

Genomic medicine must reduce, not compound, health inequities: the case for hauora-enhancing genomic resources for New Zealand

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ABSTRACT

Precision medicine seeks to draw on data from both individuals and populations across disparate domains to influence and support diagnosis, management and prevention in healthcare at the level of the individual patient and their family/whānau. Central to this initiative is incorporating the effects of the inherent variation that lies within genomes and can influence health outcomes. Identifying and interpreting such variation requires an accurate, valid and representative dataset to firstly define what variants are present and then assess the potential relevance for the health of a person, their family/whānau and the wider community to which they belong. Globally the variation embedded within genomes differs enormously and has been shaped by the size, constitution, historical origins and evolutionary history of their source populations. Māori, and more broadly Pacific peoples, differ substantially in terms of genomic variation compared to the more closely studied European and Asian populations. In the absence of accurate genomic information from Māori and Pacific populations, the precise interpretation of genomic data and the success and benefits of genomic medicine will be disproportionately less for those Māori and Pacific peoples. In this viewpoint article we, as a group of healthcare professionals, researchers and scientists, present a case for assembling genomic resources that catalogue the characteristics of the genomes of New Zealanders, with an emphasis on peoples of Māori and Polynesian ancestry, as a healthcare imperative. In proposing the creation of these resources, we note that their governance and management must be led by iwi and Māori and Pacific representatives. Assembling a genomic resource must be informed by cultural concepts and values most especially understanding that, at a physical and spiritual level, whakapapa is embodied within the DNA of a person. Therefore DNA and genomic data that connects to whakapapa (genealogy) is considered a taonga (something precious and significant), and its storage, utilisation and interpretation is a culturally significant activity. Furthermore, such resources are *not* proposed to primarily enable comparisons between those with Māori and broader Pacific ancestries and other Aotearoa peoples but to place an understanding of the genetic contributors to their health outcomes in a valid context. Ongoing oversight and governance of such taonga by Māori and Pacific representatives will maximise hauora (health) while also minimising the risk of misuse of this information.

Genomic medicine is poised to generate substantial health benefits for both the individual and at the population health level.¹ The increasingly detailed understanding of the structure and breadth

of variation across the human genome,² coupled with an expanding capability to define and measure the subset of genetic variants that impact upon health traits, has driven the development of multiple diagnostic tests

in recent years. Together with the development of individualised digital health records and the implementation of linked 'big data' resources, personalised genomic information stands as a central pillar of what has come to be known as 'precision medicine'.³ This term, popularised by President Obama in his State of the Union address in 2015, embodies the assertion that the inherent variability of many of the multiple contributing factors that impinge on health will be both resolvable and measurable. Moreover, the claim is that this approach will guide healthcare at the level of the individual as well as populations in the foreseeable future.^{4,5} This view of healthcare is starting to supplant the paradigm of choosing diagnostic, treatment, management and prevention options guided by evidence obtained from the study of populations, but agnostic to the inherent biological variability between individuals and subgroups within these populations.

The accurate interpretation of genetic data will be pivotal to the aspiration of precision medicine and will require precise and affordable laboratory and analytical capability over a diverse set of countries and health jurisdictions. Indeed international umbrella organisations such as the Global Alliance for Genomics and Health have begun to systemically address many of these challenges to arrive at solutions that could be generally applicable. Some issues, however, will remain as distinctly local concerns and require the development of tailored solutions to make genomic medicine accurate, beneficial, acceptable, ethical and equitable for regional populations.⁶ The promise of emerging health technologies can be inequitably realised, as the applicability and access often focuses on well-resourced nations and individuals.⁷ The cost of this technology and the information systems on which they are founded could therefore result in genomic medicine becoming a contemporary manifestation of Hart's inverse care law.⁸

A key aspect for the effective application of genomic medicine is the interpretation of genetic variation in the context of the populations from which patients originate.⁹ Genomic epidemiology has mapped widespread and pervasive differences in the nature, distribution and frequency of genetic variants in genomes across the globe.^{2,10} As

human populations dispersed around the world, their demographic histories, interactions with their environment and their interactions with other peoples have shaped their genomes in distinctive and diverse fashions.⁹ Much of this genetic diversity remains poorly mapped and understood simply because the scientific hegemony of the western world has placed excessive emphasis on the study of numerically and economically dominant European and Asian populations.¹⁰ As a deeper understanding of the genetic underpinnings of so many disease traits has been defined, it has become increasingly apparent that specific genetic variants can be considered of greater or lesser importance to health outcomes depending on the populations being studied and the ancestral history of their genomes.¹¹ Several notable instances exist where misinterpretation of genetic data has led to significant and adverse health outcomes for minority populations.¹²⁻¹⁴

The genomes of individuals living in Aotearoa reflect the ancestral origins of their forebears. Our population structure and pattern of variation continues to be moulded and influenced by the degree of admixture of individuals of different ancestry. An important context for Aotearoa New Zealand is the migration of Pākehā following first European contact. Subsequent waves of migration have introduced genomes from across the globe, most notably from the near Pacific (Western and Eastern Polynesia) as well as South and South East Asia^{10,15} resulting in differing levels of admixture even between groups and complex and diverse patterns of ancestral self-identification that in some cases do not reflect self-declared ethnicities. The net result is a modern-day admixture that is a mosaic of DNA of diverse and multifarious origins. Depending on the historical origins and genetic adaptations that these genomes have undergone prior to their arrival in Aotearoa, they will have been shaped by their migrations across Europe, Asia, Island Southeast Asia and the Pacific.^{10,16} Sequence changes arise due to many forces, including selective pressures imposed by the environments with which these genomes have interacted, which may in turn have subsequent medical consequences in modern Aotearoa environments.¹⁷

These influences will have shaped the genomes of Māori and Pacific peoples during their ancestral migrations to Aotearoa—the last temperate landmass to be inhabited by human beings. The genomes of Māori and Pacific peoples are likely to have acquired unique variants that have been positively selected as their tīpuna (ancestors) traversed diverse geographical regions.¹⁸ Additionally other genetic variants will have increased or decreased in frequency through combinations of genetic drift, bottlenecking events and introgression from other populations. Some of these functional genomic adaptations are likely to have significant relevance for health. Thus it is imperative to understand these genetic adaptations and how they interact with the modern environment to impact on health in contemporary Aotearoa.

The challenge before us is to generate capability and knowledge that will benefit those peoples in New Zealand who are most under-represented in the current international genomic knowledge base. To avoid perpetuating health inequity, this under-representation needs to be addressed since this knowledge gap will lead to disparities in the application and clinical utility of genomic technologies^{9,11} and reduce the capacity for research to generate future genomic medicine strategies relevant to these population groups.¹¹ Further, this effort must be conducted locally, as there is little incentive for globally dominant international genomics institutions to undertake this work due to the distinctiveness of this country's population genetics in addition to the cultural concept of DNA as a precious taonga. More importantly, it is an imperative derived from Article 2 of Te Tiriti o Waitangi that the rights, interests and taonga of Māori be protected and that this extends to ancestral lore and whakapapa,¹⁹ hence encompassing DNA and its associated information.²⁰ Additionally, Article 3, by extending to Māori the rights and privileges of British subjects mandates an equal share in the technological dividend offered by genomic medicine.

New Zealanders with ancestral origins located in Western Europe and South East Asia are currently poised to benefit the most from precision medicine incorporating genomic information. The variation and structure of the genomes of these major

population groups are well-studied and understood from analysis of their source populations.¹⁷ Consequently, there is a lesser imperative to study European and Asian genomes in the local context simply because this has already been comprehensively achieved elsewhere. In sharp contrast, knowledge of genomic factors that impact on the health of people with Māori and Pacific ancestry is acutely lacking. Despite this, the limited research undertaken to date indicates that genomes of individuals and populations with Māori ancestry are significantly different from western European and Asian genomes.^{21–23} Moreover, there is evidence for differences between Eastern (Cook Island Māori, Hawaiian, Tahitian and Aotearoa New Zealand Māori) and Western (Samoa, Tonga, Niue, Tokelau, Tuvalu, Rotuma) Polynesian genomes and those of other Pacific populations.²⁴ These differences include variants at either lower or higher frequencies than observed elsewhere, together with novel variations that are not present at all in large catalogues of genomic variation derived from other populations (TM, SR unpublished).^{22,23} Even more importantly, these studies have shown that some genetic differences may explain some of the differential susceptibility to conditions such as gout and diabetes that are more common in Māori and Pacific relative to European populations.^{22,23} Similarly, there is apparent potential to identify genetic resilience factors (variants that confer a protective effect) for conditions that are under-represented in Māori such as rheumatological disorders and some cancers.

Illustrating these observations, a prevalent and apparently population-specific, variant in the Samoan population—a so-called favourable adiposity genetic variant in *CREBRF*—has recently been associated with increased rates of obesity, while simultaneously conferring a protective effect on the development of type 2 diabetes.²² These data suggest that some novel genetic factors localised to the South Pacific region contribute distinct pathogenic mechanisms for highly prevalent complex disease traits.²³ Such data may be relevant for both medical treatment and reduction of risk through preventative strategies such as the prescription of appropriate drugs¹³ and/or other interventions such as 'green' prescriptions.

Having uncharacterised genetic differences embedded throughout the genomes of New Zealanders has three principal repercussions for their healthcare. The first and most immediate concern is that the interpretation of genetic test results could be inaccurate because the reference genomic data being used as a comparator is derived from individuals of entirely different ancestries. A striking example has been recently recognised during genetic testing carried out under the auspices of The New Zealand Cardiac Inherited Disease Registry, which aims to uncover the cause of sudden unexpected deaths in New Zealand. It is known that highly lethal, yet very treatable, familial conditions are common causes of sudden unexpected death in the young.²⁵ A variant in the cardiac sodium channel gene *SCN5A* known as R1193Q causes Brugada syndrome or long QT syndrome and is very rare in Western European populations. Despite this link, and the observation that it confers distinct functional cellular abnormalities *in vitro*,²⁶ it is present in 10% of the Han Chinese. In Aotearoa, this variant is present among some Māori who have died from sudden unexplained death in early adulthood.²⁵ Presently it is unclear if this genetic variant can be considered causal of these presentations and hence whether other family members are at risk or not. Genomic data from Māori and Pacific populations are needed, with some urgency, to answer this question.

A parallel situation also exists in indigenous Americans: in a recent report reviewing pharmacogenetics of indigenous North American populations, the authors stated “*Not only do Indigenous groups often have different allele frequencies compared to other global populations but marked differences in allele frequencies can also be found between subcultures within a given geographical region*” in regard to genes with important clinical outcomes.²⁷ Several examples are now recorded internationally where genetic tests have been misinterpreted and individuals misdiagnosed and mismanaged because their genomic ancestry was not factored into analysis of their genetic tests.^{9,12} Most notable are instances where individuals of African-American origin have had adverse health outcomes relating to diagnosis of drug side effects

and cardiac disease.¹² Similar inequitable outcomes are distinct possibilities in Aotearoa unless genomic medicine is established along with the appropriate resources that facilitate accurate and appropriate analysis for all New Zealanders, particularly Māori and Pacific peoples.

A second ramification of our lack of knowledge of the Māori and Pacific components of the Aotearoa genome relates to understanding the causes and natural history of disease states that confer significant morbidity and mortality in Aotearoa. These studies will inevitably involve addressing the complex interplay between genes and environment in determining outcomes. Knowing the differences in susceptibility present within populations can inform interventions to minimise risk and target scarce health resources.^{28,29} A lack of appreciation of the full gamut of genetic variation embedded within New Zealanders' genomes will inhibit the development of this understanding, limit its potential to improve health³⁰ and may perpetuate health inequities. Emerging findings in this area point to the potential of adopting this as a health research priority.^{31,32}

A third repercussion of the lack of knowledge of Māori and Pacific genomes is the impaired ability to undertake research studies with Māori and Pacific cohorts to the same level of precision as is possible in other major Aotearoa population groups. The relative paucity of genetic studies in minority populations is now recognised internationally.³³ Representation of Indigenous Americans, Australian Aborigines and Pacific peoples in catalogued genome-wide association studies (GWAS) has fallen since 2009.³³ In Aotearoa, Māori are yet to be represented in a single such study. The only GWAS conducted to date in a Polynesian population (addressing obesity; in Samoans living in Samoa and American Samoa) had to suffice with a genotyping platform designed for use in European, African and East Asian populations. Consequently, it was not possible to comprehensively survey the genomic complexity of the study population owing to the unavailability of an appropriate genomic dataset that reflected the constitution of the local population.²³

A strong imperative therefore exists to establish hauora-enhancing genomic

resources for Aotearoa that are focused on Māori and Pacific health priorities. Such resources should survey and catalogue the distribution and extent of genomic variation present in a large cohort of modern day New Zealanders, oversampled for peoples of Māori and Pacific ancestry. The construction of such resources will be central to the equitable deployment of genomic medicine for all New Zealanders. The utility of these resources for Māori and Pacific peoples will be most immediately evident in the clinic where individuals and whānau who undergo genetic testing will have their results interpreted with appropriate precision.³⁴ It also will be evident where whānau, hapū/iwi and their healthcare providers use precise genetic information about causal mechanisms that contribute to highly prevalent diseases in their communities to mitigate or reduce their risks of developing these diseases, in addition to informing their diagnosis and treatment. Ongoing research on the genetic contributors to major and significant diseases such as cancer, cardiovascular disease and type 2 diabetes will be greatly facilitated by a deeper and more accurate understanding of the genomes of the source populations under study.^{11,23} This work will be best enabled if engagement with Māori and Pacific communities occurs at all levels, including addressing the acute capacity issue in the Māori and Pacific healthcare and research workforce.

Having envisioned this future dividend, it is important to acknowledge that genetic research in Aotearoa has a chequered history, specifically concerning lack of respectful and positive relationships with Māori and their associated communities. Notable successes that have had significant translational outcomes have occurred,^{35,36} while less enlightened initiatives have misapplied genomics and simultaneously failed to be based on genuine partnerships with iwi or Māori in general to improve health outcomes as a primary objective.^{37,38} Such studies had negative outcomes for Māori, mirroring similar experiences with other technologies.³⁹ Any research of this nature carries with it the risk of multiple negative outcomes—not the least being the reinforcement of negative stereotypes, inequities and related power relationships.

Therefore, appropriate safeguards must be established and adhered to, to ensure that the utilisation of this resource remains true to its intent. Recently explicit tikanga-based guidelines (*Te Mata Ira*) for conducting genomic research with Māori have been developed with some iwi by a Māori-led research team and they should be widely adopted as best practice in the context of these research partnerships.²⁰

An important issue relating to the generation of genomic resources is that surrounding sovereignty of the data generated. The *Te Mata Ira* guidelines explicitly affirm the view of Māori that DNA samples and the data generated from them have intrinsic links with whakapapa.²⁰ The contiguous relationship between these three domains exists because they are expressions of the same wairua—the spirit that enjoins the ancestral, physical and metaphysical components of an individual's being. Consequently, DNA samples and genomic data are considered intertwined as a whole and to be a taonga and therefore both need to be subject to appropriate kaitiaki (guardianship) arrangements.²⁰ Moreover, a related set of considerations are currently being undertaken by Te Mana Raraunga, the Māori Data Sovereignty Network (www.temanararaunga.maori.nz) in the context of international and other national Indigenous Data Sovereignty projects (eg, <http://fnigc.ca/>). The Te Mana Raraunga work seeks to formulate and enunciate Māori and also iwi-specific perspectives on the governance and management of data resources, including genomic datasets. The views of different iwi and hapū, and even whānau within them, may vary in many of these respects, not only in terms of the tikanga around these resources but also the regulation of the collection, storage and use of the data.^{20,34} While a unified national genomic resource may offer the most diagnostic and scientific utility to deliver health benefits, this will require Māori communities to agree to have genomic data derived from their people managed collectively under agreed protocols. These conversations have yet to occur and they will be essential before plans to progress a model of a single, as opposed to multiple, genomic resources can be developed.

We contend that the best way to achieve this is a programme of work that is explicitly co-led, co-curated and governed by iwi-mandated⁴⁰ and Pacific representatives. This will include involvement of these representatives in how genetic and genomic resources are used in diagnostics and the science that it potentiates. This oversight will extend to how the results of research are interpreted, disseminated and explained to the general public and, above all and as a priority, with the communities with whom the research was conducted. In genuinely moving towards this goal, a more substantial and explicit effort must be made to grow future leaders in genomics/genetics/bioinformatics who are Māori and/or from Pacific communities and can both lead this research and its governance, and who also have the skills to form relationships with their communities and to share and communicate research findings and knowledge with them. We think that the development of this proposed genomic resource needs to include upskilling Māori and Pasifika to ensure that future needs and applications can be addressed within a community health provision environment. In addition,

there is a need to increase responsiveness of non-Māori researchers and clinicians, including a readiness for them to acknowledge, understand and enact the tikanga that will govern this work, especially initially when the number of Māori and Pacific experts will be outnumbered by tauwiwi (non-Māori/non-Pacific) experts. From the outset it must be clearly understood that facilitating research designed to primarily make comparisons between populations, rather than understand the genetic factors for ill-health within populations, is not the primary goal of the creation of these resources and the aspiration of precision medicine that it supports.

We foresee that the generation of hauora-enhancing genomic resources for Aotearoa New Zealand is essentially the formal creation and cataloguing of a unique national treasure—a taonga—that will be key to equitably delivering positive healthcare outcomes. As genomic medicine gathers pace, we have the opportunity, if not an imperative seated in Te Tiriti o Waitangi, to ensure that it does not contribute to more healthcare disparities on the basis of ancestry.

Competing interests:

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