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Equitable expanded carrier screening needs indigenous clinical and population genomic data

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Title

Clinical and population genomic data for Aboriginal and Torres Strait Islander peoples is crucial for equitable provision of expanded carrier screening in Australia

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Abstract

Expanded carrier screening (ECS) for recessive monogenic diseases requires prior knowledge of genomic variation including DNA variants that cause disease. The composition of pathogenic variants differs greatly among human populations, but historically research about monogenic diseases has focused mainly on people with European ancestry. By comparison, less is known about pathogenic DNA variants in people from other parts of the world. Consequently, inclusion of currently under-represented Indigenous and other minority population groups in genomic research is essential to enable equitable outcomes in ECS and other areas of genomic medicine. Here we discuss this issue in relation to the implementation of ECS in Australia, which is currently being evaluated as part of the national Government's Genomics Health Futures Mission. We argue that significant effort is required to build an evidence base and genomic reference data so that ECS can bring significant clinical benefit for many Aboriginal and/or Torres Strait Islander Australians. These efforts 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 involvement 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 specific and articulated cultural and health needs of Indigenous people. Until this occurs, people who do not have European ancestry are at risk of being, in relative terms, further disadvantaged.

Introduction

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[1–4]. 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 a range of different recessive diseases [5–7].

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 recessive condition due to ancestry or based on clinical information[8]. It has been extremely effective, e.g., in reducing the incidence of Tay-Sachs disease (MIM: 272800) in Ashkenazi Jewish populations around the world[9,10]. 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[11,12].

The Australian government is evaluating the potential benefits and challenges that ECS presents[7,12–17] with a view to its introduction into the national healthcare system[18]. Our focus here is on the significant challenges of achieving inclusion and equitable benefits for

Indigenous Australians from this approach and, by extension, medical genomics generally. While our focus is on Indigenous Australians, many of the points we raise apply to other groups that are under-represented in current genomic reference data.

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 ESC; 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 harmonised with 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 this approach; how screening will be administered through community controlled and other local health services; and whether there is the capacity for culturally safe counselling and follow-up clinical care.

Fully articulating these complex issues for health professionals and Indigenous communities is a substantial undertaking that needs adequate resourcing to ensure appropriate support. 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 this process.

The core challenge 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 or sub-optimal applicability to other populations[19–27].

As Australia is a culturally and ancestrally diverse nation, there is a need 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[28] and access to health services[28,29] compared with non-Indigenous Australians.

We discuss how the involvement of Indigenous people must be fully embedded within national health genomics initiatives such as ECS to ensure that the needs of Aboriginal and Torres Strait Islander people are met, and to ensure that these initiatives 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).

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:

1. provide the pathways for the development of new diagnostics, medicines and treatments from genomics research
2. expand genomics research effort and reach, allowing researchers and commercial partners to sustain efforts in discovery
3. build evidence for scaling applications, and build new markets
4. ensure that later stage translation and flagship work is not hampered by a lack of investment in early research.

Pathogenic variants are generally rare and population-specific

Most monogenic diseases are caused by many different DNA variants in one or more specific genes[7], almost all of which are rare. These variants may occur only in people with ancestry from a particular 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). Approximately 1 in 3,000 people are affected by CF in northern Europe[30]. Elsewhere, however, it is much rarer and is usually caused by local, rare variants that are not found in European patients[31]. Thus for example, in China and in the many substantial Chinese communities elsewhere in the world, where CF, although rare, affects an estimated 20,000 people, carrier screening panels designed for ancestrally European populations fail to detect most CF carriers[32].

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 novel variants may cause already described clinical phenotypes. It is likely, however, that even if they have similar molecular properties to known variants some will cause different phenotypes. These include milder or more serious forms of disease and different treatment responses[33]. Clinical and functional investigation will generally be required to establish their pathogenicity and associated disease phenotypes[34].

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. However, in a society with many people of mixed ancestry many novel combinations of variants are likely. These novel combinations may cause novel disease phenotypes and have differing effects on treatment responses.
4. Genomic-background, environment and lifestyle are more likely to influence the phenotypic manifestation of recessive diseases caused by pathogenic variants, even potentially causing normally pathogenic variants to become benign[35] or normally benign variants to become pathogenic[36,37] because:
    I. The environment and lifestyle of many people has rapidly changed due to alterations in 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[7,38] 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 with ancestry from Europe and other parts of the world. Many may 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[39] and a complex phenotype resulting from an *MTOR* gene variant[40], little is known about pathogenic variants originating within Indigenous populations.

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 there 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, currently 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[41] and comparison with data from the Simons Genome Diversity Project[42], genomic differences among Aboriginal communities across Australia are as great as those between populations across Europe and Asia combined. Thus, for example, using information about people from the Northern Territory as a basis for treating people in South Western Australia, would be equivalent to treating people with British ancestry on the basis of information about people from Cambodia.

These data can be accessed and used for specific purposes, as determined by the NCIG Indigenous-majority Board, in accordance with the CARE data sovereignty principles[43] and *the National Centre for Indigenous Genomics Statute, 2016 (Cth)*[44].

Current lack of evidence means that for many people with Aboriginal and/or Torres Strait Islander ancestry, ECS will produce greater uncertainty, revealing more 'likely-pathogenic variants' (LPVs) and 'variants of unknown significance' (VUSs) than for those with ancestry from Europe and other parts of the world where the causes of monogenic diseases are better understood. This uncertainty could potentially lead to inappropriate clinical intervention if benign variants are incorrectly reported as pathogenic, as has occurred elsewhere[45–47].

The risk of variants being falsely reported as pathogenic can be avoided by increasing the threshold of evidence required to assign pathogenicity. This approach, which reduces the risk of false positive reports, also tends to cause under-reporting of pathogenic variants because some do not meet the higher threshold of evidence. The same evidence-based criteria will have a differential effect when applied to populations for which there are different levels of available evidence. Pathogenic variants will tend to be under-reported to a greater extent in populations where there is a relative lack of evidence, as there is for people with Indigenous ancestry.

The result is greater "residual risk", i.e. more couples with a risk of having an affected child that is not identified by ECS. High residual risk is equivalent to low sensitivity, i.e., high rates of false negative findings. Thus, when residual risk is high, negative findings have little predictive value. For the great majority of prospective parents who test negative, testing provides little information. Thus, participation in testing may raise awareness of potential risk but leave most participants with high levels of residual uncertainty about their own risk.

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 [48]. If the expected yield for the general population is 1–2%, the lower expected yield for couples with Indigenous ancestry 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.

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 amount of 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 when 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 [40,47,49] and for correct assignment of pathogenicity [45–47].

How to address the current disparity?

The validity of ECS depends on population reference data and 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[50 34 51] 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 [19–26] has led to programs aimed at achieving diversity in genomics, e.g., India[52], Asia[53]; Africa[54]; Aotearoa/New Zealand[55], USA[56].

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. 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[57]. As in other areas of healthcare[39,58,59], 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 health and wellbeing of Australians with Indigenous ancestry the current dearth of evidence and lack of reference data must be addressed. To ensure their culturally safe conduct, national genomic medicine programs must ensure that Indigenous communities are empowered by incorporating Indigenous leadership, co-conceptualization and co-design and implementing the principles of Indigenous sovereignty over genomic data.

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 Australians with Indigenous ancestry 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[60]. This comparative advantage derives from Australia's ancient history and geographical isolation. 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.

Declaration of interests

None of the authors has a conflict of interest.

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References

1. Yap, P., and Savarirayan, R. (2016). Emerging targeted drug therapies in skeletal dysplasias. Am. J. Med. Genet. A *170*, 2596–2604.

2. Baynam, G., Pachter, N., McKenzie, F., Townshend, S., Slee, J., Kiraly-Borri, C., Vasudevan, A., Hawkins, A., Broley, S., Schofield, L., et al. (2016). The rare and undiagnosed diseases diagnostic service - application of massively parallel sequencing in a state-wide clinical service. Orphanet J. Rare Dis. *11*, 77.

3. Boycott, K.M., Rath, A., Chong, J.X., Hartley, T., Alkuraya, F.S., Baynam, G., Brookes, A.J., Brudno, M., Carracedo, A., den Dunnen, J.T., et al. (2017). International cooperation to enable the diagnosis of all rare genetic diseases. Am. J. Hum. Genet. *100*, 695–705.

4. Dawkins, H.J.S., Draghia-Akli, R., Lasko, P., Lau, L.P.L., Jonker, A.H., Cutillo, C.M., Rath, A., Boycott, K.M., Baynam, G., Lochmüller, H., et al. (2018). Progress in rare diseases research 2010-2016: an IRDiRC perspective. Clin. Transl. Sci. *11*, 11–20.

5. Gregg, A.R., and Edwards, J.G. (2018). Prenatal genetic carrier screening in the genomic age. Semin. Perinatol. *42*, 303–306.

6. Mastantuoni, E., Saccone, G., Al-Kouatly, H.B., Paternoster, M., D'alessandro, P., Arduino, B., Carbone, L., Esposito, G., Raffone, A., De Vivo, V., et al. (2018). Expanded carrier screening: A current perspective. Eur. J. Obstet. Gynecol. Reprod. Biol. *230*, 41–54.

7. Antonarakis, S.E. (2019). Carrier screening for recessive disorders. Nat. Rev. Genet. *20*, 549–561.

8. King, J.R., and Klugman, S. (2018). Ethnicity-based carrier screening. Obstet. Gynecol. Clin. North Am. *45*, 83–101.

9. Lew, R.M., Burnett, L., Proos, A.L., Barlow-Stewart, K., Delatycki, M.B., Bankier, A.,

Aizenberg, H., Field, M.J., Berman, Y., Fleischer, R., et al. (2015). Ashkenazi Jewish population screening for Tay-Sachs disease: The international and Australian experience. J. Paediatr. Child Health *51*, 271–279.

10. Cecchi, A.C., Vengoechea, E.S., Kaseniit, K.E., Hardy, M.W., Kiger, L.A., Mehta, N., Haque, I.S., Moyer, K., Page, P.Z., Muzzey, D., et al. (2019). Screening for Tay-Sachs disease carriers by full-exon sequencing with novel variant interpretation outperforms enzyme testing in a pan-ethnic cohort. Mol. Genet. Genomic Med. *7*, 1–12.

11. Fridman, H., Behar, D.M., Carmi, S., and Levy-Lahad, E. (2019). Preconception carrier screening yield: effect of variants of unknown significance in partners of carriers with clinically significant variants. Genet. Med. *22*, 646–653

12. Kraft, S.A., Duenas, D., Wilfond, B.S., and Goddard, K.A.B.B. (2019). The evolving landscape of expanded carrier screening: challenges and opportunities. Genet. Med. *21*, 790–797.

13. van der Hout, S., Holtkamp, K.C., Henneman, L., de Wert, G., and Dondorp, W.J. (2016). Advantages of expanded universal carrier screening: what is at stake? Eur. J. Hum. Genet. *25*, 17–21.

14. Stevens, B., Krstic, N., Jones, M., Murphy, L., and Hoskovec, J. (2017). Finding middle ground in constructing a clinically useful expanded carrier screening panel. Obstet. Gynecol. *130*, 279–284.

15. Gregg, A.R. (2018). Expanded carrier screening. Obstet. Gynecol. Clin. North Am. *45*, 103–112.

16. van der Hout, S., Dondorp, W., and de Wert, G. (2019). The aims of expanded universal carrier screening: Autonomy, prevention, and responsible parenthood. Bioethics *33*, 568–

576.

17. Rowe, C.A., and Wright, C.F. (2020). Expanded universal carrier screening and its implementation within a publicly funded healthcare service. J. Community Genet. *11*, 21–38.

18. Delatycki, M., Laing, N., Moore, S., Emery, J., Archibald, A., Massie, J., and Kirk, E. (2019). Preconception and antenatal carrier screening for genetic conditions. Aust. J. Gen. Pract. *48*, 106–110.

19. Gurdasani, D., Barroso, I., Zeggini, E., and Sandhu, M.S. (2019). Genomics of disease risk in globally diverse populations. Nat. Rev. Genet. *20*, 520–535.

20. Martin, A.R., Kanai, M., Kamatani, Y., Okada, Y., Neale, B.M., and Daly, M.J. (2019). Clinical use of current polygenic risk scores may exacerbate health disparities. Nat. Genet. *51*, 584–591.

21. Sirugo, G., Williams, S.M., and Tishkoff, S.A. (2019). The Missing diversity in human genetic studies. Cell *177*, 26–31.

22. Ndugga-Kabuye, M.K., and Issaka, R.B. (2019). Inequities in multi-gene hereditary cancer testing: lower diagnostic yield and higher VUS rate in individuals who identify as Hispanic, African or Asian and Pacific Islander as compared to European. Fam. Cancer *18*, 465–469.

23. Kwon, D.H.-M.M., Borno, H.T., Cheng, H.H., Zhou, A.Y., and Small, E.J. (2019). Ethnic disparities among men with prostate cancer undergoing germline testing. Urol. Oncol. Semin. Orig. Investig, *38*, 80.

24. Claw, K.G., Anderson, M.Z., Begay, R.L., Tsosie, K.S., Fox, K., Garrison, N.A., Bader, A.C.C., Bardill, J., Bolnick, D.A.A., Brooks, J., et al. (2018). A framework for enhancing ethical genomic research with Indigenous communities. Nat. Commun. *9*, 2957.

25. Bentley, A.R., Callier, S., and Rotimi, C.N. (2017). Diversity and inclusion in genomic

research: why the uneven progress? J. Community Genet. *8*, 255–266.

26. Baynam, G., Molster, C., Bauskis, A., Kowal, E., Savarirayan, R., Kelaher, M., Easteal, S., Massey, L., Garvey, G., Goldblatt, J., et al. (2017). Indigenous genetics and rare diseases: Harmony, diversity and equity. Adv. Exp. Med. Biol. *1031*, 511–520.

27. Haendel, M., Vasilevsky, N., Unni, D., Bologa, C., Harris, N., Rehm, H., Hamosh, A., Baynam, G., Groza, T., McMurry, J., et al. (2019). How many rare diseases are there? Nat. Rev. Drug Discov. *19*, 77–78.

28. Australian Indigenous HealthInfoNet (2019). Overview of Aboriginal and Torres Strait Islander health status 2018 (Perth: Australian Indigenous HealthInfoNet).

29. Gwynne, K., Jeffries, T., and Lincoln, M. (2018). Improving the efficacy of healthcare services for Aboriginal Australians. Aust. Health Rev. *43*, 314–322.

30. Bonadia, L.C., De Lima Marson, F.A., Ribeiro, J.D., Paschoal, I.A., Pereira, M.C., Ribeiro, A.F., and Bertuzzo, C.S. (2014). CFTR genotype and clinical outcomes of adult patients carried as cystic fibrosis disease. Gene *540*, 183–190.

31. Schrijver, I., Pique, L., Graham, S., Pearl, M., Cherry, A., and Kharrazi, M. (2016). The spectrum of CFTR variants in nonwhite cystic fibrosis patients: Implications for molecular diagnostic testing. J. Mol. Diagnostics *18*, 39–50.

32. Zheng, B., and Cao, L. (2017). Differences in gene mutations between Chinese and Caucasian cystic fibrosis patients. Pediatr. Pulmonol. *52*, E11–E14.

33. Cooper, D.N., Krawczak, M., Polychronakos, C., Tyler-Smith, C., and Kehrer-Sawatzki, H. (2013). Where genotype is not predictive of phenotype: Towards an understanding of the molecular basis of reduced penetrance in human inherited disease. *132*, 1077–1130.

34. Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., Grody, W.W., Hegde, M.,

Lyon, E., Spector, E., et al. (2015). Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet. Med. *17*, 405–424.

35. Chen, R., Shi, L., Hakenberg, J., Naughton, B., Sklar, P., Zhang, J., Zhou, H., Tian, L., Prakash, O., Lemire, M., et al. (2016). Analysis of 589,306 genomes identifies individuals resilient to severe Mendelian childhood diseases. Nat. Biotechnol. *34*, 531–538.

36. Harper, A.R., Nayee, S., and Topol, E.J. (2015). Protective alleles and modifier variants in human health and disease. Nat. Rev. Genet. *16*, 689–701.

37. Sun, H., Guo, Y., Lan, X., Jia, J., Cai, X., Zhang, G., Xie, J., Liang, Q., Li, Y., and Yu, G. (2019). PhenoModifier: a genetic modifier database for elucidating the genetic basis of human phenotypic variation. Nucleic Acids Res 48, D977–D982.

38. Nguengang Wakap, S., Lambert, D.M., Olry, A., Rodwell, C., Gueydan, C., Lanneau, V., Murphy, D., Le Cam, Y., and Rath, A. (2020). Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur. J. Hum. Genet. *28*, 165–173.

39. Carr, J.J., Lalara, J., Lalara, G., O'Hare, G., Massey, L., Kenny, N., Pope, K.E., Clough, A.R., Lowell, A., and Barker, R.N. (2019). "Staying strong on the inside and outside" to keep walking and moving around: Perspectives from Aboriginal people with Machado Joseph Disease and their families from the Groote Eylandt Archipelago, Australia. PLoS One *14*, e0212953–e0212953.

40. Baynam, G., Overkov, A., Davis, M., Mina, K., Schofield, L., Allcock, R., Laing, N., Cook, M., Dawkins, H., and Goldblatt, J. (2015). A germline MTOR mutation in Aboriginal Australian siblings with intellectual disability, dysmorphism, macrocephaly, and small thoraces. Am. J. Med. Genet. Part A *167*, 1659–1667.

41. Holsinger, K.E., and Weir, B.S. (2009). Genetics in geographically structured populations: defining, estimating and interpreting F(ST). Nat. Rev. Genet. *10*, 639–650.

42. Mallick, S., Li, H., Lipson, M., Mathieson, I., Gymrek, M., Racimo, F., Zhao, M., Chennagiri, N., Nordenfelt, S., Tandon, A., et al. (2016). The Simons Genome Diversity Project: 300 genomes from 142 diverse populations. Nature *538*, 201–206.

43. Hudson, M., Garrison, N.A., Sterling, R., Caron, N.R., Fox, K., Yracheta, J., Anderson, J., Wilcox, P., Arbour, L., Brown, A., et al. (2020). Rights, interests and expectations: Indigenous perspectives on unrestricted access to genomic data. Nat. Rev. Genet. *21*, 377–384.

44. National Centre for Indigenous Genomics Statute 2016 (Cth). Retrieved from https://www.legislation.gov.au/Details/F2016L01873

45. Walsh, R., Thomson, K.L., Ware, J.S., Funke, B.H., Woodley, J., McGuire, K.J., Mazzarotto, F., Blair, E., Seller, A., Taylor, J.C., et al. (2017). Reassessment of Mendelian gene pathogenicity using 7,855 cardiomyopathy cases and 60,706 reference samples. Genet. Med. *19*, 192–203.

46. Wright, C.F., West, B., Tuke, M., Jones, S.E., Patel, K., Laver, T.W., Beaumont, R.N., Tyrrell, J., Wood, A.R., Frayling, T.M., et al. (2019). Assessing the pathogenicity, penetrance, and expressivity of putative disease-causing variants in a population setting. Am. J. Hum. Genet. *104*, 275–286.

47. Manrai, A.K., Funke, B.H., Rehm, H.L., Olesen, M.S., Maron, B.A., Szolovits, P., Margulies, D.M., Loscalzo, J., and Kohane, I.S. (2016). Genetic misdiagnoses and the potential for health disparities. N. Engl. J. Med. *375*, 655–665.

48. Guo, M.H., and Gregg, A.R. (2019). Estimating yields of prenatal carrier screening and implications for design of expanded carrier screening panels. Genet. Med. *21*, 1940–1947.

49. Karczewski, K.J., Weisburd, B., Thomas, B., Solomonson, M., Ruderfer, D.M., Kavanagh, D., Hamamsy, T., Lek, M., Samocha, K.E., Cummings, B.B., et al. (2017). The ExAC browser: displaying reference data information from over 60 000 exomes. Nucleic Acids Res. *45*, D840–D845.

50. Grody, W.W., Thompson, B.H., Gregg, A.R., Bean, L.H., Monaghan, K.G., Schneider, A., and Lebo, R. V. (2013). ACMG position statement on prenatal/preconception expanded carrier screening. Genet. Med. *15*, 482–483.

51. Claussnitzer, M., Cho, J.H., Collins, R., Cox, N.J., Dermitzakis, E.T., Hurles, M.E., Kathiresan, S., Kenny, E.E., Lindgren, C.M., MacArthur, D.G., et al. (2020). A brief history of human disease genetics. Nature *577*, 179–189.

52. Sivasubbu, S., and Scaria, V. (2019). Genomics of rare genetic diseases—experiences from India. Hum. Genomics *13*, 1.

53. McGonigle, I., and Schuster, S.C. (2019). Global science meets ethnic diversity: Ian McGonigle interviews GenomeAsia100K Scientific Chairman Stephan Schuster. Genet. Res. (Camb). *101*, e5.

54. Bentley, A.R., Callier, S., and Rotimi, C. (2019). The emergence of genomic research in Africa and new frameworks for equity in biomedical research. Ethn. Dis. *29*, 179–186.

55. Kennedy, M.A. (2018). A genome project for Māori and Pasifika: Charting a path to equity in genomic medicine for aotearoa. N. Z. Med. J. *131*, 8–10.

56. Khoury, M.J., Bowen, M.S., Clyne, M., Dotson, W.D., Gwinn, M.L., Green, R.F., Kolor, K., Rodriguez, J.L., Wulf, A., and Yu, W. (2018). From public health genomics to precision public health: A 20-year journey. Genet. Med. *20*, 574–582.

57. Pratt, G., Vidgen, M., Kaladharan, S., Pearson, J., Whiteman, D., and Waddell, N. (2019).

Genomic partnerships: guidelines for genomic research with Aboriginal and Torres Strait Islander peoples of Queensland (Brisbane).

58. Peiris, D., Brown, A., and Cass, A. (2008). Addressing inequities in access to quality health care for indigenous people. CMAJ *179*, 985–986.

59. Panaretto, K.S., Wenitong, M., Button, S., and Ring, I.T. (2014). Aboriginal community controlled health services: leading the way in primary care. Med. J. Aust. *200*, 649–652.

60. Clarkson, C., Jacobs, Z., Marwick, B., Fullagar, R., Wallis, L., Smith, M., Roberts, R.G., Hayes, E., Lowe, K., Carah, X., et al. (2017). Human occupation of northern Australia by 65,000 years ago. Nature *547*, 306–310.