Title

Expanded carrier screening for monogenic diseases for Australians of Aboriginal and/or Torres Strait Islander descent

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Abstract

Accounting for ancestral diversity is essential in medical genomics. For this reason, inclusion of Indigenous and other under-represented populations in genomic research is necessary to ensure equitable outcomes and access to precision medicine and disease prevention. Here we discuss this issue in the context of a national program of pre-conception expanded carrier screening (ECS) for recessive monogenic diseases, funded by the Australian Government as part of its Genomics Health Futures Mission. Current knowledge and research about monogenic diseases are mainly based on people with European ancestry and little is known about pathogenic DNA variants in people of Aboriginal and/or Torres Strait Islander descent. We argue that significant effort is required to build the evidence base and genomic reference data required before ECS can bring significant clinical benefit for many Aboriginal and/or Torres Strait Islander Australians. Research programs and creation of reference data are required to correct this bias. They are essential steps to achieving the Australian Government's objectives and its commitment "to leveraging the benefits of genomics in the health system for all Australians". They require culturally safe, community-led research and community engagement embedded within national health and medical genomics programs that ensure that new knowledge is integrated into medicine and health services in ways that address the cultural and health needs of Indigenous people. Until this occurs, Australians of European ancestry stand to benefit most and, as a consequence, Indigenous Australians and other minority groups in the Australian population are at risk of being, in relative terms, further disadvantaged.

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Introduction

Monogenic diseases account for most rare diseases (diseases with a prevalence of less than 5 in 10,000), 70% of which occur exclusively in children[1]. These diseases can have devastating consequences for affected people and their families. Individually – since most are rare – they contribute little to the overall burden of disease. Collectively, however, they have a substantial effect on the disease burden in all countries, regardless of socio-economic conditions affecting health[2,3]. It is estimated that there are more than 10,000 separate monogenic diseases[4] affecting ~6% of the human population[1,5].

Genomic technologies have enabled major advances in understanding and treating rare monogenic diseases. Greater accessibility to genomic data and the knowledge to interpret it have: improved diagnostic rates for existing conditions; greatly expanded the number of diseases for which diagnostic tests are available; led to greater understanding of biological processes underlying pathology; enabled development of better and targeted therapies; and resulted in improved prenatal and preimplantation testing[6–10]. Genomic technologies have also created the possibility of pre-conception expanded carrier screening (ECS), by which prospective parents are simultaneously screened as potential carriers of many different recessive diseases[5,11–14].

Pre-reproductive carrier screening is generally targeted at specific genes and carried out where there is increased risk of a child being born with a specific condition due to ancestry or based on clinical information[15]. It has been extremely effective, e.g., in reducing the incidence of Tay-Sachs disease (MIM: 272800) in Ashkenazi Jewish populations around the world[16,17]. ECS is an extension of this approach that involves simultaneous screening for many pathogenic variants responsible for a broad range of diseases in the general population. This broad-scale approach to screening is achieved by sequencing the entire

genomes (genome sequencing) or the fraction of the genome that encodes proteins – the exome (exome sequencing) – of prospective parents. Although data are obtained for the whole genome or exome, screening is often targeted at a predetermined subset of genes and/or variants. [18,19,25]

The Australian government is evaluating the potential benefits and challenges that ECS presents[5,20–28] with a view to its introduction into the national healthcare system[29]. Our focus here is on the significant challenges of achieving inclusion and equitable benefits for Indigenous Australians from this procedure and, by extension, medical genomics generally. While our focus is on Indigenous Australians, many of the points we raise apply to other under-represented groups in the general population.

Ethical, cultural, social and policy considerations are of over-riding importance in genomics. Implementation of ECS in Aboriginal and Torres Strait Islander communities raises questions about: the cultural appropriateness of screening in different communities; how prospective parents should be counselled and appropriately informed about the procedure; the means by which consent should be obtained; the potential impact on social and cultural norms; the potential for group, family and/or individual stigmatisation; how screening can be integrated into cultural practices, lifestyles and traditional concepts; whether the autonomy of patients, families and communities can be preserved; the proportion of the population likely to benefit from the procedure; how screening will be administered through community controlled and other local health services; and whether there is the capacity for counselling and follow-up clinical care. Fully articulating these complex issues is a substantial undertaking that would need separate, detailed treatment to do it full justice. Consequently, we address only the salient points here. Our main focus is on scientific evidence about

genetics and its medical implications for Indigenous Australians, as a foundation to better inform such a discussion.

The core problem for ECS implementation is lack of knowledge about genomic variants in Indigenous populations and of appropriate clinical and genomic reference data. Carrier screening depends on prior knowledge of pathogenic variants, most of which comes from studies of people of European ancestry, which may have limited applicability to other populations[30–43].

Australia is a culturally and ancestrally diverse nation. There is a need, therefore, to recognise how genomic information is interpreted, incorporated and translated meaningfully in the lives, experiences, and healthcare of individuals from diverse cultural and ethnic backgrounds. In particular, there is a national imperative to ensure equitable benefit for Aboriginal and Torres Strait Islander Australians, who collectively experience significant disparity in morbidity and mortality[44] and access to health services[44,45] compared with non-Indigenous Australians.

We discuss how Indigenous involvement at all levels, from co-design to governance and implementation, within national health genomics initiatives such as ECS is required to ensure that the needs of Aboriginal and Torres Strait Islander people are met, and to avoid the risk of their further marginalization, disadvantage and disillusion. Such involvement is essential for these initiatives to deliver outcomes consistent with the equity principles that underpin Australia's public healthcare system: universal cover and universal access.

Medical genomics in Australia

The national introduction of ECS is being evaluated as part of the Genomics Health Futures Mission (GHFM), a program funded by the Medical Research Future Fund (MRFF). Projects

funded through the GHFM operate within the policy settings provided by Australia's National Health Genomics Policy Framework (NHGPF) developed by the Australian Health Ministers' Advisory Council (AHMAC) and agreed by the Council of Australian Governments (COAG) Health Ministers in November 2017 (Box 1).

The NHGPF recognizes the importance of addressing the requirements for Indigenous inclusion in the implementation of genomic medicine (Box 1). We focus specifically on ECS as the first application of genomics to be funded under the GHFM, as a way of highlighting the importance of proactive Indigenous leadership in the design and development of medical genomics programs in Australia.

Box 1. The National Health Genomics Policy Framework, Medical Research Future Fund (MRFF) and Genomic Health Futures Mission (GHRM)

The NHGPF provides the blueprint for embedding genomics in the Australian health system. It "presents a shared commitment to leveraging the benefits of genomics in the health system for all Australians"

The principles underpinning NHGPF priorities are:

- The application of genomic knowledge is ethically, legally and socially responsible and community trust is promoted
- Access and equity are promoted for vulnerable populations
- The application of genomic knowledge to health care is supported and informed by evidence and research.

Recognising the importance of equity and inclusion, particularly in relation to Indigenous Australians, the priority areas of action of the National Health Genomics Policy Framework 2018–2021 include:

- 1.5. exploring the potential for discrimination, and evaluating the delivery of genomic services in terms of being accessible, appropriate and culturally secure and responsive for Aboriginal and Torres Strait Islander peoples.
- 5.2. Promote culturally safe and appropriate genomic and phenotypic data collection and sharing that reflects the ethnic diversity within the Australian population, including for Aboriginal and Torres Strait Islander peoples.

The intended outcomes of the Medical Research Future Fund (MRFF) are:

1. life changing discoveries such as new treatments, drugs and devices
2. continuous improvement and innovation in the health system that benefits all Australians
3. strengthening domestic research capacity through support, collaboration and the development of expert talent
4. positioning Australia's health and medical research sector at the forefront of the innovation economy
5. improving Australia's reputation as a global leader in health and medical research.

The objective of the Genomics Health Futures Mission (GHFM) is to:

1. deliver better diagnostics and targeted treatments
2. avoid unnecessary health costs
3. improve patient experience and outcomes.

The fund supports research projects that aim to:

Pathogenic variants are generally rare and population-specific

Most monogenic diseases are caused by as many as thousands of different DNA variants in one or more specific genes[5], almost all of which are rare. They may be found only in one geographic region, in one small community, or even in a single family. Thus, for example,

more than 2,000 different known pathogenic variants in the *CFTR* gene (MIM: 602421) can cause the recessive monogenic disease cystic fibrosis (CF; MIM: 219700; http://www.genet.sickkids.on.ca/Home.html). Approximately 1 in 3,000 people are affected by CF in northern Europe[46]. Elsewhere, it is much rarer and usually caused by local, rare variants that are not found in European patients[47]. In China, for example, CF, although rare, affects an estimated 20,000 people, nearly as many as the ~30,000 people affected in the United States. Because pathogenic *CFTR* variants are different from those in Europe, carrier screening panels designed for ancestrally European populations do not detect CF carriers in China or in the many substantial Chinese communities elsewhere in the world[48,49].

The rarity and geographically restricted origins of pathogenic variants have important consequences for Australia's diverse society.

1. The makeup of pathogenic variants is likely to be unique, reflecting the unique diversity of Indigenous peoples and the ancestral makeup of settlers and immigrants.
2. For the same reasons, it is likely that there are many pathogenic variants that have not been previously characterized. These may cause different clinical phenotypes and treatment responses even if they have similar molecular properties to known variants[50][46]. Clinical and functional investigation will generally be required to establish their pathogenicity and associated disease phenotypes[11,51,52].
3. For recessive diseases, many novel combinations of pathogenic variants are likely. A recessive disease can be caused by $(n(n-1)/2)+n$ combinations of n pathogenic variants. Only a small fraction of these combinations can occur where the geographic distribution of variants is restricted. In a diverse society with many people of mixed ancestry, however, many novel combinations of variants are likely that may cause novel disease phenotypes and have novel effects on treatment.

4. Genomic-background, environment and lifestyle are more likely to influence the phenotypic manifestation of pathogenic variants, potentially causing normally pathogenic variants to become benign [53] or normally benign variants to become pathogenic[54,55] because:
    I. The environment and lifestyle of many people has rapidly changed due to changed economic or social circumstances, changes in diet, or as a result of displacement or migration.
    II. There are many people of mixed ancestry in whom the effect of a variant on disease may have changed after it arrived in a genomic background different to the one in which it had previously existed.

Pathogenic variants in Aboriginal and Torres Strait Islander communities

Global prevalence estimates[1,5] suggest that, to a first approximation, more than 30,000 Aboriginal and Torres Strait Islander people may be affected by monogenic diseases, and that many more may be carriers of pathogenic variants. Many of these variants will be different from those causing the same diseases in people of non-Indigenous ancestry in the broader Australian population. Many are likely to cause either formerly unknown diseases or phenotypic manifestations of known diseases that have not previously been encountered in a clinical setting.

Some Aboriginal and/or Torres Strait Islander people have pathogenic variants inherited from non-Indigenous ancestors. However, with few exceptions, like Machado-Joseph Disease [56–58] and a complex phenotype resulting from an *MTOR* gene variant[59], little is known about pathogenic variants originating within Indigenous communities.

Unpublished data compiled by the National Centre for Indigenous Genomics (NCIG) for 160 people from four Aboriginal communities show that:

1. Approximately 25% of all DNA variants in the genome of an Aboriginal person, disregarding variants inherited from non-Aboriginal ancestors, are unknown in people from outside Australia. Among the large number of Aboriginal and Torres Strait Islander-specific variants the will be some that are pathogenic. These will not be represented in international or Australian clinical databases or in current screening panels. These databases and panels may, therefore, be of limited value for screening in Aboriginal and Torres Strait Islander communities.

2. Of these Aboriginal-specific variants, ~40% are likely to be found in a single region or community. Overall, based on F_{ST} distances[60] and comparison with data from the Simons Genome Diversity Project[61], genomic differences among Aboriginal communities across Australia are as great as those between populations across Europe and Asia combined. Thus, using information about people from the Northern Territory, for example, as a basis for treating people in South Western Australia, would be equivalent to treating people in the UK based on information about people from Cambodia.

Current lack of evidence means that for many people of Aboriginal and/or Torres Strait Islander descent ECS will produce greater uncertainty, revealing more 'likely-pathogenic variants' (LPVs) and 'variants of unknown significance' (VUSs) than for European Australians. This uncertainty could potentially lead to inappropriate clinical intervention if benign variants are incorrectly reported as pathogenic, as has occurred elsewhere[62–64].

The risk of variants being falsely reported as pathogenic can be avoided by increasing the threshold of evidence required to assign pathogenicity. This approach, however, tends to

result in under-reporting of pathogenic variants because some do not meet the higher threshold of evidence.

The result is greater "residual risk", i.e. more couples who are at reproductive risk that is not identified by ECS. High residual risk is of concern even if negative findings are not reported. If prospective parents are properly informed about their increased residual risk, negative findings may cause significant levels of needless anxiety and concern (Box 2).

In addition, increasing the threshold of evidence for pathogenicity reduces the "yield", i.e. the number of couples identified as being at risk. The result is that, overall, fewer people benefit from screening[65]. This effect will be particularly pronounced for people of Aboriginal and/or Torres Strait Islander descent for whom a greater proportion of detected variants will be novel. If the expected yield for the general population is 1–2%, the lower expected yield for Indigenous couples means that many hundreds of couples may be screened without any of them receiving a report that they are at risk of giving birth to a child with a monogenic disease.

Lack of knowledge about variant pathogenicity adds to the challenges of counselling prospective Aboriginal and Torres Strait Islander parents and of supplying the accurate information they need in order to make informed decisions about undergoing ECS. This point can be illustrated by considering information that prospective parents would require for their consent to be fully informed (See Box 2).

Novel variants identified through ECS can be functionally and clinically investigated. These investigations are unlikely, however, to provide useful information to prospective parents because of the time required to carry them out. They may, nevertheless, give rise to new evidence that improves the quality of screening for future patients.

These indirect benefits might provide ethical justification for ECS as a medical intervention if it were not possible to obtain them in other ways, even if there is little potential benefit and considerable risk for patients. Novel pathogenic variants can, however, be more effectively identified and their phenotypic effects better characterized at greatly reduced risk through direct clinical investigation of affected patients and their families. This more direct approach is greatly enhanced by characterization of genomic variation in patient communities, which can be critically important for variant discovery [59,64,66] and for correct assignment of pathogenicity [62–64].

How to address the current disparity?

The validity of ECS depends on a preexisting evidence-base linking specific DNA variants with disease phenotypes, which has been painstakingly built up through decades of careful direct clinical investigation of affected patients and relevant family members[11,51,52,67] mainly in people of European ancestry. Equitable inclusion of Indigenous Australians in the benefits of ECS, and medical genomics more generally, requires a similar level of evidence.

The critical importance of ancestry in the many other areas of health care where genomics now plays an important role [30–43] has led to programs aimed at achieving diversity in genomics, e.g., India [68], Asia [69]; Africa [70]; Aotearoa/New Zealand [71,72], USA [73].

An equitable approach in Australia would require prioritization of research involving people of Aboriginal and/or Torres Strait Islander descent, as well as other under-represented groups, as an integral part of national medical genomics programs. The approach must build on existing community engagement and leadership, and avoid duplicated effort that leads to an unnecessary burden on communities. National programs should include: 1. Detailed characterization of genomic variation in Aboriginal and Torres Strait Islander peoples; and 2.

Careful study, with community involvement and leadership, of pathogenicity and the general clinical, cultural and social consequences of diseases.

Programs must be designed and sufficiently resourced to include Indigenous community leadership to ensure appropriate research conduct at a time when community acceptance of genomics is critically important[74]. As in other areas of healthcare[57,75–79], extending approaches developed for the general population or retrofitting systems that were not designed to meet the specific needs of Indigenous people will not be effective and may do more harm than good. Hence, there is a need, at all levels and stages, for Indigenous co-design and development and incorporation of Indigenous data governance and custodianship as the foundations of national medical genomics programs.

Finally, it is essential to account for the significant genomic differences as well as the significant socio-cultural differences among the many Indigenous communities across the Australian continent.

Conclusion

ECS is one of many medical applications of genomics that, collectively, can transform the healthcare system for the better. For these developments to contribute usefully to the

Box 2. Appropriate information for prospective ECS participants of Aboriginal and/or Torres Strait Islander descent

If you decide you want pre-reproductive carrier screening, we will sequence both of your genomes to characterise DNA variants in a panel of genes. We have chosen these genes because we know that if both parents have certain variants in these genes there is a chance that their child will be affected by a serious disease. If we discover that this is the case for you, we can inform you of the risk, which will allow you to make a more informed decision about your reproductive options.

Because you are an Aboriginal/Torres Strait Islander couple, it is likely that you will have variants in these genes that have not been detected before in people from other parts of the world. Most of these variants are likely to be benign, but some of them may cause disease. However, because the variants that are only in Aboriginal and Torres Strait Islander people have not been researched, we won't know. We refer to these kinds of variants as either likely-pathogenic variants (LPVs), if they are similar to pathogenic variants we do know about, or as variants of unknown significance (VUSs).

Because at least one of you is of Aboriginal/Torres Strait Islander descent, we are less likely to find variants that we can be sure are either pathogenic or benign, and it is more likely that we will discover LPVs, than would be the case if you were a European Australian couple.

The reason is that we have chosen genes with variants that are known to cause diseases in European people because they have been extensively studied over many decades. In contrast, we know almost nothing about pathogenic variants that people have because of their Aboriginal and/or Torres Strait Islander descent.

Even if we find variants that we know are pathogenic or benign in European Australians, it is likely that we will not be sure that they will also be pathogenic or benign for your child, because the effect of a variant can depend on other parts of your genomes and on your lifestyle and environment.

There is a reasonable chance that after the screening we will have to advise you that you share variants that might put you at risk of having a child with a disease but that we can't be sure. This outcome is more likely for you than it would be if you were a European Australian couple.

Some people find this uncertainty distressing because they are left feeling that they could make a bad decision either way. If they avoid reproducing or terminate a pregnancy it may be for no good reason. Alternatively, if they give birth, the child might have a serious genetic disease, which the doctors don't know much about because they have never treated someone with a disease like this before.

You can instruct us not to tell you about LPVs we find during the screening. If you decide to do this, we cannot guarantee that LPVs we find are not pathogenic. You may, therefore, decide to have a

health and wellbeing of Indigenous Australians the current dearth of evidence and lack of reference data must be addressed. Communities must be empowered through Indigenous leadership, co-conceptualization and co-design of national programs to ensure culturally safe conduct, and the principles of Indigenous sovereignty over genomic data must be implemented

Australia has an opportunity to embrace the challenges presented by the cultural and ancestral diversity of its people to deliver research and clinical outcomes with significant global impact. New discoveries leading to therapeutic innovation are more likely from clinical investigation of people whose health and disease have previously been neglected, and of illnesses, which, until now, have been ignored, than from focussing on better understood problems in well-studied populations.

In addition, addressing the specific requirements of Indigenous Australians and other under-represented groups would directly support the Australian Government's commitment to equity and inclusion. It would redress past inequities and provide a model for better healthcare practice in Australia and internationally.

Australia has a unique opportunity for medical genomics innovation leading to improved prediction, prevention, treatment and cure of disease that is based on the distinctive characteristics of genomic diversity and its relationship to disease in Indigenous people, a reflection of their continuing ancient presence on the Australian continent[80,81]. This comparative advantage derives from Australia's ancient history. In realising it, the central role and importance of Aboriginal and Torres Strait Islander peoples must be recognised, they must be at the forefront of national programs, and they must stand to gain an equitable share of the resulting benefits.

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Declaration of interests

None of the authors has a conflict of interest.

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