically, we focus on existing inequalities in the Australian public health system in relation to Indigenous access to clinical genetics services and the lack of genetic and phenomic reference data to inform diagnoses for Indigenous populations. We provide examples of ways in which these inequities are being addressed in Australia and in doing so we illustrate the imperative to embark on this journey in partnership with Indigenous people and communities.[1] With such an approach, there is the potential to progress in a harmo-

[1] Historic blood samples collected from Indigenous Australians could connect members of the stolen generations to their families and improve healthcare for chronic diseases, but not without confronting a troubled legacy of scientific exploitation and racial classification. About 7000 samples were collected from 43 remote communities in northern Australia in the 1960s and 1970s as part of a range of studies. The samples were used by researchers until ethical concerns about the use of Indigenous DNA prompted a moratorium in the 1990s, and have spent the intervening years preserved in Canberra. They are now collected at the Australian National University's **National Centre for Indigenous Genomics**, which has begun the process of tracking down the donors and their next of kin and getting consent to make sequenced genomes available to researchers. The process has been helped by the possibility the DNA bank could help members of the stolen generation find their lost families "*Because of that it's such a cultural, sensitive, and difficult issue for*

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nious and inclusive way to ensure that benefits from traditional wisdom, community knowledge and shared experiences are interwoven to support and inform implementation of new knowledge from genomics, precision medicine and precision public health. This will serve to deliver benefits to all of our diverse citizens, including Indigenous populations.

Rare diseases (RD) are typically complex, chronic and often multisystem disorders associated with significant rates of morbidity and mortality. Cumulatively they are estimated to affect up to 6–8% of the population [3, 4, 13–15, 33, 34]. In the absence of available data, there is no *a priori* reason to believe that rare diseases are less prevalent in Indigenous populations. In Australia, Aboriginal and Torres Strait Islander (hereafter respectfully referred to as Indigenous) people, represent 3% of the total population of 24 million [2], suggesting that 43,000–58,000 Indigenous people are living with a rare disease; over a third of which are likely to be children.[2]

Since 80% of rare diseases are genetic in origin, most Indigenous people living with rare diseases would at some time require access to clinical genetic services for

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some of the Indigenous community … so we were driven to create the very best example of Indigenous participation that exists." That includes a world-first "dynamic consent" model which allows the DNA donor to provide or revoke consent for specific projects even after they have consented to their sequenced genome being held on file, Emma Kowal said. Every application to access the data would be decided upon by the Indigenous governance board, which is chaired by the Indigenous human rights commissioner Mick Gooda. Also on the board is Prof Mick Dodson, who was opposed to the genome projects of the 1990s on the grounds that DNA was collective cultural property. https://www.theguardian.com/australia-news/2016/aug/18/indigenous-dna-at-centre-of-ethical-furore-could-help-reconnect-stolen-generations

[2] The Aboriginal and Torres Strait Islander population has a relatively young age structure, in 2011 the median age of the ATSI population was 21.6 years. http://www.abs.gov.au/ausstats/abs@.nsf/Products/C19A0C6E4794A3FACA257CC900143A3D?opendocument

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diagnosis of their condition. However, the nature of clinical genetics practice in Australia suggests that Indigenous people face significant challenges in accessing these services, which creates a disproportionate burden for those with rare diseases [21]. These challenges include referral bias, generally meaning a lack of referral from general practitioners (family physicians) to specialist services, and the fact that many Indigenous people live in remote locations that can be hundreds and thousands of kilometres from where clinical genetics services are based, even with, sometimes geographically broad, outreach services. Around 1 in 5 (21.4%) Indigenous people live in either remote or very remote areas of Australia. This compares with 1.7% of non-Indigenous Australians living in the same areas. Nearly half of Indigenous people (43.8%) live in 'regional Australia' ('regional' being closer to a major city than a remote area) and just over one-third (34.8%) live in a Major City Area, compared to almost three-quarters (71.3%) of the non-Indigenous population [1].

This contributes to Indigenous people being under-represented in patient populations of Australian clinical genetic services, in some jurisdictions by approximately two-thirds in the Northern Territory (personal communication, 2015, Professor Ravi Savarirayan, Consultant Clinical Geneticist, Victorian Clinical Genetic Services and also Director Northern Territory Clinical Genetics Service). This can be especially problematic since some rare diseases in Aboriginal Australians are geographically concentrated in remote areas. An example is the presence of the dominantly inherited Machado-Joseph disease (spinocerebellar ataxia type 3) in Arnhem land, a region of the Northern Territory that is 500 km from the capital city Darwin, where 93 Aboriginal people currently have the disease and 624 Aboriginal people are known to be at risk (personal communication, 2015, Professor Ravi Savarirayan, Consultant Clinical Geneticist, Victorian Clinical Genetic Services and also Director Northern Territory Clinical Genetics Service; and also personal communication Libby Massey, Machado-Joseph Disease Foundation).

A recent study found that nearly one-third (30%) of Australians living with rare diseases wait 5–30 or more years for a diagnosis [26]. In part, this may be a reflection of the relatively uncoordinated approach to rare diseases within the Australian public health system, which is predominantly oriented to address more common chronic conditions. Given that Indigenous people face extra challenges accessing health services in Australia, it could be expected that the diagnostic odyssey is long for an even greater proportion of Indigenous Australians living with rare diseases. This highlights the reality that rare diseases and Indigenous health (including genetic health) have a shared underlying paradigm[3] of inequity, which is greatest at the intersection of the two domains. Lack of access to clinical genetics services will impact on the opportunities for Indigenous people to participate in game changing approaches that are reducing the diagnostic odysseys of individuals living with rare diseases. For example, in Western Australia the implementation of massively parallel sequencing in the statewide clinical genetics service has led to the development of a refined diagnostic

[3] **Human Genetics Society of Australasia (HGSA)**, 39th Annual Scientific Meeting, August 2105, Perth Australia. Rare Diseases and Indigenous Genetics https://www.hgsa.org.au/documents/item/4559 Accessed August 2016.

pipeline which in turn has generated a threefold increase in molecularly confirmed diagnoses [7]. The diagnostic benefits of these new approaches to clinical service delivery are less likely to be experienced by Indigenous people, given that their access to such services is restricted, compared to the general Australian population.

It is important to acknowledge that any activity, whether service delivery or research, associated with the term 'genetics' in Indigenous people has a particular historical resonance, associated with distrust of research in general [37], and of genetic research in particular [22]. Accordingly, even today, there is often a scepticism towards 'genetic' activities, which can only be overcome through a scrupulous regard for ethics, true consultation and joint ownership of both process and outcomes between researchers and Indigenous communities [30]. It is also critical to more completely and rigorously ascertain the levels of use of, and unmet need for, clinical genetic services among Indigenous people across the whole of Australia. Based on current knowledge, it appears there is an urgent need to improve models of care for the equitable delivery of, and access to, such services for Indigenous Australians. In recognition of these issues, two national research organisations recently jointly funded an initiative to support improved clinical genetics service delivery. Firstly, the Lowitja Institute, an Indigenous organisation working for the health and wellbeing of Australia's First Peoples through high impact quality research, knowledge exchange and by supporting a new generation of Indigenous health researchers; and secondly, the National Health and Medical Research Council which is Australia's peak funding body for medical research. The project aims to improve models of care for Indigenous people by using community consultation and participant groups, and patient journey methods, to assess four current models of genetic health care provision in Australia. The aim is to support the ability of clinical genetics services to meet patient and family needs to provide access to, delivery of, and follow up from culturally appropriate genetic health care. It will also build capacity amongst Aboriginal health care workers to collaborate in the provision of genetic health services, such capacity building may help to partly address a number of challenges for rare diseases service provision, including medical staff turnover in remote regions. An enhanced workforce of Aboriginal health care professionals has the potential to increase referrals to genetic services (reducing referral bias) and to ensure greater proliferation and utility of genomics knowledge in a range of settings including remote locations.

In addition to equitable access to clinical genetics services, ascertaining appropriate genomic and phenomic reference data is also critical for enabling the diagnoses of rare and more common diseases for Indigenous Australians. In Australia, as globally, there is a paucity of such reference data for Indigenous populations [6]. This is problematic since the interpretation of results of any genetic or genomic investigation requires an understanding of the range of normal genetic variation and this is partly population specific [17]. Notably, "rare" genetic variants (occurring in less than 5% of the world's population) are disproportionately important [23, 24], most directly as the cause of rare monogenic disease, and also in contributing to the heritability and risk of complex diseases, and for pharmacogenomics.

Rare variations are often population specific, and therefore, reference data from historically geographically isolated and marginalised populations are required to determine pathogenicity [11]. Until recently there has been no publically available Indigenous genomic reference data and that which exists [36] is limited in size and in the proportion of communities that are represented.

The need for Indigenous genomic reference data is well illustrated by a case example of a 10-year diagnostic odyssey in an Aboriginal Australian family. Over an 8 year period, three siblings were seen with a similar phenotype, characterised by various overlapping combinations of macrocephaly, shared facial dysmorphology, small thoraces, connective tissue dysplasia, intellectual disability, seizures, immune dysfunction and intracranial anomalies (megalencephaly and perisylvian polymicrogyria) [6]. The proband was referred for genetic consultation in early childhood and the two siblings were first seen as newborns. Multiple non-informative monogenic tests were performed to ascertain the cause of their condition. Ultimately, based on phenotypic features, massively parallel sequencing targeting interrelated biological pathways was performed. This approach identified a co-segregating variant in the *MTOR* gene. However, the absence of Australian Aboriginal genomic reference data was a challenge to the definitive confirmation of pathogenicity, especially because this was potentially the first reported case of a familial phenotype due to an *MTOR* mutation. Consequently, there was a 2 year delay in diagnosis while functional confirmation was sought and completed. Functional studies showed the expected gain of function and importantly normalisation with the addition of the MTOR inhibitor Rapamycin. These *in vitro* analyses supported the possibility of an unanticipated novel therapeutic intervention through drug repurposing. On the basis of the functional confirmation, a diagnosis of a new disorder was made. This disorder was named the MINDS[4] syndrome (the acronym **M**acrocephaly, **I**ntellectual Disability, **N**euroDevelopmental **D**isorder, **S**mall Thorax), reflecting key phenotypic components and serving as an aide memoire for diagnosis. A new disease code (ORPHA457485) was created for the disorder in the Orphanet database of rare diseases (orpha.net.au) and following publication of the diagnostic findings, other families with an MTOR mutation have been reported [27] and the spectrum of the condition has expanded to include Autism and other more common phenotypes. This case illustrates that Indigenous populations' reference data are necessary to improve our understanding of disease pathogenesis and to support the timely diagnosis of genetic disease among Indigenous populations. These data also have utility for defining a genetic perspective from which to view environmental risk; to facilitate disease risk prediction; and to identify opportunities for drug repurposing, novel therapeutics and pharmacogenomics.

In response to the delayed clinical diagnosis of a rare genetic disease in this Aboriginal family, and similar challenges in interpreting genetic tests in other families that are directly attributable to the lack of a suitable genomic reference, clinical genetics services in Australia have begun to seek ways to improve the availability of

[4] http://www.orpha.net/consor/cgi-bin/Disease_Search_Simple.php?lng=EN&diseaseGroup=minds Accessed July 2016.

Indigenous reference data. Fortunately, genome-wide studies, including whole exome sequencing, had been performed in Aboriginal Western Australians on research cohorts unselected for monogenic disease [36]. These studies proceeded with extensive culturally appropriate community engagement and governance [36]. Study participants agreed to the deposition of their genomic data in a public database and application can now be made to the Data Access Committee to obtain allele frequency information to assist clinical diagnostic work in the Australian public health system [36]. This has already been applied to the interpretation of clinical genomic tests in Western Australia [7]. While this is an important first step, critically it must be augmented with additional Indigenous reference data, including for other regions of Australia. Facilitating this, The National Centre for Indigenous Genomics (NCIG), which was established in 2013 by the Australian National University, is establishing protocols for uses of a repository of research biological samples collected in the second half of the twentieth century from approximately 7000 Indigenous people across northern and Western Australia. NCIG is governed by an Indigenous-majority Board and aims to enable appropriate and respectful genetic and genomic research that will benefit Indigenous donors, their communities and descendants, the broader Indigenous community and the general Australian community. In 2014, NCIG commenced a process of consultation with Indigenous communities, families and individuals representing the respective communities. Thereby, NCIG is enabling Indigenous peoples to become involved in genomics in accordance with their desires and cultural and social values. This fusion of the world's oldest culture and new genomic technology is beautifully reflected in an animation video at the NCIGs website.[5]

Ultimately, and complementary to current NCIG initiatives, a prospectively ascertained combination of genomic and phenomic data will be required for maximum clinical utility. Enablers to the collection of phenomic data in a standardised way include precise objective facial assessments, [8–10] and knowledge management platforms that can be aligned to research and clinical processes. For the former, 2-dimensional approaches include the Clinical Phenotype Face Space [16] and the Atlas of Human Malformation Syndromes in Diverse Populations [28]. Furthermore, 3D facial analysis [28] is a data rich approach that provides additional precision, which can be combined with 2D approaches. For the latter, platforms that can text-mine free text and which are adaptable to multiple language formats, such as Patient Archive,[6] are particularly valuable. These platforms standardise the way data is stored and reported, enable cross-cultural interoperability and thereby the sharing of data globally for the purpose of clinical diagnosis. Engaging the Aboriginal community around data sharing will be a key to combined genomic and phenomic initiatives to facilitate the diagnosis of rare diseases, epidemiology and healthcare.

[5] About NCIG: an introduction for donor communities. http://ncig.anu.edu.au/ncig-collection/current-projects/community-engagement/about-ncig-introduction-donor-communities Accessed July 2016.

[6] Patient Archive: Phenotype is fundamentally important to identifying the cause/origin of both rare and complex disorders, and substantially reducing the search-space for genomic variation. http://www.garvan.org.au/research/kinghorn-centre-for-clinical-genomics/clinical-genomics/about-kccg/teams/phenomics-team#Patient_Archive

To improve access to clinical services and the availability of Indigenous genomic and phenomic reference data demands approaches that are developed in a culturally sensitive manner, requiring continuous open discussion amongst all relevant parties [22]. This highlights the importance of understanding and appropriately using language, which is another way that rare diseases and Indigenous health overlap. The genetic 'language' that is important for rare diseases is written in the four biological letters (A,C,T,G) of our DNA; this language differs in populations around the globe in a way that is poorly understood. We also need to develop the appropriate verbal language to communicate with the Aboriginal and Torres Strait Islander communities about their genetic health care. There is the need for deep community engagement as failure to continuously interact with Aboriginal and Torres Strait Islander Australians in a conversation about genetic health care may contribute to a continuation, or widening, of health disparities [19, 20]. Strategic frameworks relating to Aboriginal Health emphasise it is "everybody's business" to link into a language idiom and community reference used by Aboriginal communities.[7]

In this chapter we have illustrated two areas in which there are opportunities to improve equitable access to the diagnosis and management of rare and genetic diseases for Indigenous people in Australia. Firstly, the ways in which clinical genetics services are organised and delivered require reconsideration to reduce inequities in access experienced by Indigenous people. Secondly, advances in genomic testing and phenomic analyses are increasingly moving towards expanded daily clinical genetic application, providing an increasing requirement to collect and understand data on Indigenous specific variation. To maximise benefit and minimise harm in both of these spheres requires an inclusive approach that is culturally appropriate for the Indigenous community. Reassuringly, there are a number of initiatives that are beginning to address these needs and given that we are still in the early stages of the clinical implementation of genomic knowledge, precision medicine and precision public health, there is an opportunity for Indigenous people to participate, receive benefit and minimise harm at a similar rate to non-Indigenous people. Proceeding in this manner will promote a harmonious and inclusive approach that resonates with the Aboriginal narrative and that acknowledges and benefits from diversity.

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[7] WA Aboriginal Health and Wellbeing Framework 2015–2030 to articulate the commitment and a set of guiding principles, that also articulates the multi-dimensional aspects of health and wellbeing from an Aboriginal perspective and which recognises that Aboriginal people bring a diverse range of skills, including the ability to break down the cultural barriers between our cultures that can prevent best health care for their communities. http://ww2.health.wa.gov.au/Improving-WA-Health/About-Aboriginal-Health/WA-Aboriginal-Health-and-Wellbeing-Framework-2015-2030 Accessed August 2016.

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