Connecting to Country: An Australian Indigenous Metagenomics Strategy
Environmental Scan and Research Gap Report

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Karabena Consulting

Authors: Professor Kerry Arabena, Chris Holland and Lauren Penny

Managing editor: Jane Yule @ Brevity Comms

Editor: Cathy Edmonds

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A note on terminology: Throughout this report, the terms 'Aboriginal and Torres Strait Islander' or 'Indigenous' are generally used when referring to the First Nations' peoples of Australia.

Professional disclosure statement: This report was completed by Karabena Consulting for the consideration of the Aboriginal and Torres Strait Islander Advisory Group on Genomics. It has been prepared in good faith based on the research and information available to Karabena Consulting at the date of publication without any independent verification, and may not be accurate, complete or up to date. Before using any part of this report, users must obtain independent professional advice to determine the suitability of the content of this report for their intended use.

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Preface

Aboriginal and Torres Strait Islander peoples, Australia's First Peoples, are so much more than the embodiment of negative colonial processes. While we appreciate the 60,000 years of 'genius' that is in our Indigenous DNA (deoxyribonucleic acid) (Garma Festival 2019), our metagenomic vision for our current and future families is still very much under the gaze of a colonial lens. Colonisation's lockstep march with evolving genetic science is not 'history'; the past is still very much with us in contemporary times. The genocidal momentum of Australia's colonisation will remain in place until it is recognised and proactively reversed. It persists as government paternalism, neglect, tolerance of poverty, police brutality, massive incarceration, substandard housing and gaps that, if they are to be closed, will require far greater political and economic commitment than evident so far (Holland 2018).

Colonisation's impacts are likely to persist in epigenetic alterations to Indigenous DNA that distort its original instruction and ancestral intent. Intergenerational trauma, with epigenetics implicated, pervades all too many of us, and is continually reinforced by institutional and other forms of racism that could be registering in our DNA if anyone cared to look.

Genetics is implicated in our suffering, and in our emancipation. As is well known, 'saving the souls of heathens' was used as Christian-religious sugar-coating for 400 or so years of European colonisation, which involved the deaths, enslavement, dispossession, exploitation and suffering of potentially hundreds of millions of Indigenous peoples around the world. But, equally, the Darwinian 'survival of the fittest' genetic principle (and versions thereof) was applied to Indigenous peoples to provide a pseudo-scientific natural law veneer (Rowley 1970). Inherent to the notions of genetic inferiority that were propagated are those of cultural inferiority. How could a genetically inferior race produce *anything but* an inferior culture?

Throughout the colonial era, and into very recent history, the superior–inferior spiritual–racial–cultural paradigm was clearly seen. Indigenous and colonised peoples, like the newly encountered flora and fauna in colonised lands, became 'objects of study' to the gaze of coloniser European scientific vanguards (Peters 2017:68). As 'objects' we had no choice, let alone control, regarding and over the research agendas thrust upon our families. The idea that we might or should enjoy sovereignty over any data (i.e. data sovereignty) generated by colonial science was unrecognisable by coloniser scientists. They denied our human rights because we were not considered human. In denying our experience of humanness as emerging from, and connected to, the local ecologies and the species we co-evolved with, they were, and remain, blind to our ancient sovereign rights to exercise our care and concern for our Country, and all that responsibility entails.

From the start, our genetic (and coincident cultural) 'inferiority' justified the false terra nullius legal-political foundation of colonisation and the resulting dispossession of Indigenous Nations without treaty by massacre and frontier violence. This violence continued in policies and programs that were founded in ideas that Indigenous peoples as members of an inferior race were 'dying out' by the late 19th century and it underpinned 'protection' practices that still impact today (HREOC 1997).

In these practices were embedded power relationships, eugenics and assimilation, all predicated on the genetic unfitness of 'full blood' Aborigines and the need to control mixed-race children to ensure their eventual genetic absorption into the white gene pool. The role of Australian governments was to protect and thereby 'smooth the dying [race's] pillow' (Biskup 1968:447) while mixed-race

children were to be grateful for the effects of being civilised. These sentiments made permissible the establishment of a nationwide 200 institution-strong reserve and mission complex, and a regime of forced child removals that persisted until the 1960s (Gardiner-Garden 1999) and suited an ideological commitment to whiteness in Australia.[1] As the 1997 *Bringing Them Home* report (HREOC 1997:n.p.) makes clear, the 'Australian practice of Indigenous child removal involved… genocide as defined by international law'.

Make no mistake. While we have survived and are getting stronger, we still bear the scars of this terrible genetically justified treatment. If this sounds exaggerated, consider the ongoing tragedy of suicide among our young people. In Western Australia in 2019, the State Coroner, in summarising her findings following an inquest into the deaths of 13 Indigenous children and young people in the Kimberley, ruled that 12 were suicide deaths and that:

> The effect of intergenerational trauma… was the primary common factor that characterised the dysfunction in the home environments of all the children and young persons whose deaths were investigated at the Inquest. The cumulative effect of intergenerational and individual trauma in each case made them vulnerable to suicide. (Fogliani 2019:55)

What we are asking researchers, policy makers, funders and genetic institutions invested in metagenomics to face is the discipline's historical responsibility in the above. And, on that basis, we ask for the setting aside of non-Indigenous agendas that are deeply ingrained in the institutions that have long denied our leadership and the totality of our genetic knowledge, and the role that genomics has played in our experiences of the two states of citizenship that exist in contemporary Australian society.

The first citizenship state is a celebration of being in a dynamic, effective, non-hierarchical, and ever-changing and active relationship with all that is available to human and non-human like. This citizenship has always emerged from within cultural memories and engaged Earth-caring language, values and beliefs, between social structures and the sacred and in accordance with an Indigenous understanding of natural law, as ecological beings (Arabena 2015). In the Anthropocene – an epoch in which human activity has started to fundamentally impact our planet – what is under consideration globally is whether this form of Earth-caring citizenship could be appropriate for everyone. The second citizenship state is one in which Aboriginal and Torres Strait Islander people are below, behind, beneath or outside mainstream Australian society. This hierarchical relationship plays out in a human-to-human experience, a hierarchical relationship between people and Aboriginal and Torres Strait Islander people and societal institutions including schools, hospitals, child protection agencies and prisons.

During the journey of humans into Australia some 70,000 or more years ago, the cross of Wallace's Line[2] at Lombok was 'an event of major importance for all humanity and enabled a great leap forward for our species as a whole' (Flannery 1994:153). Somewhere about the time of this first colonisation of Australia, humanity was being transformed from its status as 'just one uncommon omnivorous species among a plethora of other large mammals' into the Earth's dominant species (Griffiths & Robin 1997:7). By crossing Wallace's Line, humans discovered lands free from tigers and

1 These ideological commitments were roughly aligned to Australia's White Australia Policy (1901–66). For more information see the Eugenics Archives website (http://eugenicsarchive.ca/).

2 A hypothetical boundary that divides the biogeographical regions of Asia and Australia (National Geographic n.d.).

leopards and a biota used to predators, where a 'managerial environmental mentality' could blossom (Griffiths & Robin 1997:7). Hence, Aboriginal and Torres Strait Islander peoples were the first to 'escape the straight jacket of co-evolution, the consequent changes in technology and thought undergone by Aboriginal people changes the course of evolution for humans everywhere' (Flannery 1994:14). And so, we must use our traditions of transformation to change the Australian landscape again.

Aboriginal and Torres Strait Islander people are adept at change and reinvention. Different environmental and human pressures on the continent have resulted in two different ways of being in the world. The first way in which humans in Australia engaged with Country was invoked with the advent of environmental managerialism; the second way emerged more than 200 years ago, with a violent rupturing in the locations and activities of our habitats, both of which have had genetic consequences for Australia's First Peoples and our flora and fauna. As stated by Crosby (2015:194):

> European immigrants did not arrive in the New World alone; they were accompanied by a grunting, lowing, neighing, crowing, chirping, snarling, buzzing, self-replicating and world-altering avalanche of animals.

We arrive at contemporary genomics with the colonial paradigm largely intact – a paradigm that excludes our principal law, which is to harmonise with the evolutionary directive of the universe (Arabena 2015:39). In developing an Australian Indigenous Metagenomics Strategy, we must acknowledge the position we are departing from in order to restart on our terms and in line with our values of care, nurturance and reverence for Country. There is no need to recount what is perhaps our seminal and now well-documented experience in the Human Genome Diversity Project[3] (Dodson & Williamson 1999), with the resultant chilling of Indigenous genetic and genomic research in Australia. A thawing of attitudes to this research only began in 2010 at the inaugural Indigenous genomics workshop held in Melbourne and hosted by the Lowitja Institute and The University of Melbourne (Kowal 2015). The report that resulted from this inaugural workshop articulated the key platforms necessary to facilitate an Indigenous-led genomics agenda. It is at this point that this report commences. To uncouple genomics research from its colonialist roots, we focus on research and research agendas since 2010 and extend these concepts to align with our custodial roles and responsibilities in the 21st century.

Our responsibilities are vast and remain largely unexplored because of the focus on human-centred genomics in the context of institutional health care, rather than embedding genomics work that celebrates our Indigenous experience of Country. While we appreciate the sentiment that 'if we get it right for Aboriginal and Torres Strait Islander people, then we can make the genetic health service delivery system right for all Australians', we reject the blinkered notion that our embodied experiences of colonisation and resultant disease states should serve to improve institutions that preserve colonial discourses and unequal power relationships. This view presupposes that, even at a molecular level, we are meant to serve institutions and be of benefit to those who acknowledge our status as First Nations people but who cannot imagine the changes that are needed to co-produce

3 Established in the 1990s, the project aimed to use Indigenous populations' genomes to understand the migration histories of their ancient ancestors – ultimately from Africa – and in that way to understand the migration history of the entire human race (Malaspinas et al. 2016). But, as well documented, the project's reliance on indigenous blood samples and consent issues resulted in it being referred to by some indigenous groups as the 'Vampire Project', with Australian Indigenous peoples ultimately refusing to participate (Kowal 2015).

an equitable and just society that embraces and makes good on the acknowledgment of the *Uluru Statement from the Heart* (Referendum Council 2017).

We unashamedly take these blinkers off in the hope that the Australian Indigenous research agenda might embrace a broader view of the care needed by our continent's microbiota. The time is right, with the National Indigenous Australians Agency (NIAA n.d.) stating that Aboriginal and Torres Strait Islander people have current landholdings totalling 40 per cent of the land mass in Australia. In order to support people to maintain a distinctive cultural, spiritual, physical and economic relationship with their land and waters, Target 15 of the 2020 National Agreement on Closing the Gap aims to achieve:

A. By 2030, a 15 per cent increase in Australia's land mass subject to Aboriginal and Torres Strait Islander people's legal rights and interests.

B. By 2030, a 15 per cent increase in areas covered by Aboriginal and Torres Strait Islander people's legal rights or interests in the sea. (NIAA 2020)

These figures suggest that Aboriginal and Torres Strait Islander people will have a leading interest in more than 55 per cent of the land mass on the Australian continent and seas. *What this transfer of tenure also does is to make us traditional custodians for more than 55 per cent of the microbiota on this continent.* As discussed in this report, an Australian Indigenous Metagenomics Strategy has the power to contribute to the sustainability of all life on earth and to provide significant international leadership in microbial community custodianship, due to the size of the land mass, compared to other sovereign nation states.

We have an ancestral responsibility and an anthropogenic duty to rebalance our biomolecular functioning while restoring the original instructions embedded in our ancestral DNA and to lead this field so that others might follow.

Summary

This report has been produced to assist the Aboriginal and Torres Strait Islander Advisory Group on Genomics in identifying current research, clinical services and consumer engagement activities in the genomics field that are of relevance to Aboriginal and Torres Strait Islander peoples. It identifies gaps in research, services and activities where increased attention would benefit Aboriginal and/or Torres Strait Islander peoples.

The purpose of the report is to assist the Advisory Group to identify relevant work related to Indigenous genomics both in Australia and internationally, and to provide a gap analysis that identifies where further research or service provision is needed.

This report has been prepared by Karabena Consulting, an Australian Indigenous business, and presents evidence that is both informed by, and culturally appropriate to, Aboriginal and Torres Strait Islander peoples. In preparing the report, we consulted with key stakeholders and members of the Advisory Group, and undertook a literature review relevant to the environmental scan and gap analysis. The Advisory Group then reviewed a draft of this report in August 2020 to ensure that its content and findings aligned with its aspirations.

Why do we need an Australian Indigenous Metagenomics Strategy?

We acknowledge the achievements of current leaders in Indigenous genomics. The potential for genomics research to benefit First Nations' peoples, and indeed all Australians, is enormous. By working together to bring Indigenous and non-Indigenous worldviews into balance, and to provide the appropriate context and foundation for an Australian Indigenous Metagenomics Strategy, we hope to restore our ancestral connections to Country.

On deeper analysis, however, this report finds that the current focus is on extending the disciplinary capacity of science and the social sciences to engage with clinically based Indigenous genomics, rather than supporting Aboriginal and Torres Strait Islander leadership of our own human genome. This focus is deficit based, in that it focuses on disease rather than on promoting cultural ideals and aspirations for prosperity premised on our connections to Country. As such, it perpetuates the ongoing momentum of colonisation. We stress here, as we do throughout this report, that without Indigenous control, any Australian Indigenous Metagenomics Strategy risks failing to connect with our people and our Country. That is, it risks failing completely.

Australia's First Nations' peoples approach genomics research in the same way we approach any issue – that is, from a holistic viewpoint. All decisions and actions to develop metagenomics strategies must be made within whole ecologies and align with our responsibilities to care for Country. This holistic view connects human health to environmental health and acknowledges it as inseparable from the health of whole ecologies. As such, it represents a fundamental understanding of health and wellbeing, and acknowledges that any consideration of Aboriginal and Torres Strait Islander peoples and metagenomic research occurs in an ecological, political and cultural context.

The difficulty in what needs to be achieved – a difficulty that the collective mindset of the science world perhaps finds particularly challenging to grasp – is to understand and accept that we are not born into societies, we are born into ecosystems.

Environmental scan

The environmental scan identifies current research, clinical services and consumer engagement activities in the genomics field that are relevant to Aboriginal and Torres Strait Islander peoples. It considers research initiatives that focus on Aboriginal and Torres Strait Islander health genomics, particularly those that are or could be translated to enhance clinical genomics services and improve our access to such services. Of particular interest are education and training opportunities to support an Aboriginal and Torres Strait Islander genomics workforce, consumer engagement and education activities. The scan provides relevant international examples from other Indigenous populations, which enable a comparison of guidelines and protocols developed for the management of Indigenous health genomics information and services.

The areas covered in the environmental scan include:

- research initiatives focusing on Aboriginal and Torres Strait Islander health genomics
- research projects that are being, or could be, translated to enhance clinical genomics services for Aboriginal and Torres Strait Islander peoples
- clinicians and health services that currently deliver clinical genomics services specifically designed for and targeting Aboriginal and Torres Strait Islander peoples, and/or projects that aim to improve our access to health genomics services, including education and training to support an Aboriginal and Torres Strait Islander genomics workforce
- consumer engagement and education activities that target Aboriginal and Torres Strait Islander peoples
- current data infrastructure, data sovereignty and governance arrangements for health genomics information in relation to Aboriginal and Torres Strait Islander peoples and relevant international examples for other Indigenous populations
- an international comparison of guidelines and protocols developed for the management of Indigenous health genomics information and services.

What the environmental scan makes clear is the need for an expanded view of genomics that goes beyond the human-centric focus of much of the work to date.

Gap analysis report

The gap analysis identifies where increased attention when implementing actions relating to genomics research, services or activities will benefit Aboriginal and Torres Strait Islander peoples. Addressing these gaps will amount to a national, comprehensive and integrated strategic approach to Indigenous metagenomics.

The gap analysis has three goals:

- to identify and analyse the information gaps relating to genomics research, services or activities of Aboriginal and Torres Strait Islander people, stakeholders and policy makers
- to suggest ways to improve knowledge (reducing information gaps) in this area by facilitating two-way communication between information providers and users (reducing communication gaps)
- to identify gaps and barriers in facilitating accessible, timely and affordable genomics services (reducing the access gap).

Overall, this report identifies four gaps:

- Gap 1: a national Indigenous metagenomic sovereignty mechanism

- Gap 2: an Australian Indigenous Metagenomics Strategy
- Gap 3: a national integrated research translation agenda
- Gap 4: a national precision medicine implementation program and national feedback mechanisms.

These constitute one overriding gap – that is, the need for an Aboriginal and Torres Strait Islander-controlled national Indigenous metagenomics umbrella institution. All other gaps relate back to this.

Recommendations

All recommendations made in this report are the views of Karabena Consulting and are provided to support the development of an Australian Indigenous Metagenomics Strategy.

Karabena Consulting recommends establishing the umbrella institution to guide a metagenomics agenda that connects to Country, disrupts the colonial gaze and begins to heal our relationship with the Indigenous Estate. We make five recommendations (summarised here and presented in full in Chapter 6) and note the centrality of Recommendation 1, from which all our other recommendations follow.

Recommendation 1: Establish an Aboriginal and Torres Strait Islander-controlled national metagenomics umbrella institution

The umbrella organisation's functions should include:

- **data governance and sovereignty responsibilities** to address gaps in Indigenous oversight and governance of sample sovereignty; train communities in data governance; develop and implement strategies that promote protection and ownership of Indigenous and regional reference genomes and relevant databases; promote culturally safe and appropriate data collection and sharing; lead cross-disciplinary discussions and First Nations engagement to promote workforce development; and strategise local knowledge and data
- **research responsibilities** to establish a centre of research excellence; develop and implement research strategies in partnership with professions that care for Country; develop policy positions and advocacy documents; support the uptake of health literacy; commission research; and support student scholarships and research partnerships
- **other responsibilities** such as collaborating with institutions/governments and health systems; overseeing a metagenomic workforce training program; and developing widespread understanding of, and engagement with, microbial community custodianship.

Recommendation 2: Develop and implement a metagenomic cardiometabolic healing research agenda within a broader Australian Indigenous Metagenomics Strategy under Indigenous control

Under the direction of the umbrella organisation, focus on:

- **molecular decolonisation** to develop an epigenetic healing research agenda that focuses on the impacts of trauma
- **metabolic healing** and adopt a metagenomic approach that accounts for adaptations to microbiota and traditional food supplies, in addition to genomic research; seek to understand the nature of matches and mismatches across diet, microbiota, microscopic life in the environment, the environment itself and Indigenous genomes; and investigate the relevance of millennia-old diet–biome–genome interactions and adaptations to the health of contemporary Indigenous populations

- **'Country-as-microbial communities'** to connect human genetic research to research occurring on Country; develop a research strategy on the genetics of microbiome exchange through birthing on Country; and widen the scope of metagenomics to include support for introduced species eradication, restore environments, and tackle animal and plant diseases.

Recommendation 3: Develop an Australian Indigenous Metagenomic Workforce Strategy

Under the direction of the umbrella organisation:

- map current Indigenous genomic education to understand health literacy needs
- develop an Australian Indigenous Metagenomic Workforce Strategy and workforce training
- balance current genetic workforces with the emergence of ecologically based genetic workforces, and further develop the genomics workforce
- advocate for the right to develop this Indigenous workforce without acquiring personal or higher educational debt
- invest in developing people's skills and capacities to work in a complex and sensitive area
- adapt scholarship programs to support Indigenous applicants or establish a separate stream
- set an Indigenous metagenomics workforce target
- develop collective best practice approaches to meaningful and longitudinal individual and family participation in becoming part of the metagenomics workforce
- join with peak agencies to promote human health in healthy ecosystems
- encourage diversity by establishing principles to reflect and respond to the needs of a diverse human population; establish diversity-enhancing strategies and programs; and progress Indigenous prosperity and build capacity for resolving the issues of diversity in lived experiences and workforce development practices.

Recommendation 4: Fund the umbrella organisation to address identified gaps in the Australian Indigenous Metagenomics Strategy

- Gap 1: A national Indigenous metagenomic sovereignty mechanism
- Gap 2: An Australian Indigenous Metagenomics Strategy
- Gap 3: A national integrated research translation agenda
- Gap 4: National precision medicine implementation program and national feedback mechanisms.

Recommendation 5: Invest in an Indigenous metagenomic strategy infrastructure

Under the direction of the umbrella organisation, invest in data infrastructure:

- to collect, aggregate and automate analysis of information; to progress social, cultural, economic and political goals; and to disrupt digital colonial practices
- to develop First Nations' manifestos and practices; invest in models that promote access, equity and Indigenous control, and commercialisation options, and that support precision medicine in Indigenous communities and health services; and explore emerging data governance models.

1 Introduction

The biological science of genetics (and now genomics and metagenomics) has its origins in millennia of cumulative human observations that specific traits are handed down from parents to offspring, and that the presence of such can be increased or decreased by controlling reproduction. Genetics is at least as ancient as agriculture. Indeed, to say an animal or plant is domesticated indicates it is from genetically modified stock – different from wild stocks – including by human selective breeding. In domesticated grain plants, for example, traits such as grains ripening simultaneously to increase harvest efficiency have become inbred and the plants' life cycles significantly depend on human intervention – by watering, manual winnowing of ripe grains and then the planting of such grains in a seasonal cycle.

As Pascoe (2014) reminds us, many pre-contact Aboriginal and Torres Strait Islander (Indigenous) peoples practised agriculture – that is, they practised genetics in common with all ancient farming cultures. Such is evident, or was evident to early explorers, by the crops' dependencies on human intervention to maintain their life cycles. While identifying several grains and the bush tomato as examples, Pascoe (2014) concludes that many Indigenous food-plants thought of as 'wild' and simply 'gathered' require genomic research to gauge the full extent of Indigenous plant domestication and pre-contact genetic practice across the continent.

Acknowledging the ancient history of Australian Indigenous genetic science is the starting point of this report. Not to look backwards, but to establish a foundation of Indigenous control, ownership and empowerment to frame the whole question of how Indigenous peoples and metagenomics associate over coming decades.

The intent of the environmental scan and gap analysis in this report is to map, for the first time, the range of key activities in genomics that are relevant to Aboriginal and Torres Strait Islander peoples. This will provide an understanding of key past, present and planned Indigenous genomics work nationally and internationally, and will help identify where further work is needed.

This report will support the Aboriginal and Torres Strait Islander Advisory Group on Genomics to develop components of the Indigenous Genomics Guiding Document to inform the national Genomics Implementation Plan. The Advisory Group asked the consultants to consider the following issues:

- consent strategies inclusive of intergenerational, multigenerational and kinship-based considerations
- data sharing – data sovereignty and effective use of data
- Aboriginal and Torres Strait Islander strengths-based leadership discourses embedded in Indigenous ways of knowing, being and doing
- effective engagement – where this is being done well through clinical research with Aboriginal and Torres Strait Islander people
- communication strategies to optimise testing and treatment options
- support for the community-controlled sector in the uptake and responsiveness to genomics issues in communities
- the development of an Indigenous genomics workforce (e.g. genetic counsellors).

In recognition of the importance of writing from a cultural context in the development of this strategy, we acknowledge the importance of Country. A key manifestation of an Indigenous-led

genetics research agenda will be to provide pathways to disrupt the singular species approach to genetics work (tied to colonial genetic research agendas) and reposition human health and wellbeing in the ecologies in which we are engaged to activate microbial community custodianship (Indigenous genetic research). This will shift the focus of institutionally based clinical research to an ecological framework opening opportunities for partnerships with other on-Country scientific institutions, landowners and Elders from various knowledge traditions and communities.[4] This will shift the focus from illness narratives that are deeply embedded in the current genetics research agenda to one of progressing health, entrepreneurship, vitality and wellbeing for the future prosperity of our people.

Post-2010 scope of the environmental scan and gap analysis report

The purpose of the environmental scan and gap analysis report is to identify the current research, clinical services and consumer engagement activities in the genomics field that are of relevance to Aboriginal and Torres Strait Islander peoples, and gaps in research, services or activities where increased attention could benefit Aboriginal and/or Torres Strait Islander peoples. The report will provide input to key Indigenous genomics work (e.g. guidelines) in Australia and internationally.

By identifying key gaps, this report will also inform future action. We reviewed contemporary national and international literature since 2010, when the first national discussion of genetics and Indigenous health that took place in Australia noted:

> many Indigenous people interpret genetic research in the context of their experiences of colonisation. Fears of genetic theft or 'biopiracy', fears that genetics will be used to determine Aboriginality and may fuel racism, poor access to the potential health care innovations that genetics may bring, bad experiences of the Human Genome Diversity Project (known by some as the 'Vampire' project) and struggles over access to DNA extracted from human remains all constitute barriers to effective research partnerships between Indigenous communities and genetic researchers. (Kowal, Rouhani & Anderson 2011:31)

Since 2010, significant positive developments in ethical frameworks, consent protocols, biobanking protocols and so on have address many of the pre-2010 concerns, and to a significant degree protect Indigenous peoples and communities in this space, even supporting Indigenous governance in institutional settings.

What is metagenomics and how can it help to close the gap?

Like genomics itself, metagenomics is both a set of research techniques, comprising many related approaches and methods, and a research field. In Greek, *meta* means 'transcendent'. In its approaches and methods, metagenomics allows for the study of the different elements of the human microbiome, enabling evaluation of the impact of multiple associations between the host and microbe, and between microbes (Ajami & Petrosino 2016; Santiago-Rodriguez & Hollister 2019). We have expanded the focus on the human microbiome to recognise that microbial communities are evident in every living system on the planet, and upon which all life depends.

It is well understood, though not widely known, that 'microbes are essential for every part of human life' and all life on Earth (National Research Council 2007:1). Every process in the biosphere

4 For example, by partnering with regenerative farmers, ranger programs, Indigenous agriculture, Indigenous enterprise (reactivating Indigenous-to-Indigenous trade routes along song lines, for example) and on-Country entrepreneurial activities.

incorporates the endless capacity of microbes to transform the world around them. Chemical cycles that convert carbon, nitrogen, oxygen and sulphur into biologically accessible forms are directed by and dependent on microbes, and we depend on microbes to make the necessary nutrients, metals and vitamins that are found in the human diet (Rowland et al. 2018). We rely on microbes to remediate toxins in the environment – both those produced naturally and those that are by-products of human activities, such as oil and chemical spills. This process is referred to as bioremediation, the process that uses mainly microorganisms to detoxify contaminants in the soils and other environments (Singh, Shitiz & Singh 2019).

Microbes are a fact of life. They modulate and maintain the atmosphere, keep us healthy, support plant growth and suppress diseases and clean up fuel leaks. Microbes live in complex, intricate, balanced and integrated communities, linking all environments to all species on Earth. The current focus of public health and prevention efforts in Aboriginal and Torres Strait Islander and non-Indigenous communities alike is focused on the biological determinants of health and wellbeing of a singular species. The Indigenous metagenomics strategy that we propose in this report moves beyond a single species approach to include our landscapes, waterways and oceans.

We emphasis this broader context because much of the focus in health setting agendas has been on human health, without considering the ecological circumstances that are fundamental to Indigenous ways of life and living. As with the Closing the Gap strategy and many government-led initiatives before, interventions implemented against known factors that influence human health have not improved the health outcomes for all Aboriginal and Torres Strait islander people. Other gaps are widening, and they impact the whole of Australian society.

At the commencement of 2020, Australia was burned by bushfires that were unprecedented on a world scale. These fast moving and uncontrollable fires generated their own weather systems, including lightning strikes that ignited more fires (Reuters 2020). Nearly 80 per cent of all Australians were affected by the fires and their sequelae (Biddle et al. 2020). Thirty-four human lives were lost directly in the fires, and their associated air pollution cost 400 lives and led to more than 4000 additional respiratory and cardiovascular presentations (Borchers Arriagada et al. 2020). The full impact on mental health and on children and pregnant women is not yet known. These fires are by far Australia's costliest natural disaster. The environmental, economic and social impacts are still being assessed and will be felt in a multitude of ways, particularly in relation to solastalgia,[5] displacement, long-term stress and other mental health issues, all of which impact on and are impacted by our human biome.

The cost of these events to our ecological biome is enormous. Australia already has the highest loss of any species anywhere in the world (ABC 2015). These fires compounded this loss with about three billion animals estimated to have died or been displaced, and many species now in danger of extinction (WWF 2020). Many Indigenous peoples have claimed these fires have emerged because of colonisation: due to forced removals, restrictions on access to lands and prohibition, Aboriginal people have not been able to practise traditional fire management, which was used over millennia as a mechanism to promote growth in flora, influence animal movements and prevent uncontrolled

5 Solastalgia is a new concept developed to give greater meaning and clarity to environmentally induced distress. As opposed to nostalgia – the melancholia or homesickness experienced by individuals when separated from a loved home – solastalgia is the distress that is produced by environmental change impacting on people while they are directly connected to their home environment (Albrecht et al. 2007).

bushfires. Since the introduction of Native Title, first peoples in Australia have continually stated that Western fire prevention methods have not worked well, advocating instead for cool fire burning (McIlroy 2019). Based on this information, our shared microbial communities have also co-evolved with cool burns, and fire contributed to precolonial abundance and plenitudes, while current fires are threats to property and assets. Specialists in human microbiome can learn a lot from ecologists and First Nations people in addressing emerging zoonotic threats (such as the COVID-19 pandemic) that arise from the disintegration of biodiversity, the devastating effects of climate change and ecosystem collapse (Tollefson 2020).

Working in a holistic way with multiple and linked microbial communities will likely have benefits for all future populations struggling with the ongoing effects of colonisation that manifest as biodiversity loss and ecosystem collapse. Recognising the human microbiome – the beneficial and diverse microbial communities that live on and within the human body – is critical for developing and maintaining normal physiological health and is a key feature of the metagenomics strategy proposed in this report, though not the sole focus. Indigenous researchers hypothesise that colonialism is not only demonstrated through the experience of poor human health, but assert that colonial processes have also interrupted environmental microbial communities that have contributed to our ancestral health and wellbeing. Such discussions are paramount in contextualising the future health and wellbeing of humans and planetary health in the Anthropocene (Whitmee et al. 2015).

To reflect cultural practices and value the role of the microbial community in all of life on Earth, we propose an Indigenous metagenomics strategy to merge top-down metagenomics approaches with classical microbiology and organism-level genomics and with traditional ecological knowledge, which reveres our peoples' connection to this continent and all we coevolved with. This approach recognises and values the balance and harmonisation with microbial communities evident in our environment, embedded in traditional life ways, and seeks to restore our Indigenous microbiome communities with all our communities in the Indigenous Estate.[6] This process then combines healing within decolonising practices to overcome the detrimental health consequences that are a legacy of colonisation (Skelly et al. 2018) and to heal our kin – those other-than-human species that provide a context for our lived experience and are part of the landscapes which, together, form the Indigenous Estate.

A call for Indigenous leadership in metagenomics

We contend that as welcome as developments since 2010 are, they are not enough. It is time to fundamentally shift Indigenous metagenomic research into Indigenous hands. Indeed, in this report we ask the largely non-Indigenous researchers, institutions and controlling powers to reshape our Indigenous genomics futures by reimagining a fit-for-purpose Indigenous metagenomics that not only responds to our history and our poor health, but also seeks to address our political, social, cultural and economic aspirations *within the Indigenous Estate and in ways that enhance our collective survivability in anthropogenic conditions*. We believe that an overarching institutional framing of this approach can support and elevate current research agendas across multiple institutions while positioning Aboriginal and Torres Strait Islander people as leaders and emerging

6 The term 'Indigenous Estate' refers to the Australian land mass controlled by Indigenous peoples or Indigenous interests.

specialists in this fit-for-purpose metagenomic strategy. This leadership can be achieved by enhancing the accessibility of the language used in genomics work.

Therefore, our audience is not just the largely non-Indigenous researchers, institutions and controlling powers in this space. To truly be in control of the emergent agenda, the information about genomics needs to be accessible, as much as possible, to the Indigenous lay reader and to people working in policy and programming – in part to awaken our brothers and sisters to the wonders of metagenomics and its deep healing potential and to decolonise metagenomics to include the renaissance of our politics, our Countries, our cultures, our prosperity, and our health and collective happiness both now and in future.

A note on terminology

We have chosen to use the umbrella term 'metagenomics' in this report because, inherent in the ecological approach adopted in this paper, it is impossible to consider Indigenous genomics apart from the microbiome and epigenetics. The word covers all.

We also note the etymology of the word 'gene' (including as a component of metagenomics, genetics, epigenetics and genomics etc.) is 'genos' – Ancient Greek for 'race' (Fine 1983). 'Genos' also provides the foundation of the word 'genocide' (Lemkin 1946). And so, metagenomics includes problematic fields of study for Indigenous peoples because of the genocidal practices used against them, which genetic science has justified historically, and because of the potential of such genetically justified abuses to continue.

Throughout this report we also use the term 'national Indigenous kincentric ecological metagenomic research strategy/agenda'. The term can be understood as follows:

- 'national' and 'Indigenous' refer to Aboriginal and Torres Strait Islander people in the Australian context
- 'kincentric ecological' refers to an Indigenous worldview (see Gap 2 in Chapter 5 for further discussion)
- 'metagenomic research' refers to a field of study which is gaining importance for Aboriginal and Torres Strait Islander people as evidenced by the small but increasing number of Indigenous people addressing the health gap through genomics and microbial research.

To improve readability, we shorten the phrase in some places to the Australian Indigenous Metagenomics Strategy.

In this report we generally use the terms 'Aboriginal and Torres Strait Islander' or 'Indigenous' when referring to the First Nations' peoples of Australia.

2 Background: metagenomics within whole ecologies

> Every disease has two causes. The first is pathophysiological; the second political. (Ramon Cajal 1899, cited in Brant 1993)

Human genetic research is at the forefront of medical research, but the political, social, cultural and economic contexts in which metagenomic research takes place are critical. On this basis, it is not just research into disease states that matters, but the problematic location of the entire field outside an Indigenous ecological, political, social, cultural and economic context.

Indeed, the foremost concern in any consideration of Indigenous peoples and metagenomic research – including this report – *is and must be* acknowledgment of the ecological, political and cultural context in which it is occurring. For although ethical frameworks, intra- and inter-institutional Indigenous governance committees, protocols for engagement with Indigenous communities and Indigenous community study participant cohorts are important developments over the past few decades, they have done little to shift paradigms around 'who is looking at who' under the proverbial research microscope – who controls and decides the agenda? And whose aspirations are forwarded in the agenda?

This report therefore calls, first, for political change in this space – placing Indigenous peoples in control of research agendas decided by Indigenous peoples – and, second, for a flow-on resetting of the cultural context within which research occurs into a 'best of both worlds' space of balance with Indigenous belief systems and perspectives.

The research agenda we propose is likely to include the following streams:

- molecular decolonisation, which is described as the 'process of embracing, restoring, and honouring our original selves at the foundational level of being… [with] the potential to re-balance our biomolecular functioning while *restoring the original instructions embedded in our ancestral deoxyribonucleic acid*' (Redvers et al. 2020:3, our italics); we further suggest this agenda is particularly compelling in relation to likely trauma-induced epigenetic changes to the original instructions in our DNA, and therefore its expression
- metabolic healing, focusing on the genome–microbiota and dietary mismatch experienced by many contemporary Indigenous peoples and which is *literally* killing them
- the restoration of 'Country-as-ecology', including supporting ecological, cultural and economic bases at both the micro and macro scales. This stream aligns with Indigenous understandings of what health is – that is, a positive state of ecological balance, with a focus away from human disease states towards a health-positive agenda that embraces plants, animals, microbiota and food crops. This is the basis of an Indigenous prosperity agenda with sustainable, environmentally respectful development of the Indigenous Estate.

This articulation of a three-stream approach is meant to broaden the current focus on the role genetic factors play in human health and solving problems of disease and disability. Mostly, we advocate for a disruption of narratives that are framed around the illness of Aboriginal and Torres strait Islander people seeking supports of non-Indigenous led genetics studies, and replacing these assumptive narratives with agreements that progress the development of guidelines with each nation of Indigenous peoples: power-sharing relationships must be used in the development of guidelines and practices and, where possible, need to combine traditional ecological knowledge with strategies that grow the capacity of communities to participate fully in community consultation,

sample collection, and informed consent use and storage of biological materials, prioritisation of research uses and post-research obligations to communities and to Country. For this to occur, theories of emergence and systems theories are needed to underpin engagement efforts in the development and refinement of this strategy.

Theoretical approaches to develop a metagenomics strategy linked to whole ecologies

Emergence is a pivotal concept for interpreting the reality of natural and social human life in all its processual complexity (Baggio & Parravicini 2019). Different forms of emergence can widely refer to biology, metaphysics and philosophies of the mind, as well as to social sciences, and often manifest as the result of interconnections of other existing entities. Emergence as a concept has been used in the Indigenous-developed and led First 1000 Days Australia movement to take issues to scale; in doing so, it has focused on the creation of self-organised networks that replicate living systems rather than focusing on hierarchy and control mechanisms (Arabena et al. 2020). This has been done because holistic health concepts rely on the principle of self-organisation where individuals and species recognise their interdependence and organise in ways that support the diversity and viability of all:

> Our work fosters critical connections and joins together Indigenous world views with modern science and lived experiences… allowing a process of emergence to cultivate new relationships, new knowledge and ways forward to emerge, rather than developing strategies or implementation plans…emergence is a patterned response which strongly aligns to the nature based principles of caring for country or belonging to country and other cultural determinants of health (Arabena et al. 2020:234).

Theoretical approaches acknowledging complexity are strongly aligned to Indigenous Australian ways of knowing, being and doing. In addition to emergence theories, we would recommend the adoption of a 'system of systems' approach to developing metagenomics strategies within whole ecologies. As the Australian Indigenous Metagenomics Strategy emerges from within community and on-Country contexts, an additional field of study will make an important contribution to the integrity of the system as a whole – that is to study the interdependencies within and between key metagenomic infrastructure. This additional genomics research strategy can be contextualised within the Country as ecology stream of activity and should address issues such as whether 'integration' is more effective than 'coupling', and address issues such as providing security to and overall assessments of the integrity of the metagenomics system. This is the work of the proposed singular authority governing and guiding the development of this kincentric metagenomics agenda and should disrupt and refocus the over-reliance of illness narratives to engage Aboriginal and Torres Strait Islander people in genomics research. These deficit-laden illness narratives are structured by colonial discourses and are not compelling enough to guarantee the population-level participation of subjugated, colonised peoples whose primary responsibility is to care for colonised lands and our other-than-human kin.

Recognising that Indigenous and non-Indigenous worldviews are different

The preface to this report discusses the largely non-Indigenous control of Indigenous genomic research to date, and how the research that has occurred tends to reflect a non-Indigenous worldview because the history and ongoing momentum of colonisation is pervasive, privileged and otherwise taken for granted as the context for such research – as if it is equivalent to truth.

Here we focus on the need not only for Indigenous control of future research, but the need to bring the non-Indigenous and Indigenous worldviews into balance as the necessary context and foundation for establishing an Indigenous metagenomic research agenda.

The starting point is recognition that Indigenous and non-Indigenous worldviews are different. To illustrate this, Table 2.1 locates values and perspectives as if binary opposites in either the purview of an Indigenous or non-Indigenous worldview.

Table 2.1: Non-Indigenous and Indigenous worldviews as binary opposites (Duran & Duran 2000)

Non-Indigenous worldview	Indigenous worldview
Focus on individualism	Focus on collectivism
Linear time orientation	Non-linear time orientation
Dualistic and reductionist epistemologies to explain things and relationships	Holistic epistemologies to explain things and relationships
Health – a disease and illness-focus	Health – a health and wellness focus

While there are many terms used by Indigenous Australian scholars to describe the holistic relationships between Country, health and wellbeing, the term we use to describe the Indigenous worldview in this report is 'kincentric ecological', with reference to the work of American Indigenous scholar and thought leader Enrique Salmon (2000). In Salmon (2000), the articulation of what kincentric means begins with reference to two related concepts from the author's own Rarámuri culture, which is in the ecologically rich lands in the Sierra Madres of Chihuahua, Mexico, where his people practise hunting and gathering, horticulture and agroforestry:

- *iwigara*, which is 'the total interconnectedness and integration of all life in the Sierra Madres, physical and spiritual', based on its shared origins in Onoruame, the Rarámuri Creator (Salmon 2000:1328)
- *numati,* which makes the above concrete. The term translates as 'things of the natural world are relatives' (Salmon 2000:1329) It stems from a Rarámuri belief that prior to this world the Rarámuri were half plant. And when Rarámuri-as-humans emerged into this world, many of their former plant parts followed – as peyote, datura, maize, morning glory and brazilwood; and with similar familial-type explanations for coyotes, crows, bears and deer. By these narratives, plants and animals are not 'othered' by the Rarámuri but understood as 'humans-in-different-form'; and, as Salmon (2000:1329) writes, the 'Rarámuri feel related to these life-forms much as Euro-Americans feel related to cousins and siblings'.

For Rarámuri then, concrete (i.e. not abstracted) kin relationships between plants, animals, environments and human beings exist. Such was Salmon's starting point for a broader Indigenous kincentric ecological model with resonance across otherwise diverse Indigenous cultures.

Australian Indigenous science

While a survey of such is not possible here, most Aboriginal and Torres Strait Islander cultures have broadly equivalent versions of the two concepts above – as evidenced by the widespread cultural phenomena among Indigenous peoples of cosmogony, animism and sacred, sometimes totem, relationships with animals and/or plants. This is certainly evident in Aboriginal and Torres Strait

Islander science, which is founded on principles of interconnectedness, reciprocity and respect for nature (Popp 2018). Traditional ecological knowledge is essentially the cumulative body of knowledge associated with ecological relationships, which is handed down through generations by Indigenous peoples the world over (Diver 2017). These knowledge systems have provided valuable insights into environmental change, wildlife population monitoring, sustainable harvesting practices, behavioural ecology, ecological relationships and much more (Bennett et al. 2018). There has also been an increased effort to merge interdisciplinary research and build collaborative links between humanities/social sciences and the physical/natural sciences, which will impact the quality and calibre of the work done by professionals in place-based metagenomic activities (Barthel & Seidl 2017).

Science knowledge is embedded in modern forms of cultural expression and can be seen in eco-poetry, fiction, art and film, social movements, representative bodies, industry and in entrepreneurial activities. To progress Indigenous knowledge through the implementation of an Indigenous metagenomics strategy, and allowing for local and regional variations, there are three universal science strands embedded in Indigenous knowledge systems being implemented across Australia (ACARA 2019):

Science as a **human endeavour** (SHE) – Strategies that are typically embedded into processes of learning, and knowledge exchange between generations and for use in innovation and entrepreneurship. These types of exchanges can progress over several years.

Science as inquiry (SI) – Often referred to as Indigenous methodologies, this includes reference to skills, behaviours, attitudes and norms embedded in community consultation and/or co-design, on-Country collaborations and coalition building, research or developing locally specific evaluation techniques and processes.

Science as understanding (SU) – Incorporates an understanding of organising ideas, personal and social capabilities, critical and creative thinking, ethical understandings and Intercultural exchange.

Each of these strands has the capacity to encompass and extend disciplinary knowledge, skills and understandings, and generational capabilities and to support local priorities.

We use these sciences and acknowledge that contemporary visions of nature continue to be deeply affected by the ongoing interaction and interpenetration of science, nature and society (Drenthen, Keulartz & Proctor 2009). As part of the process of reimagining Indigenous-led metagenomics, we must also reimagine the complexity of nature – first as it is experienced, encountered and instrumentalised, and to explore micro-nature and the world of contemporary genomics and also explore perceptual and conceptual boundaries between the human and the natural, or between an 'out there' and 'in here' (Drenthen, Keulartz & Proctor 2009:277). We need to appreciate how nature has been publicly and genomically constructed, known and described through metaphors and reenvisaged in terms of landscape and place. This could be achieved through the adoption of multidimensional worldviews as implicit to Indigenous knowledge systems.

Multidimensional worldviews[7]

Specific examples can be seen among Australia's Aboriginal Western Desert peoples; for example, Jukurrpa is a complex multidimensional worldview that has been described as a 'religion grounded in

7 I reference Central Australian and Torres Strait Islander worldviews because of the intimacy of my connection with these two nations.

the land itself' (Nicholls 2014), including seamless creation and ecological narratives and social processes, such as kinship regulation (including to people, Country and its plant and animal inhabitants, morality and ethics). In relation to this, the clumsy translation of Jukurrpa as 'Dreamtime' has been criticised as reducing 'an entire epistemology… to a single English word' (Nicholls 2014). Indeed, Jukurrpa is so different that anthropologist W. E. H. Stanner, after decades of observing Western Desert peoples, observed in 1956 that it was almost impossible for non-Indigenous people to comprehend it in its entirety (Stanner & Manne 2009) – at best they could comprehend it as a series of component parts (myth, social rules and so on). This is partly because Jukurrpa operates in non-linear time – that is, time that is not reduced to past, present and future – which Stanner referred to as 'everywhen' (Nicholls 2014).

The narrative of Tagai is a primary source of intelligence about our human place in the universe. Tagai is a cosmological patterning in the Torres Strait, which continues to exist despite sustained encroachment from people with deeply contrasting ways of living and different meaning systems (Sharp 1993). It and other stories are central to the philosophical frameworks that create Torres Strait Islander thinking, that all human roles are continuations, further elaborations, expansions and fulfillments of these stories. Torres Strait Islander people represent this unbroken continuity as a state of being, our oneness with all that is. Contemporary Torres Strait Islander identity is grounded and gains strength from the diversity of smaller island communities that make up the whole. The context of diversity can be understood as a system of systems. Torres Strait Islanders are members of a meta community (Torres Strait islanders) and strengthened by the diversity of local Torres Strait Islander people living a range of life ways on individual islands.

Eco-patterning and lived experiences

Torres Strait Islanders have intimate understanding of marine systems, cloud formations and star constellations. Over millennia, living on Country, many communities have developed a sophisticated appreciation of their local ecosystems and the climatic patterns associated with them. Recorded in local languages and documented in seasonal calendars, this knowledge is used to direct hunting, fishing and planting, as well as to inform many seasonally dependent cultural events, and filling in gaps in climate data for northern Australia and informing culturally appropriate adaptation strategies (Green, Billy & Tapim 2010).

Such worldviews then are *fundamentally* different from non-Indigenous, anthropocentric ones. Non-Indigenous ecologies are often conceptualised as hierarchies, with the human parts at the apex of the pyramid given dominion over, and even blessed to exploit, the 'lower layers', where the 'soul-less' plants and animals, rivers and mountains, climate and land (soil, minerals) are relegated (Arabena 2015). Indeed, kincentric ecological models do not support the privileging of the lines of influence from the human *onto* the environment (down the pyramid, so to speak). Rather, they acknowledge multiple lines of influence between all ecological elements, with the humans just one locus in a web of reciprocally influential forces that comprise the ecology itself.

Kincentric viewpoint

Critically, kincentric ecological thinking carries the message that human health and wellbeing is not possible in an unhealthy or unwell environment, so economic and related activity in balance with the environment is important. This holistic viewpoint, which connects human health to environmental health, potentially changes the emphasis of genomic research away from understanding and rectifying genetically determined disease states in human beings, and away from efforts to improve

human health as if separable from the health of enclosing ecologies. Indeed, from a kincentric ecological perspective, this represents a fundamental, at-root misunderstanding of what health and wellbeing are, and how they might be studied.

Over his career, Salmon has continued to expand on the implications of the kincentric ecological model, with Salmon (2015) himself translating the concept to urban spaces in recent years. An example of these possibilities in application was provided in Curridabat township, Costa Rica, in 2020 when every pollinator – bee, bat, hummingbird and butterfly, as well as the native plants and trees that support them – was granted citizenship and concurrent rights and protections by the town's mayor in recognition of their major contribution to both the town's agricultural economy and liveability as an urban space (Greenfield 2020).

In Australia these principles are actively engaged with by Aboriginal and Torres Strait Islander people in care for Country initiatives, through local workforces that have a demonstrable connection to place. Custodianship is concerned with relations between the sexes and between the sacred and non-sacred, between materialism and spirituality. Custodianship forms part of a complex kincentric system of positivist knowledge focused on developing and sharing subsistence techniques that impact the life cycles of our other-than-human kin and affect and nurture social organisation and relationships. A key feature of our work and effort is to produce diversity. The disappearance of diversity in all its forms accelerated in the later part of the 20th century, and understanding the criticality of the interactions of complexity inherent in all Earth's components, entities and processes, including the atmosphere, hydrosphere, geosphere, biosphere and mind spheres, is an important consideration for the future of life on Earth.

Indigenous kincentric ecological metagenomics, then, as determined by Indigenous peoples, scientists and the scientific institutions that control it, is just as likely to be concerned with the health of whole ecologies and – only within this broader context – the health of their human collectives and individuals. It would not, in other words, be a human 'specist' strategy, but one which focuses on a wide range of ecological influences and the web of health and wellbeing they create for First Nations people in Australia.

Transitioning from monocultured actions to stewardship in genetic research agenda setting

Monoculture(d) is a term used to describe the practice of actively preserving a culture to the exclusion of external influences (Shiva 1989). 'Monoculture' is also used in this enquiry as a descriptor for homogeneity and uniformity. Monocultures make diversity disappear from perception and, in doing so, reinforce a way of thinking and living that negatively impacts on diversity in all its forms. Monocultures generate models of production that destroy diversity and legitimise that destruction as progress, growth and improvement. They are also centralised political systems of power spread through mechanisms of control. To reduce the impact of monocultured processes, implemented through monocultured institutions, we need to reposition these and other strategies to a context of diversity and value the ethic of stewardship. This ethic embodies cooperative planning and management of environmental resources with organisations, communities and others to actively participate in the prevention of loss of habitat and facilitate recovery in the interests of long-term sustainability. We do this to recognise the genetically related community of beings bound together in an inseparable relationship in space and time, and to recognise that we are connected by our ancestral responsibility to the quality of life experienced by those we share our Country with. To

do this, we propose a 'best of both worlds' approach to the development and implementation of the Australian Indigenous Metagenomics Strategy.

Locating Indigenous metagenomic research: a 'best of both worlds' approach

We propose a powerful agenda for consideration within Indigenous kincentric ecological metagenomics. As discussed in passing so far, *molecular decolonisation* is a focus among some contemporary Indigenous thought leaders. Its starting point is within kincentric ecological contexts, with a focus on the micro elements and how they shape the macro. And as already quoted above, a molecular decolonisation research agenda includes the:

> process of embracing, restoring, and honouring our original selves at the foundational level of being… [with] the potential to re-balance our biomolecular functioning while restoring the original instructions embedded in our ancestral deoxyribonucleic acid (DNA). (Redvers et al. 2020:3)

It has long been recognised that microscopic life is critical to ecological functioning. An illustrative example is the well-documented plant and tree dependencies on microbial communities in their root balls (Habiyaremye et al. 2020), which keep soils healthy, increase nutrient availability and uptake, suppress diseases, protect against various forms of plant stress and assist plants to rapidly adapt to new conditions. Indeed, the plant root microbiota is so important to plants and their ability to adapt to a range of environments that it has been described as 'the powerhouse of plant adjustment to local conditions' (Vandenkoornhuyse et al. 2015, cited in Habiyaremye et al. 2020).

Molecular decolonisation then is concerned with the *micro impacts* of colonisation – on the potential epigenetic impacts of colonisation and its aftermath on Indigenous DNA, including interactions and mismatches between Indigenous genomes and microbiota – and its *macro effects* on Indigenous individuals' physical and mental health, and even behaviours. Redvers et al. (2020) even propose planetary-level macro effects to the degree Indigenous kincentric responsibilities (and influence) in relation to the wider environment are diminished by these micro impacts.

The co-existence of two worldviews in one space is not inherently problematic. While Indigenous cultural forms (art, languages and so forth) are no longer suppressed, the worldview behind these forms is nonetheless ignored and neglected, misunderstood and widely devalued. Indeed, its relevance to the contemporary world is perhaps only just being grasped as we enter the Anthropocene era facing the consequences of centuries of collective ecological irresponsibility.

In considering this, it is important to revisit the discussion in the preface about the inherent connections between long-held ideas of coloniser genetic superiority and the cultural superiority that persists today. As such, it behoves contemporary metagenomics to recognise its historical, political and cultural legacy, at very least, in this space and work to bring the Indigenous cultural worldview into a non-hierarchical space of balance with the non-Indigenous worldview as a new context to locate Indigenous metagenomic research.

It is important to recognise that this is not a kneejerk reversal of the zero-sum coloniser paradigm, which is based on 'winning' and 'losing' worldviews, and which places the Indigenous worldview above the non-Indigenous. Rather, it is a 'best of both worlds' approach. As such, Indigenous kincentric ecological metagenomic research is free to incorporate the best and most useful of the, to date, almost entirely non-Indigenous-determined, human species-focused metagenomic research, including that focused on understanding disease states, but is also open to integration with new and wider research horizons, including the idea of molecular decolonisation.

Such Indigenous kincentric ecological metagenomics will have integrity as long as Indigenous peoples, scientists and scientific institutions control it and determine the balance of approaches required to develop and sustain a uniquely 'fit for Indigenous purpose' form of the relevant disciplines, with a focus on research translation and making the greatest possible gains for Indigenous peoples and the animals, plants and environments within their kincentric circles. This throws down a challenge to contemporary metagenomics to ultimately help save the world – and not just the humans (and particularly already privileged humans) therein.

Best of both worlds: cultural, social and emotional wellbeing research strategies

Cultural, social and emotional wellbeing (CSEWB, or more commonly 'SEWB', although we use the former here) is itself an ecology (of cultural determinants that support Indigenous wellbeing). The *National Strategic Framework for Aboriginal and Torres Strait Islander Peoples' Mental Health and Social and Emotional Wellbeing 2017–2023* describes CSEWB as:

> the foundation for physical and mental health for Aboriginal and Torres Strait Islander peoples. It is a holistic concept which results from a network of relationships between individuals, family, kin and community. It also recognises the importance of connection to land, culture, spirituality and ancestry, and how these affect the individual. (Australian Government 2017:6)

Indigenous people's understanding of CSEWB varies between Nations, but there are enough shared elements for a broad CSEWB model consisting of seven overlapping domains to have emerged and now be widely accepted. Figure 2.1 shows how the cultural determinants act as protective factors against the often-negative determinants of health and wellbeing associated with colonisation.

Figure 2.1: A model of social and emotional wellbeing (Gee et al. 2013 in Australian Government 2017:6)

Key elements include a strong and positive Indigenous identity grounded in a collectivist perspective, but the model also emphasises the strength and health of connections to body; mind and emotions; family and kin; community; culture; Country; and spirituality and ancestors as health determinants.

Many elements of CSEWB are discussed in other contexts in this report, such as the strength and health of connections to body (what we might consider as physical health, aligned with the original instructions in the ancestral DNA), and mind and emotions (free of trauma, or otherwise integrated). Connections to Country and kincentric ecological connections are discussed below, but there are

two other focuses where metagenomics might contribute to CSEWB – by connections to family and kin, and to spirituality, particularly as mediated by relationship to ancestors. This might include connecting Indigenous individuals to families, clan groups and Nations where these remain unknown to them for colonisation-associated, or other, reasons. But a note of caution – while genomics holds significant promise here, it also carries risks relating to identity, which is a central CSEWB element. There are highly sensitive personal and familial legacies that would likely be detectable through genomic sequencing. Indeed, in some cases there is the potential to disrupt a person's connection to families, clan groups and Nations. The capacity for insensitively managed genetics/genomic research to do harm in this context is therefore significant and underscores the need for this to be under Indigenous control, including to help manage – as much as anything – potential cultural/identity issues that might arise.

Practical examples in action to support the repatriation and rightful treatment of ancestral remains include the recent work of the Australian National University's National Centre for Indigenous Genomics (NCIG) in partnership with the Kimberley Aboriginal Law and Cultural Centre to support communities' connection to unidentified Aboriginal people exhumed from the Old Pioneer Cemetery in Fitzroy Crossing, Western Australia, to save the remains from encroachment by the Fitzroy River. The names of those buried in the cemetery are known, but fewer than 20 of the remains could be individually identified. Working with the communities, the NCIG pre-emptively collected DNA from the unidentified remains for safekeeping. In the future, and funds permitting, the DNA from the remains can be compared with DNA from families with known deceased, allowing named graves or for the remains to be returned to Country, if that is the wish of the family (NCIG 2018).

The need for the repatriation and rightful treatment of ancestral remains equally applies to the skulls, bodily samples, artwork and cultural artefacts collected without meaningful consent by (and in many cases still in the possession of) major Western scientific and cultural institutions (Pickering 2020). Wright et al. (2018) used the strong regionalisation of Indigenous halotypes to suggest increased potential for repatriating (to their descendants) otherwise non-Nation or regionally identified Australian Indigenous (or otherwise completed unidentified) remains collected by and currently stored in museums and institutions. The capacity for sequencing ancient remains was demonstrated by Heupink et al. (2016), who successfully extracted mitogenomes from the famous Mungo Man's remains (42,000 years old). A further avenue for repatriation is the identification and restoration of implements with genetically rich organic elements – tree gum, wood, microbiota etc. – by matching with environmental samples. Recently a research grant was announced to support the matching of remnant microbiota found in ochres to various ecologies' ochres and to support identification and repatriation efforts (ARC n.d.).

As is a major focus of the work of Professor Emma Kowal at Deakin University, genomics can be expected to have potentially profound impacts on concepts of Indigenous identity, which could, in turn, have implications for CSEWB. Such impacts need careful handling and provide another argument for national oversight by the proposed institution. We do not dwell further on this other than to quote Kowal (2018): 'A focus on social processes since the 1970s has left scholarship on Indigenous identity ill-equipped to grapple with the consequences of the genomic era.'

Best of both worlds: sustainability, stewardship and the threat to ecological communities

The Australian continent and Torres Strait Islands include a vast spread of ecologies. Upon these, since 1788 enormous areas have been cleared or thinned, primarily for crops and grazing. In 2002 the Australian Government's National Land and Water Resources Audit identified 2891 threatened

ecosystems and ecological communities across Australia (ABS 2004). Of these, at December 2015, under the *Environment Protection and Biodiversity Conservation Act 1999* (Cth), 74 ecological communities were listed as threatened: 31 as critically endangered, 41 as endangered and two as vulnerable (Cresswell & Murphy 2017).

In addition to land and ecological degradation, hundreds of non-native species have been introduced into the continent, and a significant number have become established as wild pest populations, with devastating effects on Indigenous animal and plant kin. It is estimated that feral cats have already driven a significant number of species to extinction and are believed to kill more than one million native birds and 1.7 million reptiles across Australia *per day* (Hollingsworth 2019). Indeed, feral cats are identified as among the primary threats to more than one hundred species (McKay 2020). Foxes, rats and feral dogs also take a toll. Other species (feral pigs, camels, rabbits, cane toads and so on) are massively environmentally destructive.

As a result, 17 species of mammals, and numerous subspecies, are listed in the *Environment Protection and Biodiversity Conservation Act 1999* as becoming extinct since 1788. Further, in the Australian Government's 2015 *Threatened Species Strategy*, nearly one in three Australian marsupial species are listed as at risk of extinction (Nature Conservancy n.d.). Indeed, the strategy includes species-specific action plans to preserve 20 bird and animal species, as well as 30 species of plants.

The black-footed rock-wallaby, which is of significant cultural importance to the Martu peoples, is included in the species-specific strategies. And, like their counterparts, the Martu are already working with a multidisciplinary team to implement integrated approaches to preserve the rock wallaby (NIAA 2017). It is likely that many of the species in the Threatened Species Strategy are held in a similar relationship to one or many Indigenous Nations.

In kincentric ecological worldviews, human gifts/talents are not understood as existing at the expense of ecologies, or as means to escape the implications of being within an ecology. Rather, they bring with them commensurate responsibilities for the ecologies in question. But this does not mean leaving ecologies in what might be characterised as 'virgin states'. Indeed, such misconceptions of Aboriginal peoples' relationships to their Country underpinned the notion that Australia was terra nullius in 1788 – as if the presence of Aboriginal peoples barely registered on the continent's surface, leaving them otherwise without nexus to Country in ways that could be understood by the colonisers as equivalent to possession, ownership or sovereignty.

Genetics: shaping our environments

In addition to the recent work of scholars like Pascoe (2014), research demonstrates the long history of Indigenous peoples shaping their environment, even to the point of indicating that the Indigenous prehistoric migrations should be conceived of, in part, as the migrations of ecological elements from one place to another. In other words, Indigenous peoples did not just happen across the ecologies they inhabit, they have created them. For example, Kondo et al. (2012) proposed a model to explain the distribution of the red cabbage palm (an Indigenous food source), with one pocket in northern Australia and – 1000 kilometres to the south – another in Central Australia. The initial hypothesis was that these two plant populations were remnants of a widespread population that contracted to the two smaller areas. But by comparing the DNA of the two palm populations, the researchers determined that they comprised two genetically distinct groups, ruling out the 'remnant hypothesis' whereby the plants would be significantly more identical. Furthermore, that in time the ancient dispersal from one to the other areas was coincident with the settlement of Indigenous Australians in Central Australia from the north, who – the researchers conclude – are 'plausible vectors' (Kondo

et al. 2012). And with time and isolation, two genetically distinct palm varieties had emerged. The Central Australian variety is an endangered species, and one of 30 plant species that are the focus of the Threatened Species Strategy (see above).

Boab tubers are eaten by Indigenous groups in the Kimberley, Western Australia. Bell et al. (2014) proposed a similar theory to explain the dispersal of the boab tree across the region. They did so by examining DNA from 220 dispersed boab genomes. Across these, they identified only small genetic variations that suggested the plant had dispersed via an assisted gene flow of essentially one variant, most likely involving animal or human vectors (Bell et al. 2014). Further genomic research by Rangan et al. (2015) was matched with linguistic analysis of the pathways taken by loanwords to describe the boab across the region (i.e. the adoptions of a word from one to another group to describe something new – in this case the boab). This added weight to the human vector model (Rangan et al. 2015).

Rossetto et al. (2017) examined the dispersal of the black bean, or Moreton Bay chestnut, across the east coast of Australia. The plant produces a toxic seed, which, if processed correctly, becomes a nutritious food source. Significant Indigenous cultural practice informs harvesting and safe processing activities. By sequencing black bean genomes from three widely dispersed northern New South Wales locations and (as with the boab above) cross-referencing genomic data against black bean loanword evidence and the adoption and adaptation of black bean processing cultural practices, they proposed that Aboriginal peoples had deliberately dispersed the plant as a food source (Rossetto et al. 2017).

Such modification is also evident from genomic research across the widely separated Polynesian islands, including Aotearoa New Zealand, and strongly suggests human vectors for the dispersal of the breadfruit (Zerega, Ragone & Motley 2004), Polynesian bottle gourd (Clarke et al. 2006) and sweet potato (Roullier et al. 2013) food plants.

The point here is that kincentric ecological approaches are entirely compatible with sustainable and ecologically responsible food production, surplus generation and economic activity but within a different Indigenous worldview and perspective. As mentioned, kincentric ecological thinking carries the message that human health and wellbeing is not possible in an unhealthy or unwell environment, so economic and related activity in balance with the environment is the critical difference. A shift in thinking about food sustainability is evident in the appointment of Bruce Pascoe to a Professor of Indigenous Agriculture position at The University of Melbourne and in regenerative farming practices that are engaging First Nations people in cultivating the productivity of lands, shifting from petrochemical farming to fire technology and working with Country, not against it. Importantly, we are seeing a re-emergence of investment in healthy soil biology and the access to nutrients at a microbial level, which has good outcomes for landscape health and wellbeing, and better landscape resilience and performance:

> With the rise of modern industrial agriculture after the Second World War, we're now finding there are some long-term costs starting to emerge: what we're doing to soils, chemicals getting into our food, increasing desertification of our landscapes and getting hard pans under the cropping fields etc. But there is proof that techniques of ecological grazing and cropping and those sorts of things, particularly in the past 15–20 years, are leading to greater profits through better resilience and even better performance without those higher industrial inputs. So the regenerative space is really exciting and it also has all sorts of benefits … (Charles Massy cited in Australian Wool Innovation Limited n.d.)

By all accounts, global demands for food and fibre will increase up to 70 per cent by 2050, requiring an increase in agricultural productivity from existing arable land, under harsher climate conditions and with declining soil and water quality (Singh & Trivedi 2017). Additionally, future food security initiatives will need to safeguard our agricultural pursuits from new, emerging and endemic pests and pathogens, which are the scourge of current conventional farming practices. Harnessing natural resources including the 'phytomicrobiome' is proposed as a strategy to improve productivity and promote positive environmental and social outcomes (Singh & Trivedi 2017). Indigenous knowledge of microbiome, healthy soil biology and of regenerating landscapes is key.

Microbial community custodianship

Under the 2020 Closing the Gap targets and outcomes, the size of Indigenous Estate is likely to increase (Closing the Gap in Partnership n.d.a). What this does is also make us nationally recognised custodians of the microbial communities on vast areas of the lands, waters, soils and air in Australia, and requires a shift from human-centric metagenomics to place-based metagenomics and an articulation of the values and custodial responsibilities for all the country we care for and belong to, as well as all our other-than-human kith and kin. We need to identify and work with like-minded others in the implementation of both world approaches to the development of an Indigenous-led metagenomics agenda in Australia that can cooperate with those developed by other microbial community custodians. These people and institutions may best be suited to the best-of-both-worlds approach advocated for in this report.

Best of both worlds: trauma and epigenetic healing

Epigenetics was first coined as a term in 1942 by Dr Conrad Waddington to describe the process by which a fertilised egg formed into a complex, functional being (Tronick & Hunter 2016). Through until the end of the 20th century, the scope of epigenetics has evolved to include the mechanisms driving gene expression and patterns of inheritance (Gibney & Nolan 2010). Today, epigenetics studies how gene expressions are modified, affecting the way they are read without changes to the underlying DNA sequence (Handy, Castro & Loscalzo 2011).

Inherited epigenetic changes were first seen in plants such as tomatoes, which were observed to pass on chemical tags that affect an important ripening gene (Kanherkar, Bhatia-Dey & Csoka 2014). Recent research is now showing transgenerational epigenetic effects in mice and humans, with studies revealing that descendants of war veterans, Holocaust survivors and famine sufferers have higher mortality rates and exhibit other symptoms associated with trauma (Yehuda & Lehrner 2018). For Australian Indigenous peoples, the histories of colonisation and the associated trauma effects and the possible role of epigenetic mechanisms in this transmission are warranting further investigation and are focused on two broad categories of epigenetically mediated effects:

- developmentally programmed effects – those that result from our children's early environmental exposures, including postnatal care and the in-utero experience of maternal stress during pregnancy
- preconception trauma in which the different experiences of maternal and paternal trauma affects the germline and fetoplacental interactions (Yehuda & Lehrner 2018).

The stress of these experiences is thought to initiate changes that influence gene expression, creating distinct epigenetic signatures that negatively impact life expectancy, mental health, behaviour and more – across generations. This 'passing 'of epigenetic changes across generations is yet to be confirmed for humans. However, further investment in the types of studies, including

longitudinal studies, that can ensure a solid foundation to the claims of offspring and intergenerational effects of trauma is warranted.

Although this biologically embedded evidence base is important, much work is occurring in healing from the impacts of intergenerational trauma through processes that are closely aligned to community, Country and cultural determinants of health. The Healing Foundation was established to support Stolen Generations heal from their past experiences by establishing long-term partnerships with Aboriginal and Torres Strait Islander healing leadership, traditional healers, survivors, youth, therapists and academics to harness knowledge and co-design projects that combine ancient Indigenous healing knowledge with Western trauma knowledge.

Through a focus on epigenetics and a combined Indigenous and Western science lens, epigenetic considerations not only facilitate healing of whole ecologies (individuals in families, the places they live and the experiences they have) but also embeds concepts of time into whole ecological processes – particularly across, within and between generations. If these approaches were informed by the Australian Indigenous Metagenomics Strategy, and policy makers and programmers were trained in these new disciplinary domains, we could inform 'cycle of life' and 'whole of life' public policies, programming and public health initiatives that:

- consider early life interventions in increasing brain growth as health ageing prevention strategies
- consider 'cycle of life' research agendas that implement or arise from multiple inputs across the human lifespan
- overcome the experience of disadvantage by using the Australian Indigenous Metagenomics Strategy to promote evidence of intergenerational impacts of trauma and of resilience from a biological standpoint and from social and emotional wellbeing perspectives
- enhance biodiversity and care for Country initiatives for all Australians.

The Australian Indigenous Metagenomics Strategy, embedded in an overarching umbrella institution, could work to build capacity for good health and wellbeing across a person's life, reduce the negative impacts of racism and poor social and cultural determinants of health between generations, and facilitate policy and programming that considers nested life stages and the contexts in which these experiences occur.

In doing so, a key feature of the Australian Indigenous Metagenomics Strategy would be to create a dynamic expression of Indigenous families, extending to our other-than-human family, and to support humans in reimagining the spatial and temporal dimensions of human engagement in complex ecosystems, as well as providing new opportunities for multigenerational and on-Country healing, returning us to our original instructions and healing.

Best of both worlds: a cardiometabolic healing research agenda

The interaction of microbial genes, human genes, intermicrobial metabolic processes and diet makes the precise pathways by which the microbiome affects disease development hard to discern (Komaroff 2017). This makes diabetes, for example, an excellent representation of both the potential pay-off and probable difficulties of bringing precision health into the realm of complex diseases. These conditions place a considerable burden on patients and the health system, arguably warranting concerted research efforts. However, understanding how they arise, develop and can perhaps be cured is a complicated endeavour and one that requires intensive interdisciplinary efforts.

Echoing the Rarámuri belief that people were half-plant before they emerged as humans into this world (as discussed above), researchers estimate a 70-kilogram human being comprises about 38 trillion genetically human cells, matched by *at least the same number* of microbiota (non-pathogenic, non-genetically human lifeforms, including bacteria, members of the Archaea (single-celled microorganisms with structure similar to bacteria), yeasts, single-celled organisms (eukaryotes) and viruses) (Rojo et al. 2017). These presumably interact in a way akin to the relationships of plant root microbiotas to their host plants and trees (Blum, Zechmeister-Boltenstern & Keiblinger 2019), but the majority of these human–microbiota relationships are yet to be understood.

In other words, a human being comprises roughly equal quantities of genetically human cells living in mostly to-be-determined relationships with microbiota living on, or within, our bodies. 'Microbiota' and 'microbiome' are largely interchangeable terms. Here, however, the latter is used to refer to the collective genomes of microbiota, which has been estimated to contain 100 times more genes and related functions than the human genome (Gilbert et al. 2018). The contribution of these functions to human wellbeing is suggested by experiments involving the total removal of microbiota from mammals whereby health and normal functioning starts to break down (Goodrich et al. 2017). Indeed, as noted in Rees, Bosch & Douglas (2018:1):

> Evidence shows that our resident microbes orchestrate the adaptive immune system, influence the brain, and contribute more gene functions than our own genome. The realization that humans are not individual, discrete entities but rather the outcome of ever-changing interactions with microorganisms has consequences beyond the biological disciplines. It calls into question the assumption that distinctive human traits set us apart from all other animals.

Wherever possible, the focus on implementation in a best of both worlds approach should facilitate the integration of cross-strand strategies, particularly those that relate to the comprehension of Indigenous ways of knowing, being and doing and how they relate to health and wellbeing. Indigenous science-based knowledge has relevance for the implementation of the Australian Indigenous Metagenomics Strategy and has much to teach people about reverence for the microbial connections to place and healing populations of people who do not understand, nor appreciate, how we are occupied by microbiome, and how our common microbial and molecular communities could be used to inform narratives that unite all life on Earth. The foundation of these developing microbial-based decolonising narratives is premised on the need to rebalance our biomolecular functioning within and across species while dampening the supercilious viewpoint that human health should be put ahead of all others on Earth (Redvers et al. 2020).

Best of both worlds: seeking sustainable relationships

Addressing our growing planetary crisis and attendant symptoms of human and human-ecological disconnect requires a profound epistemological re-orientation regarding how societal structures are conceived and articulated, particularly those that have established their civilisations on the unceded lands of others (Williams et al. 2018). While global dynamics are vital to transnational solidarities between Indigenous peoples, these same processes have also resulted in complex and often contradictory locations and histories of peoples at local levels. These complexities tend to disrupt Indigenous/non-Indigenous binaries and can provide new foci for increasing social-ecological resilience in the context of place. First though it is worthwhile considering what 'place' means in Indigenous worldviews and what the result of 'decolonisation' is meant to achieve.

Aboriginal and Torres Strait Islander people have described innate connection to landscapes, with physical, mental, emotional and spiritual connections uniting the smallest molecular particle to the outer reaches of the universe. In a series of paintings used by Aboriginal men becoming well, the Puntu Palyarrikuwanpa Art into Health project was able to support artists describe key values that affected their wellbeing (McCoy 2011). These values are premised on the impulse to care for one another and to 'protect and celebrate ceremony and culture, to pass on generations of wisdom and learning and to maintain connection to country, family and law' (Dr Alex Brown in McCoy 2011:9).

The end goal of decolonisation strategies in this report should be understood as a desire to be 'uncolonised'; that is, not to be referent to the experience of colonisation as an experience or as a dominant paradigm.

The intention of the Australian Indigenous Metagenomics Strategy

The Australian Indigenous Metagenomics Strategy could work to facilitate an increasing congruence in the voices of Indigenous people, ecological philosophers and scientists to highlight that achievements in science, technology, industry, commerce and finance have brought humans into a new age at the expense of much of the diversity of life and the life-enhancing processes of the Earth (Arabena 2015). Across the world, life is being lost, driven to extinction by the unchecked ideals and practices of globalised capitalist development. This form of development, says Shiva (1989:3), is itself underwritten by forms of cultural imperialism, patriarchal relations and suppression of Indigenous worldviews, and of entire populations of people. The same people who have allowed modern industrial corporations to dominate entire planetary processes have managed these harmful practices of development, which have increasingly disturbed the ecological and geological functioning of the planet in a manner and to an extent that the world has never known previously.

The International Resilience Network is one example of a community of practice of Indigenous and settler-migrant peoples aimed at increasing human-social-ecological resilience (Williams et al. 2018). Others are strongly lands-based coalitions such as the Care for Country mob and Caring for the River Country, supported by the Murray-Darling Basin Authority. Similarly, initiatives such as Country Needs People, Indigenous ranger programs, the Indigenous Land and Sea ranger programs, and the Torres Strait Islander ranger program have highlighted the health and wellbeing benefits for people and 'places', creating meaningful employment for people at the same time as restoring ecosystems (Campbell 2015). These approaches are gaining stronger support, with people across Australia protesting to protect the Great Barrier Reef and coastal protected areas, and the young people's global movement of climate strikes, which have captured the world's attention (Marris 2019).

Aboriginal and Torres Strait Islander people have strong cultural connections to their Country and have been managing their lands for thousands of years (Schultz & Cairney 2017). There is increasing recognition of the value of Aboriginal and Torres Strait Islander peoples' knowledge and skills in this area. Recent breakdowns of ecological systems and harms to biodiversity have been linked to a loss of traditional forms of land management (Campbell et al. 2011). This is no longer acceptable to us as people with responsibility for the continued health and wellbeing of more than 50 per cent of the continent's microbiota.

Land management principles have governed Aboriginal and Torres Strait Islander peoples' lives, a relationship that has been respected in the development of this work. The methods used to answer the questions posed by the Advisory Group respect this context but follow standard methods of collecting and interrogating data for inclusion in the report and are discussed in the next section.

3 Methods and methodology

Karabena Consulting is an Australian Indigenous business focused on supporting agencies to achieve positive outcomes for Aboriginal and Torres Strait Islander people's health and wellbeing. Primarily engaged through the Commonwealth Department of Health, Karabena Consulting undertook strengths-based research underpinned by principles of Indigenous community-led development and research support. Our work is premised on culture being the main protective factor in ensuring the health and wellbeing of multiple generations in families. Embedding this approach throughout this project has generated evidence that is both informed by and culturally appropriate to Aboriginal and Torres Strait Islander people. Strategies first devised to implement this project needed correction due to the impacts of COVID-19 and time to gather the views of the Advisory Group. A Data Collection Plan confirmed the project questions and aligned them with key data sources necessary to address each point in the project's implementation. Karabena Consulting staff conducted a data collection meeting to determine the appropriate sources of data and methods of data collection, which are included below.

Environmental scan

The objective of the environmental scan is to identify the current research, clinical services and consumer engagement activities in the genomics field that are relevant to Aboriginal and Torres Strait Islander people. A key project question (and sub-questions) guided this work:

> Key Question 1: What genomics strategies could be implemented through the Genomics Implementation Plan if we had improved systems, knowledge, practices and resources?
>
> 1.1: How do Aboriginal and Torres Strait Islander people define issues of culture and consent about genomics?
>
> 1.2: Which genomic strategies can be implemented through mainstream and ACCHOS (Aboriginal Community Controlled Health Organisations)?
>
> 1.3: What kinds of policy and programming mechanisms are needed to implement a robust Indigenous genomics strategy based on Indigenous ways of knowing, being, doing?
>
> 1.4: What does an Indigenous genomics workforce look like?
>
> 1.5: Are there best practice examples where genomics has been implemented? What are the key findings from these examples?

In order to answer this question, research initiatives focusing on Aboriginal and Torres Strait Islander health genomics were considered, particularly those that are or could be translated to enhance clinical genomics services for Aboriginal and Torres Strait Islander people. The scan focuses on clinical genomics services and projects that improve Aboriginal and Torres Strait Islander access to health genomics services, including education and training to support an Aboriginal and Torres Strait Islander genomics workforce, consumer engagement and education activities. Relevant international examples for other Indigenous populations were sought to compare guidelines and protocols developed for the management of Indigenous health genomics information and services.

Gap analysis report

To conduct the gap analysis and address the objective of Identifying research, services or activities where increased attention would benefit Aboriginal and Torres Strait Islander peoples, we adopted the second key project question (and sub-questions) as our guiding approach:

> Key Question 2: What are the gaps when implementing actions relating to genomics research, services or activities, and how can they be addressed?
>
> 2.1: Are communities aware of genomics?
>
> 2.2: What genomics research, services, activities could be done locally, regionally and nationally?
>
> 2.3: What infrastructure is needed to support Indigenous peoples access genomics information, testing and treatment and support?
>
> 2.4: What networks can be effectively leveraged to provide support for the implementation of genomics work in Aboriginal and Torres Strait Islander nations (including Country)?
>
> 2.5: How can the implementation of genomics strategies benefit households who are experiencing cultural vulnerability?

Our gap analysis identified one overriding gap in research, in services and in activities where increased attention would benefit Aboriginal and Torres Strait Islander peoples – this gap is the need for an Indigenous-controlled national Indigenous metagenomics umbrella institution. All other gaps relate back to this requirement. Without Indigenous control of our own lives, our own research, our own data, any Australian Indigenous metagenomics strategy is compromised and risks failing to connect with our people and the microbiota that we have a custodial responsibility to care for in the context of Country.

Literature review

The literature review (Appendix A) addresses the question:

> What Indigenous-specific genomic research has occurred since December 2010, both domestically and internationally, with relevance to Aboriginal and Torres Strait Islander peoples, and that can inform a research agenda into the future?

Given the potential scope of the review, we focus on research among Indigenous peoples with similar experiences of colonisation to Aboriginal and Torres Strait Islander peoples today. To identify a 'point in time' approach to Indigenous peoples taking control of the national Indigenous genomics agenda, we reference the first ever Indigenous-led research discussion of the conduct of genetic research in Indigenous Australian communities. Conducted by the Lowitja Institute in partnership with The University of Melbourne, the round table discussions elicited responses from the participants that moved beyond the experience of 'bad research' done to Indigenous peoples in this and other countries and through a range of courageous and productive conversations on ethical issues relevant to genetic research in Indigenous communities. The responses covered issues such as genetic literacy and the role that genetics information has in precision health, and recognised the need for communities to be empowered about participating in genetic research.

Search strategy inclusions and exclusions

Key words were Microbiome, genetic, genomic, Aboriginal (or Maori, Polynesian, Native American), indigeneity, Indigenous, health research. The date range specified relevant results between 2010

through to 2020. We conducted a PubMed search and then filtered for relevance, with papers focusing on ethical and other non-topic issues removed.

We identified studies reporting on the experiences of Indigenous peoples with biobanking, tissue banking, reference databases, health care, institutional guidelines, ethics, consent, Indigenous governance and genomic research. The database searches included PubMed, Web of Science, Australian Aboriginal HealthInfoNet and Google Scholar, with all literature available from December 2010 until the search date of December 2019. The reference lists of all included papers, as well as related review articles, were manually searched to identify additional relevant studies. An inductive approach identified common themes, which are included in the next chapter of this report.

Stakeholder interviews

We conducted interviews with members of the Aboriginal and Torres Strait Islander Advisory Group on Genomics and other individuals to obtain project-relevant information and elicit stakeholder reactions and suggestions about recommendations. We engaged with relevant Indigenous genomics stakeholders identified by the Advisory Group and people managing Indigenous projects through Indigenous genomics institutions and collection agencies. Stakeholders were selected for their knowledge, wisdom and ability to provide insights based on their work and knowledge of partnerships and key projects in Australia and through the work of internationally based Indigenous scholars. Stakeholder interview questions were co-designed with the Advisory Group after the literature review phase of the project.

4 Environmental scan

This environmental scan identifies research, clinical services and consumer engagement activities in the genomics field that are of relevance to Aboriginal and Torres Strait Islander peoples. It focuses on trends and occurrences in the field of genomics as they relate specifically to Indigenous peoples in Australian contexts and other Indigenous peoples internationally. The areas covered in this chapter include:

- research initiatives focusing on Aboriginal and Torres Strait Islander health genomics
- research projects that are being, or could be, translated to enhance clinical genomics services for Aboriginal and Torres Strait Islander people
- clinicians and health services that currently deliver clinical genomics services specifically designed for and targeting Aboriginal and Torres Strait Islander people, and/or projects that aim to improve Aboriginal and Torres Strait Islander access to health genomics services, including education and training to support an Aboriginal and Torres Strait Islander genomics workforce
- consumer engagement and education activities that target Aboriginal and Torres Strait Islander people
- current data infrastructure, data sovereignty and governance arrangements for health genomics information with consideration to Aboriginal and Torres Strait Islander peoples and relevant international examples for other Indigenous populations
- an international comparison of guidelines and protocols developed for the management of Indigenous health genomics information and services.

In addition to this human-centric work, we reviewed ecological genomics work conducted by CSIRO that has relevance for an Australian Indigenous Metagenomics Strategy and can support and catalyse an expanded view of genomics. This relevance acknowledges our millennial connection to Country (Tobler et al. 2017) and is the context of our custodial responsibilities to microbiota, particularly in the Indigenous Estate. From the key past, present and planned Indigenous genomics work in Australia and internationally, at the end of this chapter we summarise key considerations for an Indigenous Australian metagenomics research agenda.

Research initiatives focusing on Australian Indigenous people's health genomics

The research projects included in this chapter highlight that successful genetic research with Indigenous Australians is achievable with effective community engagement and appropriate governance mechanisms in place and the active inclusion of Indigenous researchers. These research projects are included because they add value to what is considered best practice in genetic research. Ratified in 1997, the Universal Declaration on the Human Genome and Human Rights highlights the importance of prior, free and informed consent for research participants and that no research interest can prevail over these rights (UNESCO 1997). For the conduct of research with Indigenous peoples across the world, Tong et al. (2020) also identified the importance of respecting the rights and respect for the roles and responsibilities of safeguarding social, cultural, religious and spiritual values (ILO 1989). Tong et al. (2020) noted that these two documents provide an important framework for the conduct of genetic research with Indigenous peoples, because of the commitment to genuine partnerships and leadership from Indigenous communities and their

representatives. The following research projects build on key recommendations for furthering an Australian Indigenous Metagenomics Strategy.

Over the past decade since the first national Indigenous-led discussion on genomics occurred under the auspice of the Lowitja Institute, researchers have sought to address gaps in the knowledge about ethical practice specific to Indigenous genetic research from community. They have also sought to increase the capacity of the Indigenous genomics research workforce, ensure appropriate management of research processes and research samples, and facilitate community engagement in the research and researcher experience in working with Indigenous communities. In the development and implementation of these projects, researchers have had to manage tensions such as:

- those existing between individual consent and community consent
- culturally appropriate management of samples and data (e.g. after someone dies)
- how to assess potential benefits (and risks) of proposed studies (including whether there are existing solutions that should be applied instead of doing genomics research).

While different Aboriginal and Torres Strait Islander communities have different issues to be considered, there is a growing coherence about the role and function of genomics research in Indigenous Australian communities. This section provides information on an array of current research projects.

Australian heritage: constructing the first Aboriginal reference genome

This project aims to use DNA sequencing technologies to generate the first complete and accurate Aboriginal reference genomes and maps of genomic variation around Australia (GrantConnect n.d.a). It will combine a range of advanced analytical methods to integrate past and present Indigenous genetic diversity from human populations around the world into a new pan-human reference genome. This project will lead to a step change in our understanding of global human genomic variants and provide a range of new targets relevant to medical biology, while significantly improving our knowledge of human genetic history and its consequences in the modern day.

- **Funding:** $435,000 Australian Research Council Discovery Grant
- **Grant term:** 1 January 2019 – 1 January 2021
- **Principal investigator:** led by Dr Bastien Llamas, University of Adelaide, with a team that includes Dr Brad Chapman, Mr Erik Garrison and Professor Dr Lars Fehren-Schmitz

Better Indigenous Genetic (BIG) Health Services

This project is reviewing four different models of genetic health service provision, gaining insights about best practice and feasibility in each. With partnerships established in Western Australia, Victoria, Queensland, Tasmania and the Northern Territory, the National Health and Medical Research Council (NHMRC) and Lowitja Institute-funded project focuses on the provision of clinical genetics and genetic counselling, and service delivery gaps in the provision of these services and the continuity of care. It assesses the quality, acceptability and effectiveness of these models, through evaluative interventions, focusing on the needs required for effective service provision to Indigenous Australians. This is a workforce development project, with the evidence building capacity in the health service delivery workforce including training for Indigenous health workers in the provision of equitable clinical genetic services.

- **Funding:** Lowitja Institute and NHMRC
- **Grant term:** ongoing from 2019

- **Principal investigators:** led by Professor Margaret Kelaher with Angelina Ferdinand, Joanna Luke and Philippa Dalach

Population Variation Project

This ongoing National Centre for Indigenous Genomics (NCIG) project is well underway after having investigated genomic variation within and between Indigenous communities, including comparisons of the amount of variation when compared to that within and between other populations, and variations that might be associated with disease or conditions.

- The amount of genomic variation *within* Australian Indigenous communities is slightly less, overall, than most populations in Europe and Asia. Variation in populations in all three places is substantially less than in African populations.
- Approximately 25 per cent of all DNA variants in the genome of an Australian Indigenous person are unknown in people from outside Australia.
- Of the Indigenous-specific variants, approximately 40 per cent are likely to be found in a single region or community.

The project aims to establish a database as a resource for use by researchers and clinicians. Further sequencing will continue over 2020 (NCIG 2019). The study design includes:

- studying engagement with Indigenous communities in New South Wales
- training and employing Aboriginal staff for recruitment, consenting, enrolment and collection
- creating a reference genome.

The reference genome's detail will be enhanced by including the genomes of up to 500 Indigenous Australians to account for population variation, with a program in place to continue well beyond this number (NCIG n.d.).

- **Funding:** $500,000 grant from BioPlatforms Australia
- **Grant term:** ongoing from 2017
- **Principal investigator:** led by Professor Simon Easteal from NCIG with Bioinformatics Lead Dr Hardip Patel and PhD students Mr Tim McInerney and Mr Renzo Balboa in collaboration with A/Professor Stephen Leslie and Dr Ashley Farlow (University of Melbourne) (NCIG 2018)

Aboriginal and Torres Strait Islander Genome Project

This NCIG project aims to develop an Indigenous Australian reference genome or genomes to account for high levels of difference among the communities, possibly requiring multiple reference sequences from different regions. This proposal is to develop a roadmap for how the outcomes of this research can be developed for incorporation in the pan-human reference graph.

The project will address quality and data/metadata standards, data curation, methodological and analytical, hosting and Indigenous governance requirements, validation and documentation systems, proficiency testing, staffing, training and education requirements, participant involvement, accessibility, national coordination and international engagement (NCIG 2019).

- **Funding:** $1.4 million NHMRC Project Grant
- **Grant term:** 2018–20

Trails of migration out of Africa in harmful mutations of the First Peoples

This project aims to use genome-wide association studies (GWAS) to identify harmful mutations specific to Aboriginal Australians and related to the out-of-Africa diaspora around 100,000 years ago. The idea is to better understand ancient mutations associated with various genetic diseases (GrantConnect n.d.b).

- **Funding:** Australian Research Council Grant of just over $400,000
- **Grant term:** 22 February 2018 – 21 February 2021
- **Principal investigator:** University of the Sunshine Coast

Adaptation and diversification of the First Peoples of Sahul

This project aims to further advance work on the genetic history of Indigenous Australians and Papuans that has revealed that Aboriginal Australians have inhabited a variety of diverse and challenging environments for approximately 50,000 years (Malaspinas et al. 2016). Using novel techniques for extraction of human DNA from soil and the use of cutting-edge graph-based methods, hundreds of Indigenous Australian and Papuan genomes will be analysed. This project expects to generate new knowledge by filling in the gaps in the Australian genetic record via ancient human DNA from sediments. Expected outcomes from this project are producing a detailed picture of genomic adaptation in Indigenous Australians and Papuans and creating a comprehensive genetic history of the First Peoples of Sahul.

- **Funding:** Discovery Early Career Researcher Award of $390,000
- **Grant term:** 20 June 2019 – 30 June 2022
- **Principal investigator:** Dr Raymond Tobler (University of Adelaide)

Genetic variants introduced by Europeans and other groups into the genomes of the Aboriginal Australian population

This project aims to examine the genetic variants introduced by Europeans (and other groups) into the genomes of the Aboriginal Australian population. The rate of metabolic diseases such as diabetes and hypertension is very high in Australia's Indigenous populations. While an energy-rich Western diet has been suggested as the major cause, the contribution of genomic variants (mutations) remains unclear. Anticipated outcomes are better understandings of both the benign and deleterious variants (McEvoy et al. 2010).

- **Funding:** Linkage Projects grant of $178,464
- **Grant term:** 2016–23
- **Principal investigator:** Dr Subashchandran Sankarasubramanian, Professor David Lambert, Professor Adrian Miller, Dr Michael Westaway, Dr Ruiqiang Li (Griffith University)

Aboriginal Heritage Project

The South Australian Museum holds more than 5000 hair samples, matched to linguistic records and anthropological and archaeological data, gathered from Australia's Indigenous peoples, including Torres Strait Islanders, over the course of 52 SA Board for Anthropological Research expeditions, including to 86 different communities between 1925 and 1971.

The research (University of Adelaide n.d.) will use specimens, linguistic records, and anthropological and archaeological data to piece together a genetic map of Australia that will:

- allow Aboriginal families to trace regional ancestry with Australia when oral or written records may fail
- reconstruct personal and family genealogical history prior to the arrival of Europeans
- assist people from the Stolen Generations, and others, with reunification and/or identification of family origins
- reconstruct migration patterns within Australia
- facilitate repatriation of Indigenous cultural items and human remains held at museums in Australia and overseas.

The project aims to establish itself as a permanent service to Aboriginal Australians through help from additional funding bodies and corporate support.

- **Funding:** funded by the Australian Research Council Linkage Grant scheme with additional financial support from partner organisations: Australian Genome Research Facility and the National Geographic Society. Other support is provided by Bioplatforms SA, the Wellcome Trust Sanger Institute and the Harvard Medical School.
- **Grant term:** three years, commenced late 2015, but with the intention to run for more than a decade.
- **Principal investigators:** The University of Adelaide, Professor Alan Cooper and Dr Ray Tobler, The Australian Centre for Ancient DNA, School of Biological Sciences, leading a national and international team of 15.

Investigating the evolution of innate and adaptive cellular immunity

The researchers aim to assess the impact of geographical and genetic isolation of the Australian Indigenous population on adaptive and innate immune systems. The project will use novel DNA sequencing approaches to generate the high-resolution sequences of two genetic loci that regulate innate and adaptive immune responses, the major histocompatibility complex locus and the killer cell immunoglobulin-like receptor locus. In an initial screen, distinct variants and combinations of these genes were identified. This project aims to interrogate how variation in these critical genes impacts on the function of cytotoxic lymphocytes, providing insights into the evolutionary drivers of immune recognition mechanisms [Abstract] (Research Data Australia n.d.a).

- **Funding:** Australian Research Council Discovery Projects, $361,000 grant
- **Grant term:** 2019–22
- **Principal investigators:** Professor Katherine Kedzierska, Professor Andrew Brooks, Dr Liyen Loh, Dr Paul Norman (University of Melbourne)

Additional research projects influencing Australian Indigenous genomic initiatives

The hypothesis that mitochondria – with their own DNA – began millennia ago as independent entities in a microbiota-like relationship with early cellular life, only to be absorbed into the very fabric of the cells over time, demonstrates that the kin relations of human beings and microbiota – the micro and macro ecologies – are ancient and *concrete* (Archibald 2015).

In order to identify and characterise human microbiota, the Human Microbiome Project (USA) was launched in 2007 to facilitate genomic sequencing of its component organisms (Turnbaugh et al. 2007). A stage 2 Integrative Human Microbiome Project was launched in 2014 to attempt to understand the roles of the various microbiota in health and disease states (Proctor et al. 2019). But

for now, the relationship between the biome and the genome is just 'coming into view' (Goodrich et al. 2017), although the following is relatively clear:

- the microbiome is heritable, assembled at birth, and it develops with its host
- the microbiota is greatly influenced by environmental factors, with the impact of diet on gut microbiota being of interest to researchers (Goodrich et al. 2017).

The Human Microbiome Project is challenging what it characterises as 'artificial barriers between medical microbiology and environmental microbiology' – in other words, the connections between the microbiota, counterpart organisms living in the environment and the environment itself (Turnbaugh et al. 2007:804). The project also reports significant place (or environment)-based microbiota variation in relation to human beings (Thursby & Juge 2017).

Biome–genome interactions are only just beginning to be understood. As a starting point, research to date suggests the genome is likely to play a role in promoting a beneficial microbiome (e.g. see Eisenstein 2020). Studies of the heritability of gut microbiotas have revealed a subset of microbes whose presence is partly genetically determined by the host (Goodrich et al. 2017). Further associations have emerged that appear consistent between human populations and so could be understood to transcend environments (Karl et al. 2018).

Douglas, Bielawski and Langille (2020) have modelled the microbiota as 'environment', with a focus on gene and microbiota-as-environment interactions. This is largely to help explain the 'missing heritability' challenge – that genetic variations in isolation do not account for a wide range of phenotype heritability. In fact, it has long been surmised that actors/processes other than genes in isolation play a significant, if not determinative, role in whether otherwise inherited genes express themselves as phenotype.

Of potential interest to researchers is the relevance of historical, millennia-old Indigenous diet–biome–genome interactions and adaptations to the health of Indigenous populations today. A research agenda could focus on whether contemporary Indigenous populations that have inherited these historically positive adaptions might now be at a disadvantage because of them. The point is to be armed with the span of knowledge needed to understand and effectively treat so-called 'mismatch diseases' that occur when otherwise adaptive responses between genes, microbiota, place and food become vulnerabilities in the face of rapid, uncontrolled changes. This was a consideration for Redvers et al. (2020:2), who observed:

> Colonization continues today through Western modernity with a mismatch occurring between differing environments (i.e., traditional vs modern) through forced relocations, destroyed traditional lands, and loss of access to traditional foods… These events and processes consequently have detrimental effects on Indigenous health (e.g., higher rates of inflammation, toxic exposures and diabetes [references omitted].

The idea of mismatch is echoed by Chris Lee, Manager of Aboriginal and Torres Strait Islander Engagement, Diabetes Australia, in a specifically Australian context:

> If you have diabetes basically it's not your fault. It's in your genetics… Before whitefellas came, us mob were active every day… We never knew about diabetes.
>
> For centuries our bodies got used to a certain diet and way of life… our bodies were physically adapted to this way of life…
>
> The first case of diabetes in an Aboriginal person showed up in 1923. That's in the time of our parents and grandparents. Now, with fewer of us living a traditional lifestyle, and

> more of us being exposed to the whitefella world… our once-efficient metabolism may now be acting against us. The genetic make-up that enabled us mob to survive when food was scarce may now be a big disadvantage, encouraging weight increases, diabetes, and associated conditions such as high blood pressure and heart disease. (IAHA 2020)

Summary of key points

In this section, we have reviewed research projects that advocate for the inclusion of currently under-represented Indigenous and other minority population groups in genomics research, in recognition that the DNA variants between people and populations differ and inclusivity promotes equity (Easteal et al. 2020). Significant effort is required to build evidence and reference data so that Genetic Clinical Services (GCS's) can bring significant clinical benefit for Aboriginal and Torres Strait Islander peoples by leveraging genomics into medicine and health care systems for the benefit of all Indigenous Australians. Further works demonstrate a continuous genetic cline between Oceania and European groups and a substantive gene flow between Indigenous peoples in India and Australia, further cementing our place and contribution to the original Indigenous Estate (Hopkins et al. 2019).

Research projects that are being, or could be, translated to enhance clinical genomics services

This section considers clinicians and health services that currently deliver clinical genomics services specifically designed for and targeting Aboriginal and Torres Strait Islander people, and/or projects that aim to improve Aboriginal and Torres Strait Islander access to health genomics services, including education and training to support an Aboriginal and Torres Strait Islander genomics workforce. The summaries of these projects identify that Aboriginal and Torres Strait Islander people are concerned with issues pertaining to handling, treatment and ownership of tissue and knowledge gained from specimen analysis because of the strong connection to ancestors and traditional lands, and view biologic specimens as inseparable from these things (Aramoana & Koea 2020).

Indigenous peoples are increasingly becoming experts in genomics, bioethics and policy, and are well versed in facilitating discussions and arriving at consensus on issues such as those required to lead research in genomics. While most of the workforce is currently focused on reducing health care disparities and improving diagnostic success for families with rare illnesses, more could be done to unite Indigenous workers who are leading on-Country based microbial community work to compare and develop initiatives that combine and promote a response to metagenomics from within the Indigenous Estate. This will require further work to be done with Traditional Owners, entrepreneurs, business owners and others who are interested in framing our Indigenous selves and our responsibilities in narratives of prosperity and hedonistic sustainability[8] as necessary for thriving in the Anthropocene.

The national strategy will need to balance current genetic workforces with the emergence of ecologically based genetic workforces. Current genetic workforces include genomic policy makers, practitioners, clinicians, genetic counsellors, bioinformaticians and other scientists who improve access to, and the effectiveness of, genetic diagnosis for disorders. Vehicles such as Indigenous-led

8 Silveira (2015) explains that 'Hedonistic means to engage in the pursuit of pleasure… and sustainability means, well, a lot of things nowadays, but according to the [United Nations], it means, to be able to provide a "decent standard of living for everyone today without compromising the needs of future generations"'.

governance, community engagement, community education and professional training, improved access to precision medicine, the development of First Nations variant libraries and understanding the economic impacts of this work will be key in the development of genomics workforces under this national initiative, but not enough. We also need to engage ecologists, environmental scientists, park managers, environmental advocates and young people who are invested in building our knowledge of community values and perceptions of the natural environment.

Ultimately, what is required is a harmonisation of ecological, economic and societal values to conserve the integrity of health microbial, ecological and human communities. This will be a precedent-setting initiative, but in line with our roles and responsibilities in caring for, and progressing the interests of, the microbiota on the 50-plus per cent of the land mass of Australia that is led by Aboriginal and Torres Strait Islander people and will manifest Indigenous interests now and in future.

Achieving equity in genomic health for Indigenous Australians

The aims of the project are to increase and ensure the benefits of genomics for Indigenous Australians by improving support for equity at both a health service and health system level (GrantConnect n.d.c). The project will achieve this by:

- co-designing and implementing measures to improve the extent to which provision of genomic health services meet the needs of Indigenous Australians
- evaluating the impact of the measures on the accessibility, availability, affordability and acceptability of care
- conducting a policy analysis to identify actions at a health systems level that will ensure the provision of genomic health services will continue to meet the needs of Indigenous Australians as the field continues to develop.
    - **Funding:** Medical Research Future Fund grant of just under $500,000
    - **Grant term:** 30 June 2020 – 30 June 2023
    - **Principal investigator:** Professor Margaret Kelaher (University of Melbourne)

Genomic architecture of chronic disease in Australia's First Peoples

Chronic kidney disease is reported at particularly high rates among the Tiwi people of Bathurst and Melville islands off the Northern Territory coast. In this study by Queensland University of Technology (QUT 2020), whole genome sequencing will be employed to understand the Tiwi people's genetic links to chronic kidney disease and associated conditions such as diabetes, cardiovascular disease and high blood pressure. The study includes a research translation element.

- **Funding:** $1.6 million Medical Research Future Fund (MRFF) Genomics Health Future Mission
- **Grant term:** three years (announced 6 May 2020)
- **Principal investigator:** Dr Shiv Nagaraj (Advance Queensland Research Fellow at the Queensland University of Technology's Institute of Health and Biomedical Innovation) heads a multidisciplinary research team including Professor Wendy Hoy (project co-lead) and Dr Aideen McInerney-Leo (University of Queensland); Dr Brendan McMorran (Australian National University); Dr Ryan Taft (Illumina Inc., USA); Professor Cheryl Winkler and Dr Jeff Kopp (National Institute of Diabetes and Digestive and Kidney Diseases, USA); Professor Graeme Suthers (Sonic Genetics); and Dr Rohit Gupta (IIT, Chennai, India)

Understanding and overcoming cardiovascular and diabetes inequalities in Indigenous Australians

The South Australian Health and Medical Research Institute's Cardiometabolic Disease Research Program (Research Data Australia n.d.b) aims to understand the burden, causes and consequences of heart disease, diabetes, cancer and mental illness among Indigenous peoples from population levels through to an individual biological and genetic level. Further, it aims to clarify the factors driving disparities in cardiovascular disease and diabetes risk, disease and mortality, and develop interventions that improve the management and prevention of chronic disease among Indigenous Australians.

- **Funding:** NHMRC Research Fellowship grant of just over $700,000
- **Grant term:** 2018–22
- **Principal investigator:** Dr Alex Brown (University of South Australia)

Our MOB (Our Mind Our Brain) dementia prevention across the life course with Aboriginal Australians

Neuroscience Research Australia continues to conduct a longitudinal Koori Growing Old Well Study, which has already shown that Indigenous Australians are affected by dementia prevalence at three to five times higher rates than non-Indigenous Australians across remote, regional and urban communities.

Announced in 2018, the Our MOB (Our Mind Our Brain) research project engages with partner Aboriginal communities and organisations in New South Wales to (1) investigate the underlying causes of dementia in Aboriginal peoples in Australia, along with the prominent life course social and biomedical risk factors for dementia, (2) translate these findings into implementation of a healthy ageing program that has been co-developed with older Aboriginal people, and (3) identify priorities and strategies for future dementia prevention in young Aboriginal people. The research includes genomic research focusing on the already identified association between late-onset Alzheimer's disease and variations in a gene called apolipoprotein E (or APOE) (pers. comm., Karabena Consulting discussion with Dr Kylie Radford, 15 October 2020).

- **Funding:** NHMRC grant funding of just over $3 million
- **Grant term:** 2018–ongoing
- **Principal investigator:** University of NSW with Neuroscience Research Australia – Dr Kylie Radford with A/Professor Kim Delbaere, Mr Darryl Wright, Professor Brian Draper, Professor Gail Garvey, Professor Olivier Piguet, Professor Perminder Sachdev, Professor Robert Cumming, Professor Gerald Broe and Professor Michael Fulham

Translating molecular research into clinical applications to control scabies

To improve scabies management and surveillance, and to attempt to combat this highly contagious disease, basic scabies biomedical research will drive the development of new diagnostics and therapeutics. It will aim to understand mite biology, scabies pathogenesis and the mechanisms underlying the three-way interactions of mites, bacteria and skin immunity. The team will collaborate with Aboriginal health professionals and Aboriginal communities, as well as experts in genomics, bioinformatics, enzymology, dermatology and drug discovery (GrantConnect n.d.d).

- **Funding:** NHMRC grant of just under $725,000
- **Grant term:** 1 January 2019 – 31 December 2023
- **Principal investigator:** QIMR Berghofer Medical Research Institute

Contribution of carbohydrate metabolism to the maintenance of endemic streptococcal pathogens

Group A streptococcal (GAS) bacterial infections within the Indigenous populations of Northern Australia are among the highest in the world. This project uses genomic analysis, mathematical modelling and experimental evolution to improve our understanding of the role that bacterial recombination – the transfer of genetic material between organisms – plays in the evolution of pathogenic GAS [Abstract] (GrantConnect n.d.e).

- **Funding:** NHMRC grant of $480,788
- **Grant term:** 1 January 2019 – 31 December 2021
- **Principal investigator:** University of Melbourne

Towards a diagnostic test for rheumatic fever

Acute rheumatic fever (ARF) and rheumatic heart disease (RHD) are a major problem for Australian Indigenous people. Accurate diagnosis of ARF allows for early preventive therapy with long-acting penicillin, which can prevent RHD from developing or worsening. This study aims to recruit a cohort of children and young people with ARF and apply the latest technologies to their blood samples, with the aim of developing a diagnostic test and open leads for potential new treatments.

- **Funding:** NHMRC grant of just under $2,150,000
- **Grant term:** 2018–23
- **Principal investigators:** Professor Jonathan Carapetis (Principal investigator), A/Professor Anna Ralph, Dr Anthony Bosco, Mr Glenn Pearson, Mr Mark Mayo (University of Western Australia)

Risk factors for diabetic retinopathy and its treatment

This research focuses on optimising treatment for diabetic retinopathy and diabetic macula oedema, which contribute significantly to rates of vision loss worldwide (Gale et al. 2017). It investigates whether genetics play a role in the development of this disease so we can develop a personalised approach to treatment. It also explores whether there are risk factors for poorer response to current treatment, and whether a new drug (Ozurdex) is a better alternative in remote communities.

- **Funding:** NHMRC postgraduate scholarship of just over $75,000
- **Grant term:** 2018–20
- **Principal investigator:** Flinders University of South Australia

Towards the elimination of tuberculosis and rheumatic heart disease in Northern Australia and our region

This research program addresses tuberculosis and rheumatic heart disease, which are leading challenges for Northern Australia and our region. Both are diseases caused by infections with long-term complications. They cause illness and death in young Aboriginal people and neighbouring South East Asian populations. There are many gaps in our ability to effectively detect and prevent these diseases. This research targets these gaps, from cutting-edge science to translation of guidelines into practice [Abstract] (Research Data Australia n.d.c).

Funding: NHMRC Career Development Fellowship grant of just over $265,000

Grant term: 2018–21

Principal investigator: – Dr Anna Ralph (Menzies School of Health Research)

Models and quality of genetic health services for Aboriginal and Torres Strait Islander people

This NHMRC-funded Better Indigenous Genetic Health Services 2015–2019 project, which is led by Professor Margert Kelaher in partnership with The Lowitja Institute, provides an example of the development of service models for the delivery of precision medicine in Australia. The project is yet to publish findings but the methodology is suggestive, as extracted from publicly available materials:

- Phase 1: understanding current models of care – through key informant interviews and patient journey mapping, the research team will identify the genetic service needs of Aboriginal and Torres Strait Islander people and assess the extent to which existing models meet these needs
- Phase 2: evaluate the performance of model of genetic service provision in the Northern Territory and Western Australia – the research team will compare the quality and acceptability of care and follow-up between 2009 and 2016 in the Northern Territory and Western Australia (a new model of coordinated care was introduced in 2014 in the Northern Territory)
- Phase 3: development of training and resources – the research team will answer the following questions: What is the local genetic health service capacity? What elements are required in order to build a good/comprehensive follow-up service? What skills or training do people need? How can this be established in a sustainable way? In answering these questions, a series of training modules will be developed to support the sustainable implementation of the project outcomes.
- **Funding:** NHMRC $710,240; and Lowitja, $382,472. Funded by Lowitja Institute and NHMRC, and partner organisations Machado Joseph Disease Foundation, Northern Territory Department of Health, Genetic Services Western Australia, Office of Population Genomics Western Australia, Department of Health and Genetic Health Queensland, University of Melbourne
- **Grant term:** 2015–19
- **Principal investigator:** Professor Margaret Kelaher (Project leader), A/Professor Gareth Baynam, Professor Emma Kowal, Professor Hugh Dawkins, Professor Ravi Savarirayan (Participant), Professor Yin Paradies, Professor Gail Garvey, Dr Misty Jenkins

Pharmacogenomics

Modern health care significantly involves the matching of diagnosed conditions to what are presumed to be safe and effective medicines. A doctor may subsequently modify dosage, or even abandon a treatment, in response to lack of effect or to side effects or adverse reactions, but the approach is essentially a ‘one size fits all’ approach with risk mitigated by monitoring patient reactions. But genetic determinants are now known to detrimentally effect the use of medicines on individuals. Examples already in use include:

- Abacavir, which is approved in Australia for the treatment of patients with HIV; because around 5 per cent of patients with a gene called HLA-B suffer a potentially fatal hypersensitive reaction to this medication, genetic screening is increasingly a part of medical assessments (NHMRC 2013)
- thiopurine medications such as azathioprine, which are used for the treatment of leukaemia, rheumatoid arthritis and inflammatory bowel disease, because about 10 per cent of patients have a TPMT (thiopurine methyltransferase) gene, which places them at risk of severe side

effects; after genetic screening the starting dose of thiopurine medications is usually reduced in such patients (NHMRC 2013).

Pharmacogenomics – the study of how genes affect a person's response to medicines – is an important part of precision medicine as it applies to individuals but also to precision public health. This is because adverse reactions to medicines can be generalised to racial groups, with implications for Indigenous peoples in Australia.

As Rae, Grimson and Pringle (2017) describe, an example is in relation to renin-angiotensin system (RAS) blockers prescribed for hypertension (high blood pressure). Already in the United States, RAS blockers have been demonstrated to be effective in Caucasian-American cohorts, but less effective in African-American populations, with the differences attributed to fatty acid metabolism and other potentially genetically determined factors. As a result, a modified treatment regime is proposed for African–Americans (Rae, Grimson & Pringle 2017).

Research on two Aboriginal populations in Australia also indicates that Indigenous genetics at the population level (Moscovis et al. 2014) may mean the effectiveness of RAS is significantly different to that found in Caucasians (Lester et al. 1999), suggesting equally that modified treatment, or alternative treatment, regimes may be required.

This is critical information given that the Australian Institute of Health and Welfare (AIHW 2020a) has estimated that hypertension was responsible for 5 per cent of the Indigenous burden of disease and 8 per cent of the health gap between Indigenous and non-Indigenous Australians in 2011. High blood pressure contributed to 64 per cent of the burden due to hypertensive heart disease, 61 per cent of the stroke burden, and 37 per cent of the coronary heart disease burden (AIHW 2020a). As such, getting this and other treatments right at the Indigenous population level will be critical to closing the health gap. It is otherwise critical to ensure that the Indigenous peoples of Australia are not being deprived of the full value of clinical care due to pharmacogenetic differences.

Growing an Indigenous genomics workforce

In developing a 21st century genomics workforce, several factors need to be considered for inclusion in the Australian Indigenous Metagenomics Strategy. The first is a set of principles to reflect and respond to the needs of a diverse human population. National and international efforts have seen an increase in the number of individuals from under-represented backgrounds who can access, and are supported to pursue careers in, genomics. Diversity-enhancing strategies and programs will be key not only to populate biomedical, clinical, behavioural and social sciences research enterprises but to ensure effective engagement of individuals who are representative of the needs of populations with disabilities, of women and of Traditional Owner groups with a responsibility to care for Country and the microbiota of our land holdings. There are enormous career opportunities in current genomics strategies embedded in and across different disciplines, but new and emerging workforces will be needed to fully realise all anticipated advances in this field.

This section of the report considers the research and workforce endeavours being catalysed in this field, and the opportunities to grow and scale the genomics workforce needed to implement the Australian Indigenous Metagenomics Strategy.

Lessons learned

As a result of thematic analysis of survey responses following a rheumatic heart disease genetic project, Tong et al. (2020) identified the following recommendations:

- strong and ongoing community engagement is paramount
- plan for a lengthy engagement, informed consent and recruitment process
- borrow on the strengths of Indigenous understandings of the basic principles of genetics and genetic research, and their enthusiasm to learn more
- Aboriginal leadership should be visible across every line: consider forming an Aboriginal Governance Committee with the right to veto
- ensure clear, regular and ideally face-to-face communication among multidisciplinary teams
- a formal staged process of study development provides space for achieving milestones before embarking on the next stage, and should include planning for post-project data storage and access.

The proposed national umbrella authority would have a clear role in supporting the emergence of these collective humancentric and ecological workforces with career paths, ongoing mentoring and coaching supports, and could consider the facilitation of communities of practice to guide these workforces. Consideration will need to be given to the length of time advocated for to engage community people respectfully, and in developing and enhancing literacy and reviewing the fresh new approach to the development of a coherent, precedent-setting research and development agenda focused on emancipation rather than illness.

Much has been done to support the emergence of these workforces. However, an enduring feature of this effort will necessarily seek long-term and sustainable investments in developing people's skills and capacities to work in a complex and sensitive area. One such national example is that of the Cooperative Research Centre in Aboriginal Health (which became the Lowitja Institute). After 20 years of investment in developing an Indigenous research workforce, there are a significant number of professors, researchers, lectures, supervisors and mentors who have united with other Indigenous researchers around the world. Our Indigenous health researchers have challenged the status quo in universities, gained considerable investment and support, and have been respectfully disruptive in institutions that until a few decades ago were denied to us until our rights to a continuing education progressed.

A national policy position that led to this generational shift in higher education was that we could participate in higher education for free, without a resultant personal tax debt. Additional considerations about the socio-economic position of Aboriginal and Torres Strait Islander people needs to be considered in developing a workforce across ecological, social and economic systems to progress our prosperity. A national authority could advocate for the right to develop this workforce without acquiring a personal debt, understanding that there are rights and responsibilities that we have to our Country, our First Nations and our Australian nation into the 21st century.

Underpinning the development of this workforce are considerable consent issues that highlight legal and ethical attributes and challenges of dynamic consent in these contexts (Prictor et al. 2020). Discussions with landowners, Traditional Owner groups and others involved in negotiating outcomes for Country (including negotiating native title, partnerships with multinational corporations, progression of workforces in mining and the work of IgNITE (Johnston 2020) in establishing Indigenous interests in Australia's free trade agreements across continents) could cross-fertilise the development of these complex but necessary processes for progressing our prosperity and building our capacity to resolve issues of diversity in our lived experiences and workforce development practices. Again, a national umbrella organisation could lead these cross-disciplinary discussions and harness the collective knowledge from First Nations engagement and participation in workforces,

and could strategise legal issues and how to control and express local knowledge and data while developing collective best practice approaches to meaningful and longitudinal individual and family participation in becoming part of the Australian Indigenous metagenomics workforce.

Locally led initiatives

WA Health has appointed two fulltime-equivalent Aboriginal Community Health Workers as entry point positions to partner with genetic counsellors and health services and support community access to treatments for genetic and rare diseases (project stakeholder interview, Gareth Baynam).

Over the past decade WA Health has implemented a coordinated suite of initiatives to improve Aboriginal genetic health care delivery through multi-stakeholder partnerships, including the Aboriginal Health Council of Western Australia (the peak body for Aboriginal Community Controlled Health Services (ACCHSs) in the state), the Aboriginal Health division of WA Health, and community organisations and research organisations (Government of Western Australia 2017). Outcomes include Australia's first clinical genetic counselling position for ACCHSs, an Aboriginal Cadetship in Genomic Policy, and an Aboriginal Cadetship in genetic and rare diseases and birth defects supported by a Precision Public Health Fellowship in Rare and Undiagnosed Diseases (project stakeholder interview, Gareth Baynam).

WA Health is also clinically implementing Australia's first Aboriginal genomic reference data for public health system use (applied to rare diseases and transfusion) and co-designing the first stage of culturally endorsed clinical educational aids specifically for clinical service delivery using Aboriginal narratives (project stakeholder interview, Gareth Baynam).

National initiatives

The proposed Indigenous-controlled institution could lead activity in metagenomic workforce training, in a similar way that the Australian Indigenous Doctors' Association led the development of the LIME Network to successfully reach population parity in Indigenous medical school enrolments over the past decade until 2020.[9] A strategic approach might include adaptation of existing scholarship programs to support Indigenous applicants, or a separate stream of scholarships overseen by the proposed institution. The American Indian Science and Engineering Society provides an international example of a similar institution working in this area. This is a non-profit professional association with the goal of substantially increasing the representation of American Indian, Alaskan Native, Native Hawaiian, Pacific Islander, First Nations and other Indigenous peoples of North America in science (among other areas), including the disciplines that comprise metagenomics in the United States.[10] (See Gap 4 in Chapter 5 for further discussion.)

To understand the current landscape of Indigenous Australian genomics education, we suggest mapping the current Indigenous education landscape. Much of our 'in-scope' work targets workforces developed in response to rare diseases, local health care system needs and new technologies rather than a strategic approach to genetic or genomic education. McClaren et al. (2018) wrote a technical report that mapped the existing educational and training for the Australian Clinical Genomic Workforce but did not include the development of a specific Indigenous workforce. As advocated for in this report, however, this approach focuses on human health and wellbeing to

9 For more information about the LIME (Leaders in Indigenous Medical Education) Network, see the Network's webpage (https://www.limenetwork.net.au/).

10 For more information about the American Indian Science and Engineering Society, see the Society's webpage (https://www.aises.org/).

the detriment of Aboriginal and Torres Strait Islander leaders engaged in on-Country genetically based initiatives, including agriculture, food production and commercialisation of naturally sourced fibres. The workforce component of the Australian Indigenous Metagenomics Strategy could be developed in concert with the Aboriginal and Torres Strait Islander staff at the CSIRO as part of the Australian Microbiome Initiative – a continental-scale, collaborative project aspiring to characterise the diversity and ecosystem service provision of the micro-organisms inhabiting natural Australian ecosystems (Australian Microbiome n.d.).

The CSIRO has a robust Reconciliation Action Plan (CSIRO 2019) and has invested in an Indigenous co-designed strategy to facilitate greater engagement between Western science and Indigenous science, producing such resources as the CSIRO Biodiversity Book (CSIRO n.d.), which features Indigenous concepts that connect people to their Country and to living things, and shares science knowledge that addresses the declines in Australia's biodiversity and engages with protected areas, farming, pastoralism and forestry, seas and coasts and inland waterways.

Specific initiatives

Australian experts have recently reported on 'precision psychiatry', stating that Australian psychiatry has yet to see the fruits of new diagnostics and therapeutics that have become routine in other medical fields (Williamson et al. 2018:59). As they become available, these benefits should be equitably accessible to Indigenous peoples in Australia.

Consumer engagement and education activities

Community engagement and outreach activities come in many forms: integrating key genomics terms in local languages, addressing the community priority areas, research translational activities, genomics governances and Indigenous leadership on these issues are particularly relevant for the development of a Australian Indigenous Metagenomics Strategy.

Epigenetics and Indigenous Australia

This project aims to investigate how epigenetics is being received by Indigenous Australians nationally and to identify the risks and opportunities that narrative of biosocial damage entails. The aim of this project is to support Indigenous health and epigenetics to make well-informed decisions of this new science.

Funding: $348,000.00

Grant term: commencement year, 2019

Principal investigator: Lead Investigator, Professor Emma Kowal (University of Tasmania)

Metagenomic literacy

To establish a precision medicine service, doctors and health care staff in contact with patients should be genomically/metagenomically literate enough to know when to order tests, how to interpret results to inform clinical decision making, how to counsel patients, how to obtain informed consent before a test or procedure, and how to ensure understanding and appropriate action following a test result or procedure.

In an Australian first, Queensland Genomics has released a set of guidelines – *Genomic Partnerships* – to help genomic health researchers work with Aboriginal and Torres Strait Islander communities in a way that respects cultural protocols (QIMR Berghofer 2019). The guidelines set out

a detailed framework for engagement in relation to research and precision medicine in Indigenous communities.

There is a need to promote metagenomic literacy across Indigenous communities, with a focus on Elders and community leaders, so they can understand and promote the value of metagenomic approaches. (Metagenomic Elders Camps were suggested to us in the course of our work because the role of Elders is critical to ethical research in our communities.)

An example of this already operating in Aotearoa New Zealand, Canada and the United States is the Summer Internship for Indigenous peoples in Genomics (SING) program. In Aotearoa, SING supports Māori understanding of genomics and brings them into conversation with renowned New Zealand and international geneticists in week-long residential internship programs to provide 'participants with knowledge and experience in wet-labs (biological samples, DNA), dry labs (computer analysis, biostatistics) and simulation labs (cultural and ethical scenarios)' (SING n.d.). SING is promoted in Australia by Professor Emma Kowal.

Intergenerational experiences of trauma

Research into the population health effects of population-wide potentially traumatic events (PTEs) during preconception builds on research among the children of Holocaust survivors (Rakoff 1966; Solomon, Kotler & Mikulincer 1988), survivors of the Armenian genocide (events occurred in 1915) (Azarian-Ceccato 2010; Karenian et al. 2011), residents of the occupied Palestinian territories who had experienced invasion (from 1966), Vietnam War veterans (–1975) (Ancharoff, Munroe & Fisher 1998; Harkness 1993; Rosenheck & Nathan 1985; O'Toole et al. 2017), Cambodian genocide survivors (–1979) (Field, Muong & Sochanvimean 2013; Münyas 2008) and Rwandans genocide survivors (1994) (Roth, Neuner & Elbert 2014). Among all these populations, preconception trauma in both parents was evidenced by trauma effects in their offspring, although non-biological secondary transmission (as above) has usually been proposed to explain this.

In Australia, the evidence for such transmission is striking, particularly among the children of the Stolen Generations who have been found to have significantly higher rates of emotional or behavioural difficulties than counterpart non-removed children. In particular, the Western Australian Aboriginal Child Health Survey (Zubrick et al. 2005) was a large-scale survey into the health and wellbeing of 5289 Western Australian Indigenous children aged 0–17 years. It included a significant cohort (about 25 per cent of the total) of children whose parents/primary carers had been forcibly removed, and a comparator cohort of children raised by parents/primary carers who had not been removed. Comparing the two cohorts, the children whose parent/primary carer had been forcibly removed from their natural family were found to be 2.34 times more likely to be at high risk of clinically significant emotional or behavioural difficulties than children whose carers were not forcibly separated (Zubrick et al. 2005). While the parent/primary carer aggregation provides the basis for further clarification as to biological as opposed to secondary traumatisation pathways, disaggregation of the data is apparently yet to occur.

Apart from mother to child intergenerational transmission, noteworthy considerations of the possibilities of the transgenerational transmission of trauma effects – from grandparent to parent to child and then onwards – have occurred in recent decades. Among these, Post Traumatic Slavery Syndrome has been proposed in the present-day United States descendants of enslaved African people. Slavery as a practice formally ceased in 1861 and it is proposed that transmission of trauma effects has occurred through several pathways into the contemporary population (although the

confounding impact of subsequent PTEs and racism – see below – must also be considered when considering the transmission of trauma effects from events that occurred 150 years ago to today (DeGruy 2005) and relevance in Australia to the descendants of Indigenous people effectively enslaved during the colonial era.

Among Indigenous peoples, proposals of colonisation-originated trauma being transmitted to the present day have also been made for contemporary United States (Evans-Campbell 2008) and Canadian (Pearce et al. 2008) populations, and some among the Māori of Aotearoa New Zealand (Pihama et al. 2014). In Australian frontier events, war and attrition, massacres and so on are the first events to consider in this light. Beginning in the Sydney region in the 1790s, such events were occurring in the more remote Kimberley, Western Australia, and Northern Territory regions until *at least* the 1920s (Schubert 2018) – traumatically impacting the grandparents of many Indigenous people living today, with subsequent traumatisation by dispossession from millennially occupied territories and lands, and incarceration within the reserve and mission system (in conjunction with the Stolen Generations practices) outlined in this report.

Healing our past by nurturing our future

The goal of this project is to promote healing for the parent and prevent inter-generational transmission of trauma to the child. This project aims to assess the acceptability, validity, safety and feasibility of *recognising* and *assessing* Aboriginal parents during the perinatal period (from pregnancy to two years after birth) to identify those experiencing complex trauma, and develop acceptable, safe and feasible awareness and support strategies that could be offered during the perinatal period to support Aboriginal parents experiencing complex trauma. Researchers and collaborators on the project expect positive outcomes of the project to include:

- identifying relevant services and key stakeholders and forming a 'community of practice'
- developing protocols to create a culturally and emotionally safe research environment for staff and parents who have experienced complex trauma
- using research findings to identify evidence gaps
- developing safe, acceptable and valid perinatal strategies for recognising and assessing complex trauma among Aboriginal parents
- developing safe, acceptable and feasible perinatal strategies for increasing awareness among perinatal care providers (trauma-informed care) and support for Aboriginal parents
- building the capacity and skills of Aboriginal and Torres Strait Islander researchers.

It is important to recognise that parents who have experienced difficulties in their own childhood may be 'triggered' during pregnancy and the transition to becoming a parent, causing distress and challenges for creating a nurturing environment for the new baby. On the flip side, growing research shows that becoming a parent offers a unique lifetime opportunity to heal from this childhood hurt and provide a nurturing environment for children. Yet, despite these opportunities for healing and the risk of triggering due to the intimate nature of perinatal care – particularly during frequent contacts with health care providers during pregnancy and the first two years after the baby's birth – there are currently no systematic perinatal strategies for supporting parents who may be experiencing complex childhood trauma. Led from the Judith Lumley Centre at La Trobe University, the Principal Investigator Catherine Chamberlain is joined by an Indigenous-majority health research team, and was able to secure Lowitja Institute and NHMRC funding for the program.

Current data infrastructure, data sovereignty and governance arrangements

Models of data governance underpinning an Australian Indigenous Metagenomics Strategy need special consideration. Dominant models of data collection have been found to exploit massive amounts of personal data and privilege multifaceted economic and social interactions within data governance models (Micheli et al. 2020). Research highlights that the asymmetry of power relations embedded in these models has negative societal implications, including biases in algorithmic decision making, manipulation and privacy violations (Beer 2017; Kitchin 2017). As technological advances have generated immense amounts of biomedical data, Indigenous data sovereignty is necessary to exert stronger control and oversight over such data from Indigenous peoples, particularly as this information has shifted from localised systems of management to being organised and stored in numerous large-scale databases, which could be accessed by people around the world (Russo Carroll et. al 2020).

The governance of large-scale databases often stands in contrast with the stricter mechanisms of protection and relationships of trust needed by Indigenous Australians to lay the groundwork for a more fair and equitable participation in biomedical research.

In examining and synthesising current discourses and practices on the governance of data, Micheli et al. (2020) scrutinised different approaches for accessing, controlling, sharing and using data in today's data management economies, and derived four emerging models of data governance. By focusing on the social practices implemented and theorised for governing big data, there is a case for the adoption of a social science-informed approach to data governance that emphasises power relationships between data 'actors'. In this process, an Australian Indigenous Metagenomics Strategy will need to consider:

- data Infrastructure – stakeholder roles, responsibilities, the articulations of value, and the organisations of governance principles, instruments and mechanisms
- data politics – which will emphasise the power relations and asymmetries affecting the processes and the goals of particular governance models and how the value created from data is redistributed
- technological legitimacy – the need to address concerns of technical changes and transparency efforts as a 'tinkering around the edges' to address the asymmetric power-imbalanced relationships to enable true engagement with the public
- data governance – shifting from a 'command and control' process to acknowledging governance as a system that acknowledges the broad set of actors and institutions involved in managing Indigenous societies:

- governance goals – the values-based objectives that different stakeholders have for governing data and increasing data subjects' control over data (Winter & Davidson 2019)
- value from the data – the kind of value that is created from data through aggregation, analytics and business intelligence, public good and self-determination (Winter & Davidson 2019)
- governance mechanisms – the strategies and instruments adopted by different stakeholders to achieve their goals and direct change in a socio-technical system (Borrás & Edler 2014)
- reciprocity – the power relations between stakeholders in accessing, controlling and using data.

The Australian Indigenous Metagenomics Strategy will need to shift from unilateral approaches to mutual data governance models in which more stakeholders take part in the governance of data, generating new forms of power relations (Ruppert, Isin & Bigo 2017:2).

Governance of biomedical data is the result of a process that does not only occur through rule making and rule enforcing, but develops also from social interactions, cooperation and negotiations between stakeholders at the horizontal level (Colebatch 2014). Data infrastructure could be considered as an evolving ecosystem, in which 'a plurality of actors [have] multiple interests, agendas, goals and strategies, and [interact] with an array of tools, mechanisms, systems, interfaces and devices for governing data' (Kitchin & Lauriault 2018).

Data infrastructure will not only need to support certain practices, but also cultivate a specific imaginary; that is, a particular vision of data and its possibilities (Beer 2017; Gray, Gerlitz & Bounegru 2018). Emerging data governance models that could be explored include:

- data sharing pools – horizontal joint initiatives among data holders to aggregate data from different sources to create more value through their combination
- data cooperatives – enabling a decentralisation of data in which Indigenous peoples would voluntarily pool their data together to create a common pool for mutual benefits (Ho & Chuangt 2019)
- public data trusts – integration of data from multiple sources to inform policy making, promote innovation and address societal challenges that adopt a responsible approach to the use of personal data (Bass, Sutherland & Symons 2018)
- personal data sovereignty – in which data subjects have greater control over their data, both in terms of privacy management and data portability. The term comes from a broader principle of technological sovereignty that concerns the regaining of control of technology, digital content and infrastructures and reduces the influence of commercial enterprises (Couture & Toupin 2019).

Professor Maggie Walter's work on Indigenous data sovereignty is an exemplar of decolonising data and Indigenous data governance, aligning with an international movement emerging in scholarship and practice worldwide. The United Nations Declaration on the Rights of Indigenous Peoples articulates the rights of Indigenous nations to control how data is used, described and stored. Data sovereignty returns authority over data back to Indigenous nations and their citizens, communities and resources from where the data was derived.

Data sovereignty in relation to reference genomes and databases is a complex issue. It is generally understood that data should be as freely available as possible to researchers, with reference to the notion that genomic research in general is for the betterment of all humankind. Indeed, the NCIG has developed a *Roadmap to integrate Indigenous genome assemblies into a national instance of the International Human Reference Genome Resource* (ARDC n.d.). A key finding of the NCIG's (2019:8) report was that there is a 'critical unmet need' for Australian Indigenous ancestral diversity to be included in a global human reference genome resource. However, as discussed in Hudson et al. (2020) in 'Rights, interests and expectations: Indigenous perspectives on unrestricted access to genomic data', Indigenous community rights and interests in data may otherwise be shaped by a different set of concerns.

A 2016 study found that only 0.05 per cent of participants in genome-wide association studies (GWAS) worldwide are Indigenous (Popejoy & Fullerton 2016). Indigenous Australians are under-

represented relative to Indigenous groups in other countries – despite recent significant sequencing efforts by the NCIG and others, including the 500 mitogenomes sequenced by Nagle, Ballantyne et al. (2017) and the c. 750-strong South Australian Aboriginal Y chromosome STR database (Bergström et al. 2016) (as discussed in Appendix A). So, clearly, and in line with Strategic Priority 5.2 of the *National Health Genomics Policy Framework: 2018–2021*, the Indigenous-controlled institution proposed in this report could be the vehicle to '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' (AHMAC 2017:13).

Although the situation in Australia has markedly improved from the pre-2010 era, it should not be assumed that these concerns have been entirely resolved. In this regard, the Indigenous-controlled institution proposed would be ideally placed to oversee resolution of these issues if and as they arise but would ultimately be empowered to withhold consent within the international and national metagenomic spaces on behalf of a Nation or community. The umbrella organisation could also roll out the 'dynamic consent' database management model, which ensures biobank participants are informed about how their samples are being used, with the option of opting out of projects while maintaining participation in the biobank (Williamson et al. 2018:91).

Data sovereignty is also appropriately asserted in relation to the growing number of ancient Indigenous genomes being found and sequenced (Nagle, van Oven et al. 2017). The Indigenous-controlled institution would support an agenda of understanding the original instructions in ancestral DNA as per a molecular decolonisation research agenda, which would also assist with the repatriation of remains and, more broadly, ensure the remains of ancestors are treated with due respect (see 'Best of both worlds: Cultural, social and emotional wellbeing research strategies' in Chapter 2 of this report).

Other databases relevant to an Australian Indigenous Metagenomics Strategy

The same data sovereignty considerations might also apply to Indigenous-specific and/or relevant microbiota banks as they are established; these would provide historical (where possible) and contemporary records and/or collections of microorganism samples and microbiomes from specific ecologies and countries, in line with regionalisation. Such records and/or collections will include wider environmental microbiota but also those of Indigenous gut, skin and other bodily locations.

More broadly, such microbiota/microbiome banks and plant and animal databases are likely to make a critical contribution to an Indigenous kincentric ecological research agenda and to a cardiometabolic healing research agenda and its translation as preventative metagenomics.

As discussed below, such databases are being developed and an Australian Indigenous Metagenomics Strategy could be promoted by the proposed Indigenous-controlled institution in partnership with other relevant institutions, such as private companies currently working with Australian museums to sequence the genomes of Australian reptiles and amphibians (Bioplatforms Australia n.d.a), and herbariums and botanical gardens working to sequence the genomes of native plants (Bioplatforms Australia n.d.b) and Australian marsupials (with an initial focus on the koala) (Bioplatforms Australia n.d.c). Other relevant institutions could also include public collections such as Kanthipartuku trruku munana ngutulitya tudnunthi (Australian Centre for Ancient DNA), which is based at The University of Adelaide and whose research areas include responses to environmental change, evolutionary biology, and population genetic studies of animals, plants, pathogens and

human evolution.[11] The work of these institutions includes the reconstruction or sequencing of ancient microbiomes to understand the current distribution of Indigenous peoples and their ancient metabolic microbiome matches, as is now being explored by researchers in the mainstream space (Research Data Australia n.d.d).

Sample sovereignty

Data sovereignty includes the question of who controls coloniser genetic, genomic and metagenomic scientific legacies, including specimens and biobanks (Taylor et al. 2012; Taylor & Henry 2012; Collins et al. 2014) and, of note:

- blood samples collected over 30 years from 7000 Aborigines in missions and settlements across Australia and held by the NCIG subject to the *National Centre for Indigenous Genomics Statute 2016* (Thistleton 2015)
- the collections of the South Australian Museum, where there are currently around 5000 hair samples from diverse Indigenous Nations in the collection database. These hair samples were collected over the course of 52 scientific expeditions to 86 communities between 1925 and 1971. Many of the samples are correlated to measurements of body shape, language, birthplace, tribal affinity and family structure as documented on data cards, along with genealogies. Taken together, these records form an enormously important record and are part of Australia's Indigenous heritage (University of Adelaide n.d.).

Decisions about sample sovereignty might, for example, result in the development of a national framework to support the cultural disposal of remains, such as the framework followed by the Christchurch Tissue Bank in New Zealand, which, while not a Māori institution, offers those who have given samples the option for them to be 'disposed of with a Māori blessing' when they are no longer required for research (Williamson et al. 2018:91).

Preventative precision medicine

Preventative precision medicine involves identifying and responding to genetic variations associated with disease states and conditions, combined with risk assessments and prophylactic responses long before their expression as phenotype or genotype. A well-known example is the use of genetic screening and adoption of preventative responses after the discovery that some gene mutations convey a dramatically increased risk for breast cancer (American Cancer Society n.d.a; Hamilton 2009). Today, women with a family history of breast cancer routinely undergo genetic screening and those with these mutations are offered genetic counselling to help them decide the best treatment options. This includes different or more intense treatment, and even prophylactic surgery (Kirk et al. 2006).

Ultimately for individuals, preventative precision medicine holds the potential for health plans to be generated (and updated as research discoveries occur) to empower them with a life course strategy for the mitigation of genetically associated health risks. Such plans could further be enhanced with epigenetic analysis as it becomes more available and less costly, including as a part of a medical response to events known to trigger epigenetic changes, including trauma.

From an Indigenous cardiometabolic perspective, precision medicine could move beyond the scope of the genome to include analysis of microbiota/microbiomes, diet and environment to empower Indigenous individuals with knowledge and preventative strategies to mitigate cardiometabolic

11 For more information, see University of Adelaide n.d.

health risks. A particular focus here would be on uncovering gene-environment 'mismatches' and empowering Indigenous individuals to 're-match' diet, microbiota and genomes to prevent, or halt the onset of, chronic cardiometabolic diseases. As discussed, such approaches would rely on the development of microbiota/microbiome databases (including ancient microbiota/microbiome databases).

Preventative precision medicine can empower *individuals* with knowledge and choice but it also has a public health dimension. This starts with the capacity to sequence the genomes of entire cohorts. This capacity is already being demonstrated – recent reports, for example, confirm that the Chinese Communist Party is building a database of 70 million male DNA profiles that connect to China's entire male population – roughly 700 million people (Cyranoski 2020). The stated aim of the program is crime prevention, but the social control implications and involuntary nature of the sampling are entirely at odds with anything being discussed here. The example is provided only to illustrate the possibilities of scale in precision public health.

Other – albeit smaller, but more appropriate – exemplars exist in relation to health: the United States Precision Medicine Initiative's All of Us Research Program is to date the cohort size standout. This program aims to collect and sequence data from one million people, alongside other biospecimens and health information, to support an enormous longitudinal study with direct benefits to the participants and other research efforts (in relation to how genes interact with lifestyle and environment to determine health), thereby further underpinning the development of better preventative precision medicine strategies (All of Us Research Program n.d.). Relatively smaller again is the 2012 United Kingdom 100,000 Genomes Project, which focused on patients with either rare diseases or cancers, the GenomeAsia 100K project and the Saudi Human Genome Program (Williamson et al. 2018).

In considering scale, it is noteworthy that the All of Us Research Program involves a larger cohort than the entire Indigenous population in Australia at the time of writing – about 700,000-strong. In other words, with political will and resources it would appear to be already possible to develop Indigenous precision public health responses that include much of the Indigenous population. Of course, working through the many and complex ethical and other issues involved would need to occur first, with participation based on free, prior and informed consent and subject to data protections, and with 'opt outs' likely to be non-negotiable. But, nonetheless, such responses are within the realm of possibility.

This correlates with the research of Gladding et al. (2010:361) that demonstrated that among a Māori cohort of several hundred, connecting genomic data to e-health or health records creates 'an effective tool to assess the longitudinal effect of gene variants on health outcomes and will aid in the implementation of personalized medicine. Larger sample sizes with longer study duration may yield clinically useful information that aids preventative healthcare.'

Likewise, in addition to what might be called public preventative metagenomics, the capacity to work at scale is being increasingly developed. As an example, the project abstract in 2019 for an Australian Research Council Discovery Project Grant for *Bacterial communities in metropolitan, rural and Indigenous Australians* (under the auspices of Monash University) noted:

> This project expects to isolate, genome sequence, classify, characterize and permanently archive 1500 bacterial species. Expected outcomes of this project include detailed knowledge of previously undiscovered bacterial species with improved methods to

measure the bacterial species that inhabit the human gut and gain a detailed understanding of the gut microbiota of Australians. (GrantConnect n.d.f)

It is critical that precision medicine affords Indigenous peoples in Australia the same rare disease diagnostic opportunities as non-Indigenous Australians. The International Rare Diseases Research Consortium (IRDiRC), an Indigenous Population Taskforce chaired by Dr Gareth Baynam (WA Health), has lobbied strongly for Indigenous inclusion in rare disease advances in this country and advocated strongly for the inclusion of genetics research in closing the health equity gap (Government of Western Australia 2020).

Addressing Indigenous rights and interests in genetic research has become increasingly challenging in an open science environment. In recognition of the equitable benefits that can only be realised through the greater participation of Indigenous communities, issues of trust, accountability and equity need to be present in Indigenous genetic research. Hudson et al. (2020) identified a number of principles and actions that genomics researchers could adopt to recognise community rights and interests in data, many of which are embedded in codes of conduct and guidelines for genetic research with Indigenous communities.

International comparison of guidelines and protocols

Despite decades of scientific transgressions across the globe, many Indigenous communities continue to be interested in genetic research. Some Indigenous communities worldwide have developed their own policies to promote responsible conduct of research and have created review boards to implement mechanisms of accountability to be research partners (Claw et al. 2018).

One reason, globally, that Indigenous people are under-represented in genomic research studies includes the failure of researchers to engage Indigenous communities in ethical and inclusive ways, lack of study transparency, historical and recent research malpractice, and a lack of informed consent. An increasing number of Indigenous peoples have developed guidelines, ethical practices and codes on working with communities.

The San people from South Africa issued a code of ethics in 2017 (South African San Institute 2017), prompted by concerns over the use of consulting terminologies, failure to communicate findings to the community, direct recruitment without authority and a lack of investment in the community (Nordling 2017). The code articulates what is meant by the principles important to the San people:

- **Respect**: including respect for culture, privacy, history, for the relationship with their environment, contribution to research, social customs and norms
- **Honesty**: open and clear exchange between researchers and community leaders, without patronisation
- **Justice and fairness**: meaningful involvement in proposed studies, learning about benefits of the research and being clear about what the participants and community might expect from this work
- **Care**: research needs to be aligned to local needs and improve the lives of the San, including to families of those involved, the social and physical environment, and high-quality research
- **Process**: use of protocols and meeting specific requirements in the research process, co-design principles and effective management of the research process (South African San Institute 2017).

Interest in the benefit-sharing experience of the San was considerable and hence it was possible to obtain further European Union funding. The GenBenefit project expanded the work with the San to include other vulnerable research populations (GenBenefit n.d.).

Te Mata Ira: Guidelines for Genomic Research with Māori (Hudson et al. 2016) in New Zealand brought together various strands connecting Māori people, the Treaty of Waitangi and Māori research ethics, and was developed to support decision making around Māori ethical issues. Through a process of community-led consultations, the guidelines seek to identify ways to protect the interests of Māori participants and groups that choose to participate in genetic research. Founded on cultural worldviews and protective of relationships and connections (genealogies, social and ecological relationships, cultural histories, family traits and ancestral inheritance), the guidelines require a level of integrity in the systems that support research and the transformation of services (research organisations, ethics committees, funding bodies, health systems). Also advocated for is the increase in health literacy in communities about their research projects and actions.

Research initiatives such as the Human Heredity and Health in Africa (H3Africa) Consortium are contributing to the development of scientific capacity and infrastructure to support genetic studies on the continent. Despite this growth, genomic research and biobanking have raised important ethical challenges for key research stakeholders, including members of research ethics committees. The H3Africa Consortium adopted several approaches to address these ethical challenges through working groups. One was the Ethics and Regulatory Issues Working Group and the other was the Community Engagement Working Group. These working groups were responsible for designing ethics and community engagement policies and guidelines for H3Africa projects, as well as supporting studies to address the ethical, legal, social and cultural implications of biobanking and genomics research (Tindana et al. 2019).

Using deliberative workshops, and ethics consultations, the working group members identified practical and ethics challenges from the perspectives of those involved across a broad range of stakeholder groups. The Ethics and Regulatory Issues Working Group developed a 'bottom up' approach to developing an ethics and governance framework and spent time articulating the concerns and the opportunities for better and regular communication between stakeholders and the importance of implementation networks.

The *H3Africa Guidelines for Community Engagement (Version 2)* lays out a process for community engagement in genomics research and methods to address health inequities in both communicable and non-communicable diseases (H3Africa Community Engagement Working Group 2017). In response to a key ethical challenge of engaging communities in genomics research, a Working Group was formed in 2015 to support the implementation of community engagement activities across the consortium. There was a deep desire on part of the community to understand the types of community engagement in the consortium, and the identification of expertise, needs, challenges and opportunities for engaging communities in genomics research. They worked to identify examples of effective models and approaches that could support genomics studies with an emphasis on community and group feedback.

The SING Consortium (Summer internship for Indigenous peoples in Genomics) have also developed a framework to engage Indigenous peoples and communities in genomics research (Malhi & Bader 2015). This framework includes six principles: (1) understand existing regulations, (2) foster collaboration, (3) build cultural competency, (4) improve transparency, (5) support capacity, and (6) disseminate research findings. The goals of the framework are to build trust, increase inclusion of

diverse groups in genomic research, and enhance ethical research practices that promote tribal research regulations (e.g. tribal oversight and consultation) and benefits to participants and their communities (Claw et al. 2018).

An Australian version of this approach is *Genomic Partnerships: Guidelines for Genomic Research with Aboriginal and Torres Strait Islander Peoples of Queensland* (QIMR Berghofer 2019). The guidelines are a product of the GenetiQs project led by Dr Greg Pratt, Aboriginal & Torres Strait Islander Health Research Manager at the QIMR Berghofer Medical Research Institute, Brisbane, in partnership with, among others, the Queensland Aboriginal and Islander Health Council. In relation to engaging with Indigenous communities for research purposes, *Genomic Partnerships* supports six core values, as articulated by the National Medical Health and Research Council (Figure 4.1).

Figure 4.1: The six core values (image adapted from NHMRC 2018:7)

In the context of precision medicine, *Genomic Partnerships* articulates a process – sometimes referred to as Participatory Action Research (PAR) in Indigenous contexts (Nunn 2019) – whereby research translation, including clinical practice and research itself, is integrated into a 'virtuous cycle' (McCosker, Matan & Marinova 2018:1). By this, progress is understood to be incremental, and contributes to the rapid evolution and refinement of – in this case – precision medicine in consultation with service users and the communities they come from.

PAR approaches incorporating the co-design of precision medicine services also align with the *National Health Genomics Policy Framework: 2018–2021* (AHMAC 2017) and represent a shared commitment to implement genomic technology into health systems for the benefit of all Australians. The application of genomic knowledge must be ethically, legally and socially responsible and community trust must be promoted. Further, access and equity should be promoted for vulnerable populations, meaning that they are tailored to the cultural and other needs of an Indigenous community, and that information is accessible.

Ecological genomics work

Metagenomics can also make a significant contribution to Indigenous wellbeing by supporting the preservation and restoration of kincentric ecologies. As noted in the 2016 Australian Government *State of the Environment* report (Cresswell & Murphy 2017), a lack of basic knowledge about species is the single biggest gap hindering effective management of biodiversity across Australia. And, as also noted, 'new genomic techniques are providing opportunities to fill this knowledge gap… but data and synthesis from them remain limited' (Cresswell & Murphy 2017:43).

Metagenomic research is critical here and can empower Indigenous communities with the knowledge needed to respond strategically to preserve threatened species. For example, genomic sequencing of the black-footed rock-wallaby has demonstrated the considerable genetic variance (to the point of subspecies being recognised) among the morphologically similar animals, suggesting – like Indigenous Nations themselves – ancient regionalisation (NESP TSR Hub 2018), as well as the need to focus across a number of subspecies to ensure the preservation of the wallaby species as a whole.

Metagenomic research and activity could be widened to include support for introduced species eradication, restoring the environments in which species thrive, and tackling animal and plant diseases. It could potentially include the restoration of extinct species for which enough DNA is available, if these technologies are deemed ethical and otherwise developed.

A noteworthy research project underway in this context is the *Healing land healing people: Novel Nyungar perspectives* project (Curtin University 2019), which aims to bring together Indigenous environmental and cultural knowledges and Western science and humanities to generate new strategies to slow decline of biodiversity in the Southwest Australian Floristic Region to demonstrate enhanced sustainability of environment *and* the strengthening of land-based and other cultural practices (ARC 2020).

We also note the importance of including microbiota in the scope of research and activity to support environments. This field is in relative infancy, and the first comprehensive microbiota mapping projects are just getting started.

Otherwise, research discoveries in relation to pathogens (which might be understood as microbiota that are hostile) suggest that regionalisation of microbiota is as likely as regionalisation of Indigenous Nations themselves. Two illustrative examples are:

- hepatitis B virus strains: Yuen et al. (2019) sequenced a hepatitis B virus strain (HBV/C4) found uniquely among Papuan and Aboriginal populations that has been proposed to have ancient origins; phylogenetic analyses and modelling suggest the strain was carried by peoples as they travelled from South East Asia, emerging around 60,000 years ago, including into Australia
- melioidosis, caused by the *burkholderia pseudomallei* bacteria, which is often transmitted by rodents (Nguyen, Smith & Hayoun 2020). After sampling and undertaking genomic research into bacterium from nine places/islands across the Torres Strait area and compiling a viral phylogenetic tree for the strains identified, Baker et al. (2013) proposed an anthropogenic dispersal model (i.e. rodents accompanying human beings in ocean travels) and otherwise identified markers that suggested island-distinct varieties had evolved over significant time, suggesting the considerable lengths of occupation, and distinctiveness, of individual island populations (Baker et al. 2013; see also Baker et al. 2018).

Considerations for an Australian Indigenous Metagenomics Strategy

This environmental scan has identified research, clinical services and consumer engagement activities of relevance to Aboriginal and Torres Strait Islander peoples in relation to genomics research, taking into consideration the international context. However, despite the breadth of information available, unless the National Indigenous Metagenomics Strategy is contextualised by Country, then we will fail to progress an Indigenous metagenomics agenda – rather, we will do little more than progress the discipline's capacity to engage with Indigenous people's genomics. Worse, we will perpetuate the ongoing momentum of colonisation.

The Australian Indigenous Metagenomics Strategy requires an expanded view of genomics that goes beyond the human-centric focus of much of the work to date. It requires acknowledgment of our connection to Country and our custodial responsibilities to microbiota. It requires an understanding that the health and wellbeing of Aboriginal and Torres Strait Islander people, indeed all people, is not separate to the health of whole ecologies.

Existing genomics guidelines, as outlined in this chapter, reference culture but they fail to specify how cultural roles and responsibilities to care for ecosystems is attended to. Again, this is due to a mindset disconnect – for people who have not grown up in environmental managerial cultures (as discussed in the preface to this report), this is a concept that cannot be engaged with readily or necessarily well, but it is an important concept. Without understanding and appreciating this concept, it is hard to envisage how an Australian Indigenous Metagenomics Strategy can progress.

None of the existing guidelines are concerned with the Anthropocene and the devolution of the quality of biospheres and habitats. There is a wisdom to be gained from pandemics, which are increasingly becoming zoonotic, and there is little point in investing in human-centric research unless we also look at Australia's biosecurity and develop capacity in a world that, more and more, is compromised by the intensification of weather patterns and an alarming decline in biodiversity. An Australian Indigenous Metagenomics Strategy could lead the way in global genomics research by focusing on clinical and other-than-clinical interventions, premised on prosperity rather than protectionism.

5 Gap analysis report

This gap analysis report identifies key past, present and planned Indigenous genomics work in Australia and internationally. Its goals are three-fold:

- to identify and analyse the information gaps of Aboriginal and Torres Strait Islander people, stakeholders and policy makers
- to offer recommendations on ways to improve knowledge (reducing information gaps) and to improve two-way communication between information providers and users (reducing communication gaps)
- to identify gaps and barriers in facilitating accessible, timely and affordable genomics services (reducing the access gap).

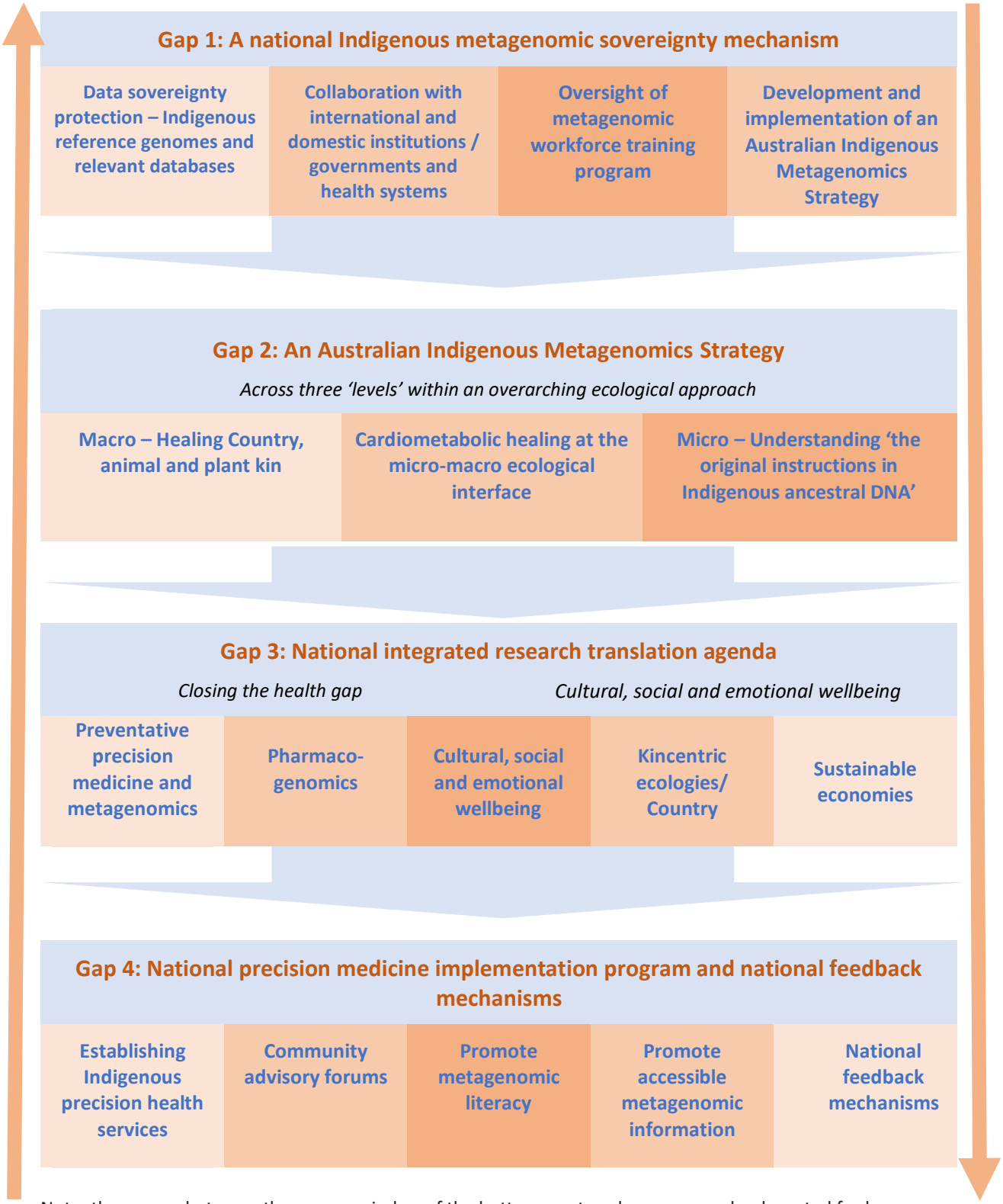
In conducting the analysis, we looked for gaps in research, in services and in activities where increased attention would benefit Aboriginal and/or Torres Strait Islander peoples. Overall, this report identifies four gaps (Figure 5.1) that relate to:

- a national Indigenous metagenomic sovereignty mechanism (Gap 1)
- an Australian Indigenous Metagenomics Strategy (Gap 2)
- a national integrated research translation agenda (Gap 3)
- a national precision medicine implementation program and national feedback mechanisms (Gap 4).

Addressing these gaps, which are discussed in this chapter, will amount to a national, comprehensive and integrated Indigenous approach to metagenomics and will redress the poor health of whole ecologies consistent with holistic concerns raised throughout this report.

The gap analysis identifies gaps and barriers to improve the body of evidence addressing clinical outcomes for genomics in line with the aspirations of Aboriginal and Torres Strait Islander people.

Figure 5.1: Gap analysis: a national, comprehensive and integrated strategic approach to Indigenous metagenomics



Note: the arrows between the gaps remind us of the bottom-up, top-down approach advocated for by Aboriginal and Torres Strait Islander people in the identification of gaps (Bulloch, Fogarty & Bellchambers 2019). Whatever the approaches taken to address the gap, strengths-based community-driven holistic designs are likely to be advantageous in progressing the field.

Gap 1: A national Indigenous metagenomic sovereignty mechanism

Gap 1 concerns the need for an Indigenous-controlled national metagenomics umbrella institution with specific functions in:

- data governance – founded in a social science framework addressing the asymmetric power imbalanced relationships in current data governance
- sovereignty protection – Indigenous reference genomes and relevant databases
- collaboration with international and domestic institutions/governments and health systems
- oversight of a metagenomic workforce training program
- development and implementation of an Australian Indigenous Metagenomics Strategy in partnership with professions that care for Country and privilege Indigenous sciences.

None of the existing clinical guidelines are concerned with the Anthropocene and the devolution of the quality of biospheres and habitats. Because of this, our gap analysis identified one overriding gap in research, in services and in activities where increased attention would benefit Aboriginal and/or Torres Strait Islander peoples – this gap is the need for an Indigenous-controlled national metagenomics umbrella institution. All other gaps relate back to this requirement. Without Indigenous control of our own lives, our own research, our own data and our own microbiota, any Australian Indigenous Metagenomics Strategy is compromised and risks failing to connect with our people and our Country.

This report proposes the establishment of such an institution (see Recommendation 1 in Chapter 6). The proposed Indigenous-controlled institution would:

- address gaps in Indigenous oversight and governance in relation to sample sovereignty
- train communities in data governance – founded in a social-cultural determinants framework addressing the asymmetric power imbalanced relationships in current data governance
- develop policy positions and advocacy documents that position human health in whole ecologies and support the wide array of human genomic activities
- support the uptake of health literacy by making genetic information accessible to the lay person, and translating genetic information into local languages and contexts
- commission whole of ecology research in partnership with funding bodies such as CSIRO, the Lowitja Institute and NHMRC, environmental philanthropists, Indigenous Business Australia, the Medical Futures Research Fund and the Indigenous Land and Sea Corporation
- develop and implement strategies that promote protection and ownership – Indigenous reference genomes, and relevant databases
- collaborate with international and domestic institutions/governments and health systems
- oversee a metagenomic workforce training program for professionals working with Indigenous peoples, and for Indigenous peoples working on their lands and seas
- develop and implement Australian Indigenous metagenomic research strategies in partnership with professions that care for Country based on the Indigenous Estate
- develop widespread understanding of, and engagement, with microbial community custodianship
- support student scholarships and research partnerships
- supporting on-Country genomic knowledge production and use, including Indigenous agriculture, commercialization of ecological genomes and microbial custodianship.

Gap 1 has:

- three specific research gaps:
  - Indigenous reference genomes are a gap in the current metagenomic space
  - a need to develop regional reference genomes to account for regionalisation
  - a need to expand human-centric research to ecologic genetic research projects relating to human health and wellbeing in the health and wellbeing of the Indigenous Estate.
- three specific service gaps:
  - the lack of genome or sequence reference databases in relation to Indigenous Australians
  - Indigenous oversight and governance of collections that hold Indigenous samples
  - a drawing together of ecologic researchers who can harmonise human genetic research with on-Country research strategies.

As noted by an Aboriginal subject matter expert interviewed as part of this project, in Australia Indigenous peoples are currently in a position where the experts in our DNA – what is most intimate to us – are largely non-Indigenous people, no matter how well meaning and honourable in their intentions.

> *Non-Indigenous people are becoming subject-matter experts on our DNA. We can't have that. We've [got to] take that power back. We've got really good people out there: Indigenous people leading the way. And I'm hoping that these really good non-Indigenous people that we're working with are able to let it go. That's going to be a really big one, particularly as we start to take control of the agendas and start to really work out what the truth of the legacy is. In our genome. There will be lots of real eager people around to have a look, [but] it's not their story.* (Project stakeholder interview)

Although a growing cohort of Indigenous experts is emerging in Australia, and their work leadership is acknowledged, the power is still largely held by non-Indigenous institutions. A noteworthy exception is the Australian National University's NCIG, which was established, and is empowered and otherwise regulated by, the *National Centre for Indigenous Genomics Statute 2016* (Cth). In the NCIG, Indigenous engagement and control of research is facilitated through an Indigenous-majority Governance Board, an Indigenous Collection Access Committee, an identified Indigenous Engagement Officer position, and Indigenous members of the Advisory Board, including Indigenous community representatives (Kowal et al. 2017). The NCIG provides a practical example of Australian Government-supported Indigenous control and governance possibilities in this space. But a gap identified here is wider than the NCIG on its own can bridge. **What is required is an Indigenous-controlled national metagenomics umbrella institution** with:

- a centre of research excellence and its own research agenda, expertise, practitioners, resources and funding, but one that also works in partnerships with other institutions as necessity dictates
- oversight governance of Indigenous metagenomic research in Australia
- other specific functions as discussed below.

The institution would straddle two spaces:

- the metagenomic kincentric research space
- the Closing the Gap/Indigenous health space.

The metagenomic research space will need to be supported by national agreements involving a range of stakeholders and research institutions, and will need to be built into the next iteration of

the *National Health Genomics Policy Framework and Implementation Plan 2018–2021* (AHMAC 2017) and by legislation along the same lines as the *National Centre for Indigenous Genomics Statute 2016* (Cth).

In the Closing the Gap/Indigenous health space – and as the relevance of metagenomic research to closing the gap in Indigenous health and other outcomes is more widely recognised by Australian policy makers – the institution could be included in the next iteration of the National Agreement on Closing the Gap. This could include membership of the Coalition of Peaks and the Joint Council on Closing the Gap, the two most powerful Indigenous bodies in the Indigenous affairs space.[12] Indeed, such an institution could provide significant impetus towards achieving the Closing the Gap target of Indigenous life expectancy equality with the non-Indigenous population by 2031.

To otherwise support a goal of self-determination, the institution would ideally also aim to become financially independent or self-funding through maximising research commercialisation opportunities (understanding, of course, that the human genome itself cannot be commercialised). The institution could attract significant funds by promoting the returns on research investment possible through metagenomic research, the primary example being through the development of Indigenous precision medicine and by shifting Indigenous health to a largely preventative footing as discussed in Gap 3 (Burns et al. 2019).

Data sovereignty protection – Indigenous reference genomes and relevant databases

> To us, any part of ourselves is sacred. Scientists say it's just DNA. For an Indian, it's not just DNA, it's part of a person, it is sacred, with deep religious significance. It is part of the essence of a person. (Late Native American geneticist Frank Dukepoo, in Kowal, Easteal & Gooda 2019)

The Human Reference Genome (HRG) is a template genome that provides location points for genetic features and against which the reconstruction of the genome can be guided (NHGRI n.d.a, n.d.b). The latest iteration of the HRG was released by the Genome Reference Consortium in 2013. The current HRG is a composite genome derived from 13 anonymous volunteers from Buffalo, New York, with samples taken in 1997 (Ligthart et al. 2018).

Yet as Kowal et al. (2017) note, Australian Indigenous genomes cannot be fully understood with reference to the genes (and reference genomes) of other populations, particularly given the ancient divergence of such from European and African lines – (see 'Aboriginal peoples and Torres Strait Islanders' (Archaeogenetics) in Appendix A). As such, **Indigenous reference genomes are a gap in the current metagenomic space**.

Further, **there is a need to develop regional reference genomes** to account for regionalisation. Research by Tang et al. (2018) among the Western Desert Martu peoples, for example, detected 70,000 genome-wide variations apparently unique to the Martu, but the researchers noted that such was likely to be the case for all regionalised Indigenous peoples in Australia.

Indeed, based on work reported by the NCIG,[13] approximately 25 per cent of all DNA variants in the Indigenous genomes it has studied are unknown in people from outside Australia and, of these,

12 For information on the Coalition of Peaks and the Joint Council on Closing the Gap, see Coalition of Peaks n.d. and Closing the Gap in Partnership n.d.b.

13 See 'Population Variation Project' in the environmental scan in Chapter 4.

approximately 40 per cent are likely to be found in a single region or community. The NCIG (2019:7) concludes:

> Overall, genomic differences among communities across Australia are as great as those between populations across Europe and Asia combined. In medical genomics terms, some Australian Indigenous communities are as different from each other as communities as far apart as North West Europe and South East Asia. So, 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 United Kingdom based on information about people from Cambodia.

This gap is in the process of being resolved through the work of the NCIG. But its development also leaves open the question of Indigenous data sovereignty, which has been defined as:

> the right of Indigenous peoples to govern the collection, ownership and application of data about Indigenous communities, peoples, lands, and resources. Its enactment mechanism Indigenous data governance is built around two central premises: the rights of Indigenous nations over data about them, regardless of where it is held and by whom; and the right to the data Indigenous peoples require to support nation rebuilding. Indigenous Data Sovereignty is now a global movement, with activities expanding from raising awareness within Indigenous nations and nation state data entities to the instituting of Indigenous data governance principles and protocols (Walter & Suina 2019).

Also relevant to data sovereignty are Indigenous genome or sequence reference databases. The thing to note here is the gap in relation to Indigenous Australians, who are under-represented relative to Indigenous groups in other countries (see Chapter 4).

And while the question of sample sovereignty is being resolved through the establishment of ethics guidelines, norms, protocols and so on by institutions, national umbrella **Indigenous oversight and governance of such collections remain as gaps** that the proposed institution could fill.

Collaboration with international and domestic institutions/governments and health systems

In addition to its centre of research excellence status, the proposed institution would promote collaboration and partnerships with domestic private and public non-Indigenous research institutions, including sharing infrastructure to manage the vast, accumulating amounts of data generated by metagenomic research.

Models for consideration are those that facilitate gender equity, racial equality, the health of whole ecologies and 'ground up' approaches to determining use, access and linkages. Data infrastructure considerations would need to be considered without making heavy infrastructure investments (expensive data warehouses, software, analytics and the like). Investments in the following key areas will need to be considered:

- collection, aggregation and automated analysis of information
- promotion of protocols that address unaccountable and discriminatory forms of algorhythmic decision making
- infrastructure that can be accessed and used productively to progress social, cultural, economic and political goals as decided by the data suppliers
- multidisciplinary and cultural investments in a 'Good Genomics Data Future' to disrupt the digital colonial practices inherent in genetics work in First Nations communities

- development of First Nations' manifestos and practices, promotion of data and justice, investment in models that promote access, equity and Indigenous control, commercialisation options and creating an understanding of good and smart data.

This would include partnerships with:

- international Indigenous and non-Indigenous research institutions relevant to Indigenous peoples in Australia
- CSIRO, Indigenous Business Australia, the Indigenous Land and Sea Corporation, Traditional Owner groups, Australian Institute for Aboriginal and Torres Strait Islander Studies and genetic institutions
- Australian governments and health systems to support precision medicine in Indigenous communities and health services (see below).

The proposed institution would also contribute to ongoing iterations of broader governmental efforts such as the Closing the Gap agenda (Baynam, Pearson & Blackwell 2016).

Oversight of metagenomic workforce training program

The workforces required to deliver precision medicine and preventative metagenomics vary. Apart from metagenomically literate doctors and health care staff in contact with patients (see Gap 4), behind-the-scenes laboratory scientists, clinical pathologists, bioinformaticians, clinical geneticists and non-genetics health care professionals all have roles to play (Williamson et. al. 2018).

In relation to estimating the needed workforces, we note the practice adopted by advocates such as the Close the Gap Campaign Steering Committee, which nominates a baseline target of population parity (i.e. at least 3 per cent of the metagenomics workforce should be Indigenous because 3 per cent of the general population are Indigenous (Close the Gap Steering Committee for Indigenous Health Equality 2010) and factors in a needs index – broadly, that Indigenous health needs based on a range of data sources are about twice those of the non-Indigenous population (HREOC 2005). Using this approach as the basis of discussions, it is possible to arrive at something like an Indigenous metagenomics workforce target of around 5–6 per cent of the total workforce spread across the types of workforces required.

Development and implementation of an Australian Indigenous Metagenomics Strategy

A primary task of the proposed institution would be the development and implementation of an Australian Indigenous Metagenomics Strategy, including:

- an Australian Indigenous Metagenomics Strategy (see Gap 2)
- an integrated research translation agenda (see Gap 3)
- an empowering, participatory action research-based precision medicine implementation program and an overarching community feedback mechanism (see Gap 4).

Critically, the overarching strategy would be guided by the ecological, political, social, cultural, economic, decolonising and healing aspirations/priorities of Indigenous communities, with a community feedback mechanism enabling that voice to reach the institution. In other words, a feedback 'loop' would allow communities and health services and on Country professionals to guide a range of institutional and on Country activities.

Gap 2: Australian Indigenous Metagenomics Strategy

Gap 2 concerns the current gaps in the development of a strategy including:

- macro – healing Country, animal and plant kin as a healthy Country context for Indigenous people's wellbeing
- cardiometabolic healing at the micro-macro ecological interface
- micro – understanding 'the original instructions in Indigenous ancestral DNA'.

More specifically, Gap 2 identifies research gaps in:

- a metagenomic approach that accounts for adaptations to microbiota and traditional food supplies
- understanding the nature of food–microbiota–genome matches and mismatches across diet, microbiota, microscopic life in the environment, the environment itself and Indigenous genomes
- Indigenous kincentric ecological research with a molecular decolonisation focus, which should include investigating and understanding the genetic and epigenetic impacts of racism.

To address Gap 2, we call for a metagenomic cardiometabolic healing research agenda within a broader Australian Indigenous Metagenomics Strategy under Indigenous control.

Macro – healing Country, animal and plant kin: microbial community custodianship

The first part of the kincentric ecology is the macro – broadly, the level of the visible. Connecting human genetic research to the genetic research occurring in on-Country genetic research is a critical link to reposition the Indigenous genomics agenda within an Indigenous genomics framework. Currently, human health and health care service systems are the focus of many projects funded through the NHMRC, the Lowitja Institute and the Australian Government. The on-Country Indigenous metagenomics agenda is funded through organisations such as CSIRO and environmental philanthropy and is evident in disciplines such as Planetary health and EcoHealth. Figure 5.2 provides an illustration of how metagenomics might operate at this level, and of Indigenous prioritisation among potential metagenomically supported activity.

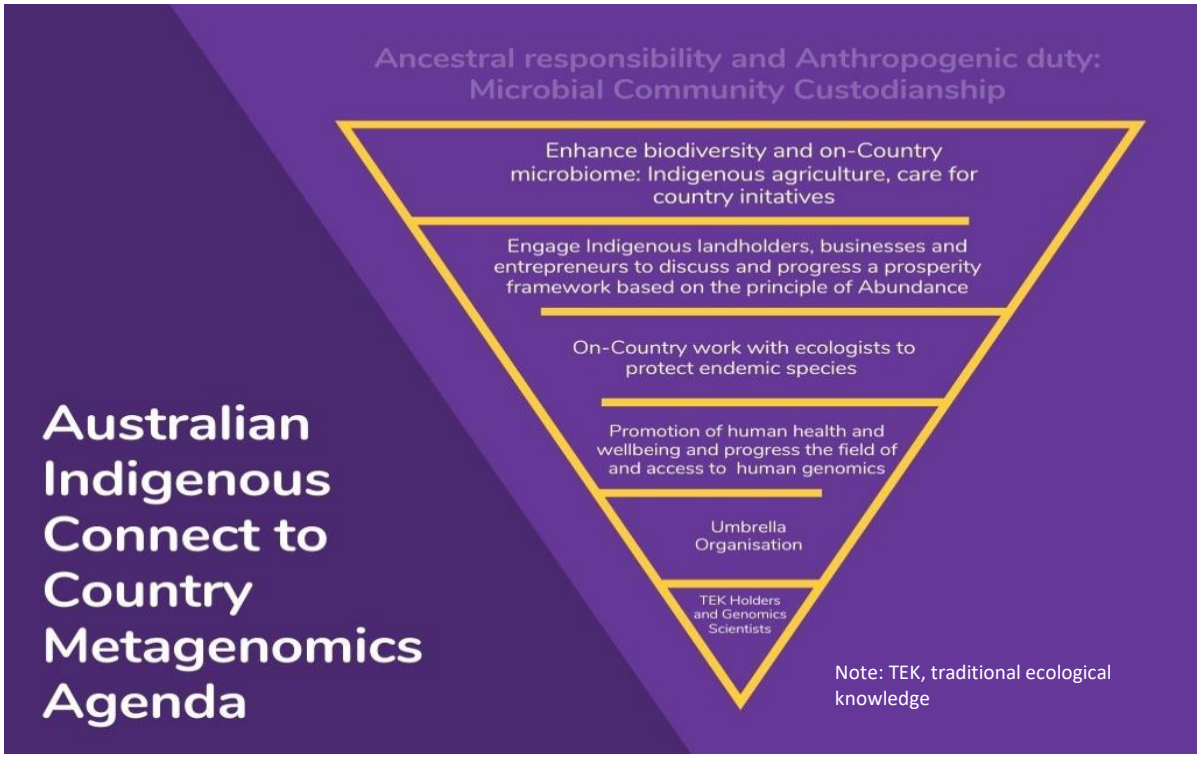


Figure 5.2: How to prioritise the placement of clinical genomics research in the context of an Australian Indigenous Connect to Country Metagenomics Agenda controlled by Indigenous interests

Cardiometabolic healing at the micro–macro ecological interface

Metabolic disease states are perhaps the primary health challenge facing Indigenous peoples today. As discussed in the environmental scan (Chapter 4) and the literature review (Appendix A), significant research in this space has already taken place, particularly in relation to type 2 diabetes, kidney disease and gout. Although of enormous value, a major gap in current genetic research is **the adoption of a metagenomic approach that accounts for adaptations to microbiota and traditional food supplies**, in addition to genomic research per se.

What is required is a metagenomic cardiometabolic healing research agenda within a broader kincentric ecological metagenomic research agenda under Indigenous control. Such is aligned with Indigenous worldview notions of a web of influences operating as an ecology without apparently privileging one element – genome, microbiota/microbiome, diet and environment – over another. So a point of difference with metabolic research involving Indigenous peoples so far is contextualisation and the need to combine such research with other disciplines to achieve a truly ecological approach. In Chapter 2 (Background: metagenomics within whole ecologies) we refer to such 'mismatch' between genes and other environmental microscopic life – specifically, viral and bacterial pathogens. In relation to some Indigenous populations of the Americas, successful genetic adaptation to pre-contact environmental pathogens is evident in sequenced ancient remains. However, to the degree that such adaptation did not arm these peoples to fight introduced pathogens, these populations were immunologically naïve or mismatched to the post-contact environmental micro-ecology (Bengtsson-Palme, Kristiansson & Larsson 2018).

By extrapolation, that food–microbiota–genome mismatches might have similarly disastrous consequences is a promising line of research. As such, an Indigenous researcher might be particularly interested in **understanding the nature of both matches and mismatches across diet,**

microbiota, microscopic life in the environment, the environment itself and Indigenous genomes. This discussion continues below in the 'Preventative precision medicine and metagenomics' section in Gap 3.

Additionally, the genetics of microbiome exchange through Birthing on Country could be another research strategy to address this gap. The Council for Aboriginal and Torres Strait Islander Nurses and Midwives have a Birthing on Country statement (CATSINaM, Australian College of Midwives & CRANAplus 2016), acknowledging the rights of Indigenous women to birth on Country. It also acknowledges Indigenous women's rights to access and control plant and animal genetic resources, such as seeds traditionally cultivated by Indigenous communities, as well as to community knowledge gained over generations as a key intergenerational need, a right and a responsibility. The proposed umbrella metagenomics institute could well partner with Indigenous professional associations in Australia and the world to progress birthing on Country, and ensure articles in conventions to which Australia is a signatory are respected and acted upon.

Micro – understanding 'the original instructions in Indigenous ancestral DNA'

The proposal here is that a, Australian Indigenous Metagenomics Strategy would likely include a significant focus on the genetic impacts of trauma.

As noted in Chapter 2, molecular decolonisation aims to restore the original instructions embedded in ancestral Indigenous DNA. What this means in this context is not only an epigenetic healing research agenda that focuses on trauma, but a research agenda that might touch on a range of cardiometabolic disease states that are associated with trauma and that are transmitted transgenerationally.

We propose several lines of trauma-related research that are current gaps and could be pursued within an Australian Indigenous Metagenomics Strategy.

The specific gaps are as follows:

- epigenetic therapies and assessment tools, particularly relevant to midwifery practices
- the need to investigate the transgenerational transmission of stress and trauma.

Overall, the potential of epigenetic therapies is only just beginning to be explored, with noteworthy successes in cancer treatment that suggest its potential.

Serpeloni et al. (2017) propose that a promising line of enquiry might be, specifically, an **investigation of the transgenerational transmission of stress and trauma**, not as trauma effects per se but as vulnerabilities to circulatory system-related diseases, including cardiovascular disease, strokes and – more broadly – kidney disease, diabetes and the range of conditions within the scope of cardiometabolic science and that are the single largest contributors to the Indigenous health inequality gap today. We believe the proposal to investigate the transgenerational transmission of stress and trauma, and the vulnerability to cardiovascular disease is only strengthened by growing evidence of epigenetic contributions to a number of cardiac dysfunctions.

Extending the above line of enquiry to *preconception* trauma could also be expected to make a significant contribution to de-colonisation (and, potentially, molecular decolonisation) practice among Indigenous peoples in Australia – particularly in relation to the Stolen Generations (see the discussion under 'Trauma' in Appendix A).

A 2013 Australian Bureau of Statistics national Indigenous health survey reported around three times the rate of high or very high psychological distress among Indigenous compared to non-

Indigenous people in Australia in the month prior to the survey (ABS 2013). The most common stressors experienced in the 12 months prior to the survey were the death of a family member or close friend (28 per cent of participants), not being able to get a job (19 per cent), serious illness (12 per cent), other work-related stressors (11 per cent) and mental illness itself (10 per cent) (Australian Indigenous Health*InfoNet* n.d.). Although the results are not correlated to pregnant women, both low birthweight babies and cardiovascular disease could be at significantly higher rates among Indigenous than non-Indigenous peoples in Australia.

A research gap that could be included in an Indigenous kincentric ecological research agenda, then, might be anticipated to include research to **understand both the specifics of in utero transmission of trauma/stress in an Indigenous context, and also the potential of epigenetic healing for cardiometabolic disease**. Further, focusing on trauma, what is the role, if any, of epigenetic drug-supported exposure therapy (as discussed in the literature review) in this context?

Further, within a multidisciplinary approach, Indigenous kincentric ecological researchers may also work with others to revive cultural, or otherwise develop new forms of, pregnancy practices, including setting expectant mothers apart from potential stressors, culturally supported social support systems and other means of in utero stress reduction.

Research gaps that could be addressed in this research stream could include:

- exploring associations between trauma and brain wave research – a line of enquiry of potential great interest to an Australian Indigenous Metagenomics Strategy
- investigating Indigenous population epigenetic-level healing of stress and trauma, which might widen their remit to include the 'love and affection' experienced by Indigenous people at a population level in terms of parenting, families and communities, a state known to Indigenous thought leaders in Australia as 'social and emotional wellbeing'
- enquiring whether trauma and stress-related impacts cause epigenetic or other changes to a potentially low alpha basal state and whether this has implications for healing, including by cultural practices such as being on Country, with the benefits of exposure to nature (as well as dancing, singing and so on) having well-documented mental health benefits to many populations (Closing the Gap Clearinghouse 2014).

As discussed in Appendix A, some researchers have hypothesised that low alpha may be a basal state – in other words, the original instructions in ancestral DNA – and the genetic foundation for alpha and high alpha determined by causal variants in European populations (Peng et al. 2017).

Such a line of research may even segue with a reconciliation agenda. Yehuda & Lehrner (2018:252) note:

> Continued research in this field will likely reveal that epigenetically induced changes are a reflection of environmental exposure, and therefore by definition malleable. Even potentially heritable changes can be modified, because environments change. The role of genetics in mediating environmentally induced epigenetic effects remains an important frontier.

Trauma, like so many other areas of scientific endeavour, has been defined, to date, primarily through a non-Indigenous and otherwise privileged lens. Hence, while the experience of trauma associated with shocking or violent events is widely accepted, the possibility that living with racism (such as experienced by many Indigenous peoples) could be considered akin to a potentially traumatic event over the life course is not generally considered. Although individual

incidents/perceived incidents of racism might not meet thresholds to be considered as potentially traumatic events, the proposal is that repeat exposure builds the cumulative effect to that level over time. In other words, repeated experiences of racism – ranging from real and perceived micro-aggressions (e.g. vague insults, non-verbal exchanges and looks that may be dismissed by others) to discrimination blatantly experienced in services in shops and so on – leads to hypervigilance and a state of traumatisation over time (Carter 2007; Chou, Asnaani & Hofmann 2012). This applies too to racism experienced vicariously – through the media/seeing or hearing others from your racial group being subject to racism (Williams 2015).

It is interesting to consider the above in relation to the assertion in Australia's *National Anti-Racism Strategy* that 'racism is a constant "background noise" in the lives of Aboriginal and Torres Strait Islander people' (AHRC 2012:5). This is no secret. Successive *Australian Reconciliation Barometer*s have consistently reported non-Indigenous respondents acknowledging 'very high' 'or 'fairly high' levels of prejudice against Indigenous peoples, with up to 95 per cent of Indigenous respondents stating that to be the case (Reconciliation Australia 2012).

Research as to whether repeated exposure to racism leads to trauma has to date considered Black populations in the United States (Gee & Ford 2011). However, in Australia, study after study has associated Indigenous peoples' experiences of racism with mental health impacts. **We propose a line of Indigenous kincentric ecological research with a molecular decolonisation focus, which should include investigating and understanding the genetic and epigenetic impacts of racism** (Recommendation 2)**.**

Gap 3: National integrated research translation agenda

The genomics health sector has made substantial gains in population health and longevity over the past two decades, with key accomplishments in the areas of rare disease, environmental health (water quality control) and ageing well. However, over the past ten years, across the world there has been a rise in resurgent infectious diseases and threats of bioterrorism, and the advance of chronic diseases continues to pose threats for First Nations people in Australia and beyond. It is a critical time to focus on the development of mechanisms that can prevent, detect and address emerging population health risks to humans and our ecosystems. This will necessarily be concerned with systems performance, evidence-generative or evidence-based practice, genomics organisations and structure, and the resources available to address these issues. Partnerships and linkages will be key in the development of an integrated research translation agenda.

Gap 3 concerns:

- preventative precision medicine and metagenomics
- pharmacogenomics
- cultural, social and emotional wellbeing
- kincentric ecologies/Country
- sustainable economies.

Further, Gap 3 has specific gaps in:

- precision psychiatry – this should be built into precision medicine services as they are developed
- lack of genetic research projects in Indigenous communities and, in particular, a lack of drug safety data

- screening and management of social and emotional wellbeing, including best practice national guidelines.

The Indigenous-controlled institution/sovereignty mechanism proposed in Gap 1 is intended to develop and implement an Australian Indigenous Metagenomics Strategy connected to the social, political, cultural, economic, decolonisation and healing aspirations of Indigenous peoples (Gap 2). Gap 3 identifies and considers oversight of the translation of that research into practical outcomes that benefit Indigenous peoples in the application of the Australian Indigenous Metagenomics Strategy.

We consider five potential streams of research translation, which fall into two areas:

- health and public health (closing the health gap)
- cultural, social and emotional wellbeing.

The dividing lines between the two areas are at best artificial, even if useful for discussion purposes. Health is a critical part of social and emotional wellbeing, and wealth-generating economic activity is key to health – this health and wealth gradient has long been established as a consensus position among public health practitioners (Braveman & Gottlieb 2014).

Indeed, in a genuinely strategic approach to research translation it might be expected that each part would build on and support the others such that the whole strategic response is greater than the sum of the parts. Such integrated approaches are increasingly being adopted by policy makers – the 2008 COAG *Closing the Gap Strategy* (Commonwealth of Australia 2019) is an early example, and the approach to suicide prevention adopted in *The Fifth National Mental Health and Suicide Prevention Plan* (National Mental Health Strategy 2017) is another.

Preventative precision medicine and metagenomics

As discussed, it is envisaged that the proposed institution would actively promote the gathering of many types of microbiota specimens and conduct analysis, including for 'mismatches' within an Australian Indigenous Metagenomics Strategy. But Indigenous public health responses are not necessarily limited to the health system, and could also include:

- promotion of Indigenous cultural practices such as welcoming baby to Country, living on Country, and the life course exposure and re-exposure to the microbiota in Country ecologies (for further discussion of the range of potential benefits of Country-connection within an Indigenous Australian cultural determinants of health framework, see Arabena 2020)
- cardiometabolic healing programs, including culturally founded fasting practices and a gradual reintroduction of traditional foods in communities, including by restoring the cultivation of traditional crops (Arabena 2020). An example of this was provided by Bruce Pascoe's recent cultivation and harvest of economically significant crops of dancing grass in East Gippsland, the first believed to have occurred in 200 or so years, with other harvested and cultivated species to be trialled for harvesting and processing (Allam & Moore 2020).
- the development of Country-specific microbiota supplements and unique forms of dietary guidance for Indigenous peoples living away from Country or if otherwise needed.

Precision psychiatry is a current gap and should be built into precision medicine services as they are developed. Subject to the need for additional research in Indigenous populations, Alzheimer's disease (which affects Indigenous people disproportionately when compared to non-Indigenous peoples) has a genetic basis that makes it a good candidate for preventative precision medicine

interventions (Hampel et al. 2016). In particular, genetic variants are associated with a heightened risk of developing Alzheimer's disease although the underlying pathways by which these variants cause disease are unclear (Mahoney-Sanchez et al. 2016). Such a diagnosis should lead to thorough genetic counselling of the patient and related family members. The Our MOB (Our Mind Our Brain) project is currently investigating this research area (see 'Research projects that are being, or could be, translated to enhance clinical genomics services' in Chapter 4).

Pharmacogenomics

'Pharmacogenomics' refers to the 'involvement of all genes in determining drug response'; a related term, 'pharmacogenetics', investigates 'the variability in response due to genetic variations in genes that metabolise drugs' (RACGP n.d.).

Pharmacogenomics allows drug therapy to be tailored to individuals, enabling maximise dose efficacy and avoiding adverse effects. This feeds into the wider concept of personalised medicine, where an individual's genetic profile is used to make decisions about all aspects of their health care (i.e. prevention, diagnosis, treatment) (Abbasi 2016; Kapoor, Tan-Koi & Teo 2016; Relling & Evans 2015; Juli & Juli 2016; Trent et al. 2013).

Pharmacogenomic testing currently has several limitations:

- cost – as there is no Medicare Benefits Schedule (MBS) rebate, testing is usually 'costly and prohibitive' for some (Polasek, Mina & Suthers 2019:103)
- turnaround time – some results can take up to 10 working days, thus extending the trial-and-error approach to dosage (RACGP n.d.)
- evolving science – pharmacogenomics is comparatively new and while confidence is growing, there is 'much work to be done in documenting the clinical utility' of pharmacogenomic testing (Polasek, Mina & Suthers 2019:101).

A current gap is the lack of genetic research projects in Indigenous communities, particularly those that are isolated. This is largely a consequence of the ethical challenges of conducting genetic research in Indigenous communities and is 'compounded by Indigenous peoples' negative past experiences with genetic issues' (McWhirter et al. 2012:702). Further, there are no Australian guidelines specifically for this issue.

According to McWhirter et al. (2012) current literature suggests that most of the ethical issues can be addressed by ensuring that there is Indigenous participation in the research process, which should be tailored to the individual needs of the relevant community. There needs to be extensive consultation prior to the commencement of any new study and regular community review throughout the process.

However, as there are no Australian guidelines, Polasek, Mina & Suthers (2019:103) recommend better reimbursement for testing, increased research in Australia, local education programs, Australian guidelines, and reports embedded in practice software and electronic health records.

According to Tucci (2011:387), there is an urgent need to identify clinically relevant issues relating to the capacity of Indigenous populations to metabolise certain medicines, as 'screening for genetic variations in drug metabolism and transport mechanisms may highlight significant variations in capacity'. This has the potential to influence whether people 'benefit from or are harmed by commonly prescribed medications' for conditions such as hypertension, type 2 diabetes, cardiac disease and depression, which are highly prevalent among Aboriginal and Torres Strait Islander populations. Thynne & Gabb (2016:16) reiterate that the 'lack of data on drug safety for Australia's

Indigenous population is concerning' as it does not have a 'robust evidence base': Indigenous Australians are often not included in drug development programs and 'few randomised controlled trials have been performed in this population'. There are also no specific requirements for drug sponsors to report adverse drug reactions for ethnic groups, including Aboriginal and Torres Strait Islander peoples. Thynne & Gabb (2016:17) note that the challenge is made even greater by having to balance the 'significant need for drug safety data' with ensuring Indigenous peoples are not further disadvantaged. They make the following recommendations:

- The community as a whole (health care providers, professional organisations, patients and regulators) needs to recognise this issue and actively participate in promoting drug safety, including adverse event reporting.
- All policies and guidelines promoting the quality use of medicine in the Aboriginal and Torres Strait Islander population must include a robust pharmacovigilance strategy and an acknowledgement of the limitations of drug safety information in this population.
- The assessment and management of potential adverse drug reactions should be part of any comprehensive health care program. All health professionals, including Aboriginal health care workers, need training in pharmacovigilance, the principles of drug safety, and the identification and reporting of adverse drug reactions.
- Health care workers should be provided with culturally appropriate resources and tools to help them and their patients identify and manage adverse drug reactions.
- Adverse drug reactions should be thoroughly investigated (Thynne & Gabb 2016:17).

Optimising drug therapies will increase in frequency as new discoveries are made, and will have implications for the health workforce and, increasingly, for those people who coordinate patient care. National regulation for pharmacogenomics, with specific reporting and interpretation templates, will overcome confusion and facilitate pre-emptive testing, companion diagnostics, point-of-care testing and decision support systems to identify needs and ensure these are quickly met. Education will optimise engagement with pharmacotherapy and precision medicine.

Cultural, social and emotional wellbeing

As outlined, CSEWB is a 'critical determinant of health outcomes for Indigenous Australians' (Langham et al. 2017:1). However, the Indigenous concept of holistic health and wellbeing (including the social and cultural determinants of health) are 'poorly understood by many policy and service providers and seldom taken into account in program development and implementation' (Closing the Gap Clearinghouse 2014:5). According to Durie 'Indigenous health status can be grouped into four main propositions: genetic vulnerability, socioeconomic disadvantage, resource alienation, and political oppression' (2003:510). 'Short distance' factors are at one end of the 'causal continuum' (e.g. the impacts of abnormal cellular processes), with 'long distance' factors at the other end (government policies and the constitutional standing of Indigenous peoples) (Durie 2003:510–11). Midway along the continuum are values, lifestyles, standards of living and culture. While health care workers are more familiar with short and mid-distance factors, a 'broad approach covering a wide spectrum of interventions' is needed to improve the health of Indigenous peoples (Durie 2003:511).

Strategies to promote cultural, social and emotional wellbeing include:

- an Indigenous health workforce that has both professional and cultural competence (i.e. cultural education)

- the adoption of Indigenous health perspectives, including spirituality and traditional healing, in health services
- socioeconomic and macropolitical interventions
- capacity building
- research
- increased funding and resources for Indigenous health
- a reduction in the inequities accompanying globalisation, and constitutional and legislative changes by states (Durie 2003).

Langham et al. (2017:2) outline the need for screening and management of social and emotional wellbeing concerns, particularly as Indigenous adults are 'three times more likely than non-Indigenous adults to experience very high levels of psychological distress'. They found that while various Aboriginal health strategies and reports have recommended social and emotional wellbeing screening and management in primary health care services, physical health has remained the predominant clinical focus.

There are no national guidelines for social and emotional wellbeing screening and management, a lack of suitable assessment tools and few published service or program evaluations (Langham et al. 2017). The results of a study conducted by Langham et al. (2017:8) suggest 'a clear need for national best practice guidelines', along with dedicated social and emotional wellbeing funding and training for health service providers. Further, more research is needed to gain a better understanding of the link between screening protocols to health outcomes. They found that the lack of a clear model or set of guidelines on best practice for screening for social and emotional wellbeing in Indigenous health may contribute to the wide variation in social and emotional wellbeing service provision.

A 2014 report, *Effective strategies to strengthen the mental health and wellbeing of Aboriginal and Torres Strait Islander people*, provides detailed information about 'what is required to effectively address Indigenous people's mental health and social and emotional wellbeing' (Closing the Gap Clearinghouse 2014:4). Of particular relevance to this gap analysis are the issues the report highlights under the heading 'What we don't know':

- The effect on mental health outcomes of culturally appropriate, early intervention programs maintained over the long term.
- The additional costs to health and mental health and wellbeing of not implementing programs in culturally responsive, appropriate and respectful ways.
- The long-term cost effectiveness of Indigenous-specific programs—there have been few program evaluations, and where evaluations have taken place, they have usually been conducted before the long-term effects could be assessed.
- The extent to which Access to Allied Psychological Services (ATAPS) Tier 2 is being delivered in accordance with the objectives and principles developed through the Aboriginal and Torres Strait Islander Mental Health Advisory Group.
- The significance of access barriers for young Indigenous people to web-based and telephone helpline services. (Closing the Gap Clearinghouse 2014:3)

Kincentric ecologies/Country

In all Indigenous peoples' key philosophies is an understanding that humans are part of an ecological family with shared origins that connect us to Country. Traditional ecological knowledge can play a

part in supporting Western genomics scientists to understand the strategies that are necessary to heal whole ecologies. By working alongside Aboriginal and Torres Strait Islander on-Country leaders, and by investing in strategies such as species conservation, fire ecology, astronomy, geoscience, geography and water management, these knowledges can support and interpret the interplay between human and ecological microbiota. Merging genomics and ecological and kincentric understandings of the relationships will also facilitate the emergence of novel questions that can be answered in ways not considered before. This field of practice is not without precedent, as it can be associated with the disciplines of evolutionary biology, population genetics and evolutionary ecology, and with sciences focused on plant and animal physiology, which have as their basis biochemistry and cell biology.

Evident in work undertaken by CSIRO, genomics is the technological advance that is enriching the quality of the findings of work, ecological resources and products deriving from investments in research. The *Australian Ecosystems Models Framework Project* (CSIRO 2020), for example, aims to collate, synthesise and summarise scientific knowledge of ecosystems dynamics to describe dynamic characteristics and drivers of Australian ecosystems. Partnerships such as the one with CSIRO will progress our understanding of ecological genomics. This is because caring and sustainably managing Country is the foundation for Aboriginal and Torres Strait Islander cultures. The use, care, cultivation and management of traditional lands by Aboriginal and Torres Strait Islander peoples has been vital to the continued flourishing of Australia's natural ecosystems.

In recognising the interrelationships between partners invested in a kincentric approach to health and wellbeing, an Australian Indigenous Metagenomics Strategy will need to support the development of:

- habitat assessment systems inclusive of the relationships between Aboriginal and Torres Strait Islander peoples and their Country
- assessments that review the ecological representativeness of Australia's terrestrial ecologies, particularly after bushfires and other natural disasters
- strategies promoting ecological engineering for biodiversity adaptation to climate change
- assessing the economic benefits of maintaining natural capital in agricultural systems
- the promotion of ecosystem resilience
- building capacity in community-level modelling.

Scientists studying a region's biodiversity typically attempt to characterise species richness and species diversity. These same measures can be calculated equivalently for the other two levels of biodiversity: genes and whole ecologies. The integrity of whole ecologies is key to the Australian Indigenous Metagenomics Strategy because the main pressures on Australia's biodiversity – habitat fragmentation, altered fire regimes, invasive species (both native and non-native), harvesting of species and climate change – are increasing, and the rate of species decline is not slowing down (Yeates et al. 2014). Understanding the link between loss of biodiversity and the increase in zoonotic disease is of critical importance in an Australian Indigenous Metagenomic Strategy. Although the management and scientific challenges may be large, the environmental and social benefits for all Australians will also be large, particularly for First Nations people responsible for the microbiota on their traditional lands and seas.

Sustainable economies

The success of Aboriginal and Torres Strait Islander people in investment, export markets and trade is central to our futures. As an exporting nation, the place of Indigenous enterprise, business and commerce is key to Australia's ongoing ambitions for a growing economy that builds wealth and prosperity for Indigenous Australians. Inclusive trade broadens the benefits for trade to Indigenous peoples and is a key measure of success – further, it is in the national interest. The Australian Indigenous Metagenomics Strategy could support initiatives that boost the number of, and the value of, Indigenous exports and market access outcomes. This may also include increased direct foreign investment into Indigenous development proposals, enterprises and companies.

Indigenous Australians hold substantial and significant interests in land and sea, commercial and development interests in northern Australia. If investors, commercial interests and private sector contributors work in partnership with Indigenous peoples in ways that are consistent with sustainable practices of development and land use and management, the Australian Indigenous Metagenomic Strategy can lift the prosperity of all Australians in the north of our nation to achieve the changes we aspire to. This aspiration is founded in the lore, cultures and languages of First Nations peoples and is essential to the health, social and emotional wellbeing of First Nations people. Initiatives to strengthen the rich and diverse cultural practices, knowledge systems and cultural expressions of First Nations people will be dependent on the protection of rights of Indigenous peoples over the use and place of their own traditional knowledges and intellectual property. For example, in the field of biodiscovery, various uses for native flora and fauna could be commercialised to assist in all aspects of life, such as healing, industry, commerce, trade, nutrition and good health. The use of traditional knowledge for biodiscovery is both an asset for Aboriginal and Torres Strait Islander peoples and, in turn, a national asset deserving of preservation, development and protection.

The Australian Indigenous Metagenomics Strategy can support the development of sustainable economies and prosperous futures by:

- working with and observing Indigenous land and sea management practices when managing the Indigenous Estate
- supporting Indigenous peoples' ambitions to expand the value of exports from the agricultural sector of our economy – there is a desire and a place for Indigenous interests in our agriculture, aquaculture and land management sectors
- sustaining Indigenous rights to commercialise Indigenous botanicals for new export markets and through trade pacts and agreements, which may include appropriate supports for the protection, certification, research, and development and commercialisation of Indigenous rights in ways that are Indigenous led and managed
- ensuring Aboriginal and Torres Strait Islander peoples' rights to biodiscovery are acknowledged, preserved, developed and protected.

The Australian Indigenous Metagenomics Strategy could support the protection of Aboriginal and Torres Strait Islander traditional knowledge and work to ensure just and equitable partnerships are formed for the use of such knowledge – with the threshold being free, prior and informed consent and shared benefit, while implementing a community prosperity agenda.

Gap 4: National precision medicine implementation program and national feedback mechanisms

Gap 4 relates to:

- the establishment of Indigenous precision health services
- community advisory forums
- promotion of metagenomic literacy
- promotion of accessible metagenomic information
- national feedback mechanisms.

More specifically, Gap 4 identifies gaps in:

- the development of metagenomic literature that is accessible to the lay and Indigenous reader
- the promotion of metagenomic literacy across First Nations communities, with a focus on Elders and community leaders, so they can understand and promote the value of metagenomic approaches.

Establishing Indigenous precision health services

Gap 3 discusses precision medicine and public medicine in the context of research translation. Here, in Gap 4, we look at what might be needed to implement precision medicine with a focus on Indigenous-specific primary health care settings, including Aboriginal Community Controlled Health Services (ACCHSs).[14] We approach this using the three-step structure provided by the *Future of Precision Medicine in Australia* (Williamson et al. 2018) report:

- workforce education, starting with general practitioners working in or through ACCHSs
- services models attuned to precision medicine
- a whole-of-community education program.

Indigenous participation through primary health care settings, especially ACCHSs, is one approach to improve Aboriginal and Torres Strait Islander access to such measures and should be viewed as a strategic solution to overcoming health inequalities.

The principles used by ACCHSs in health and wellbeing programs cover health equality, community engagement, partnerships and accountability. Such principles can be extended to precision medicine to ensure and promote its benefits. Using these principles, useful practices include:

- at the design stage of clinical research, development and implementation, embedding appropriate protocols to ensure diversity of participants
- targeting diseases that disproportionately affect disadvantaged groups
- building and promoting capacity in the research, development, implementation and evaluation of precision medicines among Indigenous leadership in relevant professions and organisations
- developing and continuously evaluating information resources in precision medicines at Indigenous and mainstream settings

14 ACCHSs are community place-based health services operated and controlled by community representative boards and answerable to the communities they serve. They range in size and services offered but have been steadily growing towards their model of comprehensive primary health care since first established in the early 1970s.

- integrating awareness of issues in precision medicines into the governance structures, formal reviews and evaluations, data collection protocols and analytical pipelines of Indigenous and mainstream research and health services projects (Williamson et al. 2018).

Community advisory forums

Community advisory forums foster partnerships between researchers and local communities, and build local capacity, trust and understanding. Importantly, they ensure that community values and cultures are given priority.

The opportunity for communities to come together to consider and discuss the multiple issues in topics as complex as metagenomics and precision medicine is essential. **The current lack of community advisory forums is a gap simply because of how new precision medicine is.**

Opportunities abound to address this gap through governance committees, think tanks, on-Country discussions, cross-institutional partnerships and the like.

The advantage of community advisory forums is that they offer the opportunity for cohesion and agenda setting that is free from colonial underpinnings of genetics.

Promote metagenomic literacy

Genomic/metagenomic literacy is vital if doctors, health care staff, patients, and family and community members are going to benefit from precision medicine. The need for an understanding of the subject is paramount.

A current gap is the need to promote metagenomic literacy across First Nations communities, with a focus on Elders and community leaders, so they can understand and promote the value of metagenomic approaches. A key stakeholder suggested that Metagenomic Elders Camps should be established – such camps would acknowledge and harness the critical role of Elders in promoting ethical research in our communities.

Another gap is that 'exciting new areas of science [such as metagenomics] typically do not appear in science classrooms and textbooks until many years after their inception. This pattern leaves undergraduate, and especially high school, biology education lagging behind scientific advances' (Jurkowski, Reid & Labov 2007). To further an understanding of metagenomics, educators at primary, secondary and tertiary levels need to engage students with a range of tailored educational frameworks and programs. Such programs could include learning about microbial communities, their influences on and interactions with other organisms in different environments, and the practical applications of metagenomics (Jurkowski, Reid & Labov 2007). Importantly, the ethical and social aspects of metagenomics need to be interwoven into subject teaching and learnings to ensure Indigenous participation and acceptance.

Promote accessible metagenomic information

Metagenomically literate Indigenous communities and individuals should be able to meaningfully consider the futures that metagenomic research may create for them, whereby the national institution proposed can be guided to determine research priorities and continue to refine a national Indigenous metagenomic research strategy connected to the social, political, cultural, economic, decolonisation and healing aspirations of Indigenous peoples.

The development of metagenomic literature that is accessible to the lay and Indigenous reader is a current gap. As noted in the *National Health Genomics Policy Framework: 2018–2021*, access and

equity should be promoted for vulnerable populations (AHMAC 2017). While the need for highly technical and precise language is acknowledged to facilitate and engage between practitioners and experts, concerted work is required to let others participate in the space without such language being a barrier.

Integrating key genomics terms in local languages and addressing priority areas in communities needs to be a key focus.

National feedback mechanisms

The lack of national feedback mechanisms is a current gap that ties in with Gap 1 – until there is an Indigenous-controlled national metagenomics umbrella institution, there is nowhere to feedback to.

At its broadest, we propose that the national institution should take participatory action research as a model when developing and overseeing an Australian Indigenous Metagenomics Strategy. Feedback mechanisms could include:

- supporting the development of, or connecting to existing, jurisdictional or regional metagenomic networks that effectively connect the national institution into a 'feedback loop' with communities
- national conferences – such as the national Indigenous suicide prevention conferences that take place every two years and gather together a wide range of Indigenous stakeholders (Australian Government 2013a) – with recommendations included in conference reports
- specific projects – for example Professor Emma Kowal's *Epigenetics and Indigenous Australia* project (see Chapter 4)
- ad hoc community forums – an example of such is discussed in *The Future of Precision Medicine in Australia*, albeit in a non-Indigenous context (Williamson et al. 2018). Two four-day deliberative public forums were held on the topic of biobanking to inform the report. Attendees were given resources in advance and had a day of presentations from experts, then spent three days debating the merits, conditions and risks associated with biobanking. Results fed into the subsequent development of the Western Australia guidelines for human biobanks (Office of Population Health Genomics 2010).

6 Conclusion and recommendations

In conclusion, our approach to an Australian Indigenous Metagenomics Strategy aims to bring together key stakeholders from research, policy and practice across different knowledge traditions to develop a structured metagenomics agenda for Australia, identify partners and research methods, identify top research priorities, and build momentum for the next steps forward. The umbrella organisation proposed to guide this approach in Australia privileges a connection to Country agenda to disrupt the colonial gaze and heal our relationship with the Indigenous Estate. This is done not to trivialise the work in human genomics to date, but to reassert our ancestral responsibility and anthropogenic duty as custodians of more than 50 per cent of the microbial communities on the lands, waters and seas of the Australian continent. We seek to shift away from government policies founded on eugenics, assimilation and trauma to policies of wealth, abundance and prosperity. To do this, we need a process of consensus-building to create a collective program of research to advance this agenda, a process in which efforts are made to include representation of all important actors from across the Indigenous Estate, agricultural and care-for-Country projects, and Indigenous landholders, businesses and entrepreneurs with scientists invested in supporting endemic species to thrive and flourish. As we said at the beginning of this report, genetics is implicated in our suffering, and in our emancipation.

In making the following recommendations, we aim to spark interest, bring focus to the work and promote collaborative inquiries in this important area of research as we enter the Anthropocene. We note the importance of Recommendation 1, from which all our other recommendations follow. We also note that all recommendations in this report are the views of Karabena Consulting. We provide these recommendations to support the development of an Australian Indigenous Metagenomics Strategy.

Recommendation 1: Establish an Aboriginal and Torres Strait Islander-controlled national metagenomics umbrella institution

The umbrella organisation's functions should include the following:

Data governance and sovereignty

- Address gaps in Indigenous oversight and governance in relation to sample sovereignty.
    - Oversee resolution of any issues that arise – the institution will ultimately be empowered to withhold consent within the international and national metagenomic spaces on behalf of a Nation or community.
- Train communities in data governance – founded in a social-cultural determinants framework addressing the asymmetric power imbalance of relationships in current data governance.
- Develop and implement strategies that promote protection and ownership of Indigenous and regional reference genomes and relevant databases.
    - Roll out the 'dynamic consent' database management model, which ensures biobank participants are informed about how their samples are being used, with the option of opting out of projects while maintaining participation in the biobank.
- Act as a vehicle to promote culturally safe and appropriate genomic and phenotypic data collection and sharing that reflects Australia's ethnic diversity, including for Indigenous peoples.

- Lead cross-disciplinary discussions and First Nations engagement to promote participation in workforce development.
- Strategise how to control and express local knowledge and data.

Research

- Establish a centre of research excellence with its own research agenda, expertise, practitioners, resources and funding that also works in partnerships with other institutions as necessary.
- Develop and implement Australian Indigenous metagenomics research strategies in partnership with professions that care for Country based on the Indigenous Estate. This would include:
    - an Australian Indigenous Metagenomics Strategy
    - the adoption of a 'system of systems' approach to developing metagenomics strategies within whole ecologies
    - an integrated research translation agenda
    - an empowering, participatory action research-based precision medicine implementation program
    - an overarching community feedback mechanism.
- Develop policy positions and advocacy documents, support the uptake of health literacy and commission research in partnership with other funding bodies such as CSIRO, the Lowitja Institute and NHMRC.
- Support student scholarships and research partnerships:
    - adapt existing scholarship programs to support Indigenous applicants or establish a separate stream of scholarships overseen by the umbrella institution.

Other

- Collaborate with international and domestic institutions/governments and health systems:
    - share infrastructure to manage the vast, accumulating amounts of data generated by metagenomics research
    - contribute to ongoing iterations of broader governmental efforts such as the Closing the Gap agenda.
- Oversight of a metagenomic workforce training program – the institution will play a key role in supporting the workforce with career paths, ongoing mentoring and coaching support, and could consider the facilitation of communities of practice to guide these workforces.
- Develop widespread understanding of, and engagement with, microbial community custodianship.

Recommendation 2: Develop and implement a metagenomic cardiometabolic healing research agenda within a broader Australian Indigenous Metagenomics Strategy under Indigenous control

Under the direction of the umbrella organisation:

Molecular decolonisation

- Develop an epigenetic healing research agenda that focuses on the impacts of trauma, including the following:

- Indigenous kincentric ecological research with a molecular decolonisation focus, including investigating and understanding the genetic and epigenetic impacts of racism
- the transgenerational transmission of stress and trauma, including a range of cardiometabolic disease states that are associated with trauma (i.e. cardiovascular disease, strokes, kidney disease, diabetes etc.); this line of research can be extended to include preconception trauma
- the specifics of in utero transmission of trauma/stress in an Indigenous context and the potential of epigenetic healing for cardiometabolic disease; this can include the role, if any, of epigenetic drug-supported exposure therapy
- associations between trauma and brain wave research
- Indigenous population epigenetic-level healing of stress and trauma, including the experience of 'love and affection' in terms of parenting, families and communities (i.e. social and emotional wellbeing)
- whether trauma and stress-related impacts cause epigenetic or other changes to a potentially low alpha basal state and whether this has implications for healing, including by cultural practices such as being on Country.

Metabolic healing

- Adopt a metagenomic approach that accounts for adaptations to microbiota and traditional food supplies, in addition to genomic research.
- Indigenous researchers can focus on understanding the nature of both matches and mismatches across diet, microbiota, microscopic life in the environment, the environment itself and Indigenous genomes.
- A research agenda could focus on the relevance of historical, millennia-old Indigenous diet–biome–genome interactions and adaptations to the health of contemporary Indigenous populations today, and whether those that have inherited historically positive adaptions might now be at a disadvantage because of them.

'Country-as-microbial communities'

- Connect human genetic research to the genetic research occurring on Country. This is a critical link to reposition the Indigenous genomics agenda within an Indigenous genomics framework.
- Develop a research strategy on the genetics of microbiome exchange through birthing on Country. The proposed metagenomics institute can partner with Indigenous professional associations in Australia and internationally to progress birthing on Country and ensure articles in conventions to which Australia is a signatory are respected and acted upon.
- Widen metagenomic research and activity to include support for introduced species eradication, restoring the environments in which species thrive, and tackling animal and plant diseases. This could include the restoration of extinct species for which enough DNA is available, if these technologies are deemed ethical and otherwise developed.

Recommendation 3: Develop an Australian Indigenous Metagenomic Workforce Strategy

Under the direction of the umbrella organisation:

- Map current Indigenous genomic education to understand the health literacy needs of people in community, and to create opportunities for the emerging genetics workforce.

- Develop the Australian Indigenous Metagenomic Workforce Strategy in concert with the Aboriginal and Torres Strait Islander staff at the CSIRO as part of the Australian Microbiome Initiative.
- Develop metagenomic workforce training.
- Balance current genetic workforces (genomic policy makers, practitioners, clinicians, genetic counsellors, bioinformaticians and other scientists) with the emergence of ecologically based genetic workforces.
- Invest in vehicles such as Indigenous-led governance, community engagement, community education and professional training, improved access to precision medicine, the development of First Nations' variant libraries and understanding of the economic impacts of this work.
- Further develop the genomics workforce by engaging ecologists, environmental scientists, park managers, environmental advocates and young people who are invested in building our knowledge of community values and perceptions of the natural environment.
- Advocate for the right to develop this Indigenous workforce without acquiring personal or higher educational debt, understanding that there are rights and responsibilities that we have to our Country, our First Nations and our Australian nation into the 21st century.
- Establish long-term and sustainable investments in developing people's skills and capacities to work in a complex and sensitive area.
- Adapt existing scholarship programs to support Indigenous applicants or establish a separate stream of scholarships.
- Set an Indigenous metagenomics workforce target of approximately 5–6 per cent of the total metagenomics workforce spread across the types of workers required.
- Develop collective best practice approaches to meaningful and longitudinal individual and family participation in becoming part of the metagenomics workforce.
- Join with peak health and ecological agencies to develop certificates of practice, ecological and health literacy strategies, and new-look workforces that promote human health in healthy ecosystems.

Diversity

- Establish a set of principles to reflect and respond to the needs of a diverse human population.
- Establish diversity-enhancing strategies and programs.
- Through cross-disciplinary discussions led by the national umbrella organisation, cross-fertilise the development of the complex but necessary processes for progressing Indigenous prosperity and build capacity for resolving the issues of diversity in lived experiences and workforce development practices.

Recommendation 4: Fund the umbrella organisation to address identified gaps in the Australian Indigenous Metagenomics Strategy

Gap 1: A national Indigenous metagenomic sovereignty mechanism

- Establish an Indigenous-controlled national metagenomics umbrella institution to bridge the gap in research, services and activities where increased attention would benefit Aboriginal and Torres Strait Islander peoples (see **Recommendation 1**).
- The institution would straddle two spaces:

    - the metagenomic kincentric research space – this will need to be supported by national agreements involving a range of stakeholders and research institutions, and will need to be built into the next iteration of the *National Health Genomics Policy Framework and Implementation Plan 2018–2021*, and by legislation such as the *National Centre for Indigenous Genomics Statute 2016* (Cth).
    - the Closing the Gap/Indigenous health space – the institution could be included in the next iteration of the National Agreement on Closing the Gap.
- The institution would ideally aim to become financially independent or self-funding through maximising research commercialisation opportunities.

Gap 2: An Australian Indigenous Metagenomics Strategy

- Establish a metagenomic cardiometabolic healing research agenda within a broader kincentric ecological metagenomic research agenda under Indigenous control (see **Recommendation 2**), addressing the following gaps:
    - macro – healing Country, animal and plant kin: microbial community custodianship
    - cardiometabolic healing at the micro–macro ecological interface
    - micro – understanding 'the original instructions in Indigenous ancestral DNA'.

Gap 3: A national integrated research translation agenda

Gap 3 identifies and considers oversight of the translation of the above research strategies into the following practical outcomes that benefit Indigenous peoples in the application of the Australian Indigenous Metagenomic Strategy:

- promotion of Indigenous cultural practices such as welcoming baby to Country, living on Country, and the life course exposure and re-exposure to the microbiota in Country ecologies
- cardiometabolic healing programs, including culturally founded fasting practices and a gradual reintroduction of traditional foods in communities, including by restoring the cultivation of traditional crops
- the development of Country-specific microbiota supplements and unique forms of dietary guidance for Indigenous peoples living away from Country or if otherwise needed
- building precision psychiatry into precision medicine services as they are developed.

Gap 4: National precision medicine implementation program and national feedback mechanisms

- Establish Indigenous precision health services through:
    - workforce education, starting with general practitioners working in or through ACCHSs
    - services models attuned to precision medicine
    - a whole-of-community education program.
- Foster national cohesion and agenda setting free from colonial underpinnings of genetics through community advisory forums such as governance committees, think tanks, on-Country discussions and cross-institutional partnerships.
- Promote metagenomic literacy across First Nations communities, with a focus on Elders and community leaders.
- Promote accessible metagenomic information by developing literature that is accessible to the lay and Indigenous reader.
- Provide national feedback mechanisms through the national institution, including:

    - jurisdictional or regional metagenomic networks that effectively connect the national institution into a 'feedback loop' with communities
    - national conferences that gather together a wide range of Indigenous stakeholders
    - specific projects
    - ad hoc community forums.

Recommendation 5: Invest in an Indigenous metagenomic strategy infrastructure

Under the direction of the umbrella organisation, invest in the following key areas of data infrastructure:

- collection, aggregation and automated analysis of information
- promotion of protocols that address unaccountable and discriminatory forms of algorhythmic decision making
- infrastructure that can be accessed and used productively to progress social, cultural, economic and political goals as decided by the data suppliers
- multidisciplinary and cultural investments in a 'Good Genomics Data Future' to disrupt the digital colonial practices inherent in genetics work in First Nations communities
- development of First Nations' manifestos and practices, promotion of data and justice, investment in models that promote access, equity and Indigenous control, commercialisation options and creating an understanding of good and smart data
- partnerships with:
    - international Indigenous and non-Indigenous research institutions relevant to Indigenous peoples in Australia
    - CSIRO, Indigenous Business Australia, the Indigenous Land and Sea Corporation, Traditional Owner groups, Australian Institute for Aboriginal and Torres Strait Islander Studies and genetic institutions
    - Australian governments and health systems to support precision medicine in Indigenous communities and health services.
- emerging data governance models, including:
    - data sharing pools – horizontal joint initiatives among data holders to aggregate data from different sources to create more value through their combination
    - data cooperatives – enabling a decentralisation of data in which Indigenous peoples would voluntarily pool their data together to create a common pool for mutual benefits
    - public data trusts – integration of data from multiple sources to inform policy making, promote innovation and address societal challenges that adopt a responsible approach to the use of personal data
    - personal data sovereignty – in which data subjects have greater control over their data, both in terms of privacy management and data portability.

Appendix A: Literature review

This literature review aims to answer the question: What Indigenous-specific genomic research has occurred since December 2010, both domestically and internationally, with relevance to Aboriginal and Torres Strait Islander peoples, and that can inform a research agenda into the future? The qualifier 'with relevance to Aboriginal and Torres Strait Islander peoples' is important. The concept of Indigenous peoples is grounded in international law (Kingsbury 1998). 'Indigenous peoples' refers to the original or earliest known inhabitants of an area who maintain their traditions and cultures as minorities, even as other groups that have colonised their territories remain there (United Nations 2009). The United Nations estimates that more than 370 million Indigenous people – including at least 5000 distinct peoples – live in more than 70 countries worldwide (United Nations n.d.).

The potential scope of this review is enormous. In response, it focuses on research among Indigenous peoples with a similar experience of colonisation (past and present) to that of Aboriginal and Torres Strait Islander peoples today: namely, the Indigenous peoples of Canada and the United States, and the Māori of Aotearoa New Zealand, all currently living in the Anglosphere as it has consolidated itself – a group of nation states whose main language is English, and who have social, cultural, economic and political origins in the British imperial endeavour (Pulver et al. 2010).

This literature review focuses on research among Indigenous peoples with similar experiences of colonisation to Aboriginal and Torres Strait Islander peoples today. But even a consideration in this narrower context does not fit neatly into national borders. In Australia, Torres Strait Islander genomic studies, as they exist, require separate treatment from Aboriginal studies by virtue of the two being distinct population groups. In contrast, Māori genomics is – to a significant degree – inseparable from that of Polynesian peoples across the Pacific (QIMR Berghofer 2019). Likewise, Indigenous American and Canadian genomic studies require contextualisation regarding ancient migrations that took their ancestors from East Asia to the southern tip of South America. And the Indigenous peoples of the Arctic have unique genetic histories, albeit ones that overlap with other North American Indigenous populations.

Australian and international literature by populations

At a population level, Aboriginal and Torres Strait Islander people have poorer health and wellbeing compared to their non-Indigenous counterparts. However, the current health and wellbeing experienced by Australian populations has been achieved by ruining the integrity of ecosystems, and attributable to complex arrays of biological, sociocultural, political and economic determinants of health and wellbeing, and a lack of policy and programming focus on addressing climate change, biosecurity concerns and competing industrial chemical interests of multinational companies. While this has come about as a result of significant disruptions from the second wave of human occupation more than 200 years ago, it is critical to contextualise the current health and wellbeing of Aboriginal and Torres Strait Islander people in the movement of modern humans to this continent and to Oceania.

Aboriginal peoples and Torres Strait Islanders

Archaeogenetics

Although still the subject of ongoing research and debate, evidence suggests modern humans populated the planet starting with a single wave of homo sapiens migration out of Africa circa (c.)

100,000 years ago – these are the ancestors of all non-African modern humans, including the Indigenous populations that are the focus here (yourgenome n.d.).

The Out of Africa to Sahul model

Rasmussen et al. (2011) genomically sequenced a 100-year-old Western Australian Aboriginal male genome (without admixture) obtained from a lock of hair. Among other processes, they then compared about 450,000 genetic markers – single nucleotide polymorphisms (SNPs) – with the same markers for 1220 genomes representative of 79 populations (including Indian Cambodian, Han Chinese, Japanese, Papuan and Bougainvillea Islanders), including many already stored in reference genome databases.

By then compiling phylogenetic trees, the researchers modelled that Aboriginal peoples descended from an early human dispersal from Africa into eastern Asia c. 62,000 to 75,000 years ago and *separate* from the one that gave rise to modern Asian populations c. 25,000 to 38,000 years ago. Offshoots of this out-of-Africa wave reached the ancient continent of Sahul – a roughly contiguous land mass, the remnants of which currently include Australia, Tasmania, Papua New Guinea and the Torres Strait Islands – c. 50,000 years ago (Figure A.1).

The findings confirmed Aboriginal peoples were Australia's First Peoples, with SNP, mitochondrial haplogroup and Y-chromosome haplogroup lines, and a temporal sequence, of descent consistent with c. 50,000 years of isolation on the continent. They further demonstrated that Australia's Aboriginal populations, and with them their cultural lineages, are among the oldest examples of population-in-place continuity outside Africa.

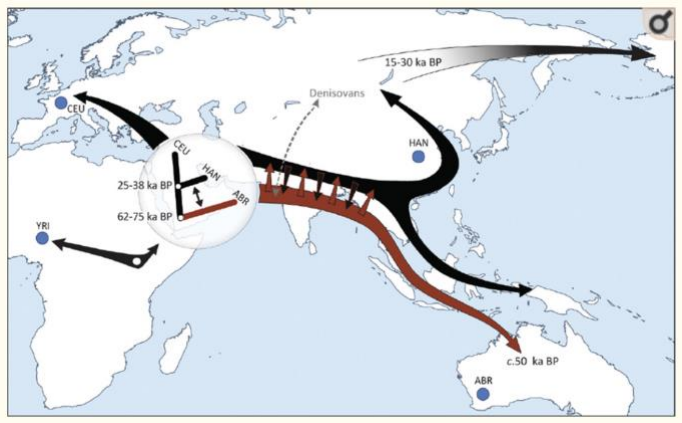


Figure A.1: The spread of modern humans from Africa to Australia (Rasmussen et al. 2011)

The above model shows the divergence of Aboriginal peoples of Australia relative to European and Han Chinese, with admixture between Australasian and Asian ancestors which ultimately led to both founding populations of the now Indigenous peoples of the Americas and the Pacific. The dotted arrow shows admixture with ancient peoples and, as evident in most other contemporary populations, including admixture with Neanderthals.

In 2015, researchers proposed an alternative model to the above – that Australasian (including Aboriginal) populations derived ancestry at least in part from an earlier wave of out-of-Africa migration –based on archaeological, fossil, climate and genetic evidence (Reyes-Centeno et al. 2015). However, this was significantly unsupported by Mallick et al. (2016) – the research team behind the Simons Genome Diversity Project reference database. Reyes-Centeno et al. (2015) did

this by deep coverage genomic sequencing of three Aboriginal, 16 Papuan and two Bougainvillean genomes and comparison with those of other genomes to confirm a phylogenetic tree connecting Australasian populations to the single dispersal of modern humans (as discussed above).

The split from Papuan populations

Malaspinas et al. (2016) add significantly more detail to the Rasmussen et al. (2011) model. The researchers sequenced 83 Aboriginal genomes from the Pama-Nyungan language group in diverse locations. This is a 300-strong language group covering most of Australia, as indicated in yellow in Figure A.2. The researchers also sequenced 25 Papuan genomes, in addition to drawing on existing reference genomes from the Simons Genome Diversity Project.

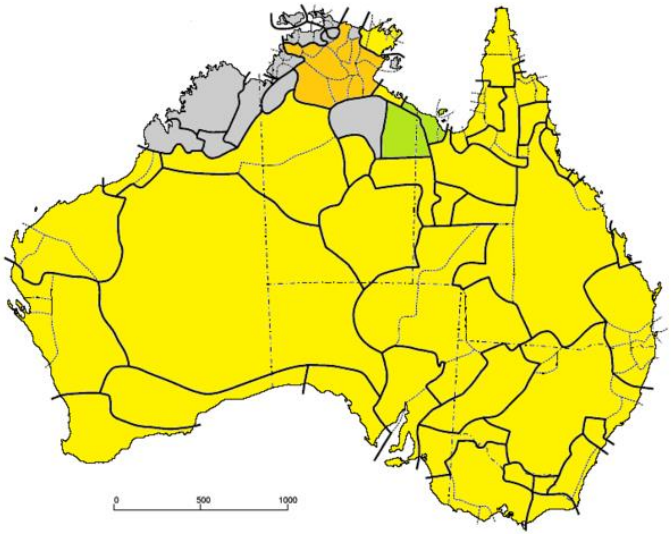


Figure A.2: The 300-strong language group covering most of Australia, as indicated in yellow (Malaspinas et al. 2016)

By organising mitochondrial haplogroups into phylogenetic trees and a temporal sequence, the researchers confirmed the Rasmussen et al. (2011) model and determined that Australasian populations diverged from Eurasian populations between c. 51,000 and 72,000 years ago following a single out-of-Africa event – but, further, that significant genetic divergence of Aboriginal from Papuan populations occurred around 25,000 to 40,000 years ago, coincident with their respective isolation from each other after sea level rises broke Sahul up into its constituent parts. Further, the Pama-Nyungan language group genomes showed descent from a single founding population that had, in turn, differentiated from other Aboriginal populations c. 10,000 to 32,000 years ago, followed by continent-wide dispersal, and then isolation, essentially mirrored by the spread of the Pama-Nyungan languages. See also Yuen et al. (2019).

Nagle et al. (2016) tested the above model by analysing Y-chromosome haplogroups from about 650 diverse Aboriginal male genomes. 17 loci were analysed for STR, and 47 loci for SNPs. When Eurasian admixture was discounted, ancient Sahul-Australasian Y chromosome haplogroups were detected (C-M130 and M-M186), along with three that were Aboriginal specific (C -M347, K-M526 and S-P308). Dating of these latter three indicates that all are at least 40,000 years old, confirming their long-term presence in Australia. The researchers modelled that Papuan and Aboriginal peoples have been isolated from each other for more than 30,000 years.

Two coastal paths of migration

Tobler et al. (2017) undertook mtDNA research using hair samples and detailed anthropological information collected from more than 5000 Aboriginal people during expeditions run by the University of Adelaide between the 1920s and 1970s. From the information accompanying the samples, it was possible to distinguish non-admixture hair samples. From these, 111 samples collected from three mission communities (Point Pearce and Koonibba, South Australia, and Cherbourg, Queensland) were selected for mitogenomic sequencing and mtDNA haplogroup analysis of descent and the timeframes involved. The researchers noted marked geographic patterns and deep mitogenomic splits down the east and west coasts of Australia that implied Aboriginal people in Australia occupied the continent by two rapid, simultaneous migrations along the east and west coasts, and that these met in southern Australia c. 50,000 years ago (see Map 4 below).

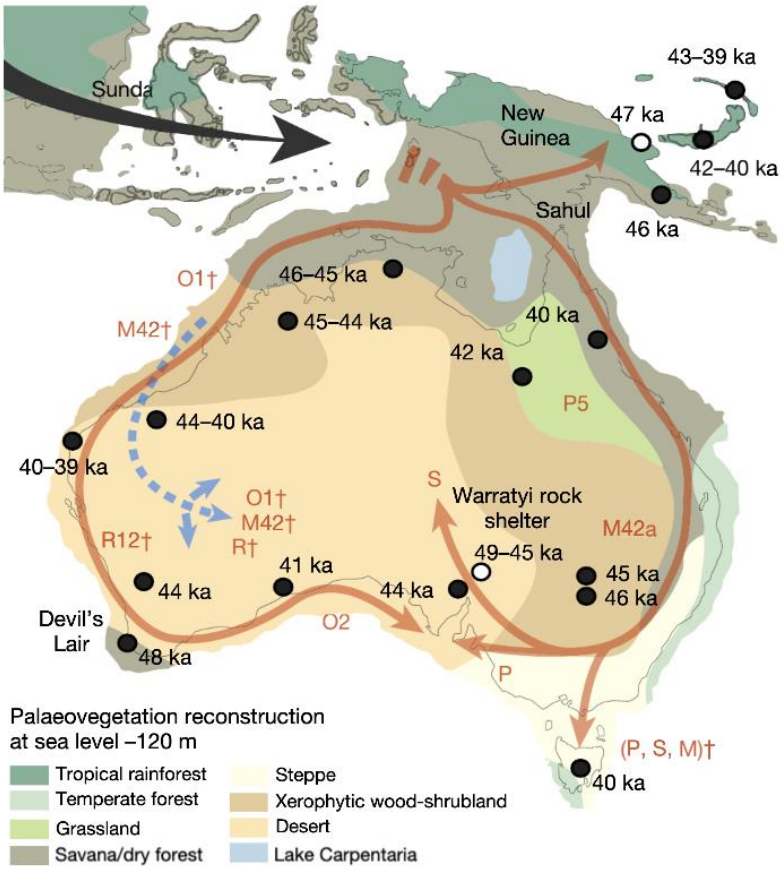


Figure A.3: The peopling of Australia (Tobler et al. 2017)

Subsequent arrivals unsupported

Malaspinas et al.'s (2016) largely unsupported hypothesis of subsequent human entry into Australia between the arrival of Aboriginal peoples and European contact was suggested by, among other things, the arrival of the dingo from South East Asia around 4000 years ago. But further genomic evidence was proposed to a model of gene flow from the Indian subcontinent to Australia around the same time.

First, in 2002, a Y-chromosome haplogroup lineage was detected in both Indian and Australian Indigenous populations and was estimated to have a most recent common ancestor around 5000 years ago, having entered Australia from India (Redd et al. 2002). Second, signs of a 4000-year-old

Indian admixture in Indigenous Australian genomes had been reported by Pugach et al. (2013). They proposed that such arrived around 4320 year ago, with the timing explicitly connected to the arrival of the dingo, which they also described as genetically closer to South East Asian dogs while morphologically more closely resembling Indian dog varieties.

Pugach et al. (2013) relied on relatively small existing datasets (i.e. from previous research) of Northern Territory Aboriginal genomes, as well as 25 Indian genomes, including that of Dravidians (the ancient Indigenous population of India) and 11 South East Asian population groups, and others, from reference genome databases. These were analysed for SNPs that were then sequenced and phylogenetic trees developed. The researchers acknowledged the possibility that (a) 'Indian-like' SNPs could have been generated in Indigenous Australian populations independently of admixture, (b) that Indian genetic signatures could have entered the groups sequenced through non-Indigenous post-colonial admixture and (c) that admixture would more likely be via South East Asian populations with Indian admixture. However, by analysis they ruled out these possibilities, only leaving further questions as to how the purported admixture might have occurred. Pugach et al. (2013) concluded by acknowledging the need for more substantial Australia-wide Indigenous datasets by which they could have reached a more definitive conclusion.

Bergstrom et al. (2016) also tested the Indian admixture model with reference to an existing database of 144 Aboriginal Y-chromosome haplotypes. Because of post-1788 admixture with non-Indigenous peoples, about 70 per cent of Aboriginal men were carrying non-Indigenous Y-chromosome haplotypes. Eventually, 13 (from Queensland, Western Australia and the Torres Strait Islands) of the 144 were recontacted and agreed to high coverage genomic sequencing. The results were then compared to 1244 Y-chromosomes haplotypes collected by the 1000 Genomes Project, including from Papuans. The researchers noted an Aboriginal–Papuan Y-chromosome haplotype divergence c. 50,000 years ago, which further supported the broad model that has emerged from Tobler et al. (2017), but no other evidence for subsequent, including Indian, admixture. Their findings were also and subsequently supported by Nagle, Ballantyne et al. (2017) and McAllister, Nagle and Mitchell (2013).[15]

Ancient connections to Country

Nagle, Ballantyne et al. (2017) sequenced 502 Aboriginal mitogenomes with focus on regions where data was patchy or missing, including for Torres Strait Islanders. With exclusion of European admixture, 461 mtDNA haplogroups were identified for high coverage scanning and a phylogenetic tree constructed. The mtDNA haplogroups were identified to be c. 39,000 to 55,000 years old, with haplogroup differences aligned with geographic regions, suggesting populations had remained on their Country as Nations and peoples for tens of millennia. This included Torres Strait Islanders, whose mtDNA haplotypes were distinct from both Papuan and Aboriginal groups. There was, further, no evidence of gene flows from other populations, such as India.

Tobler et al. (2017:183) further concluded based on studying mtDNA haplogroup lineages that:

> The long-standing and diverse phylogeographic patterns documented here are remarkable given the timescale involved, and raise the possibility that the central cultural

15 McAllister, Nagle and Mitchell (2013) further investigated the mtDNA haplogroups of the Barrinean peoples of Far North Queensland (who have a distinct morphology to other Aboriginal groups) and Tasmanian Aboriginal people in relation to potential Indian–South East Asian population admixture subsequent to the ancient arrivals discussed above. Both groups were found to cluster with Aboriginal mtDNA haplogroups, giving no support for either Indian or South East Asian admixture models.

attachment of Aboriginal Australians to 'country' may reflect the continuous presence of populations in discrete geographic areas for up to 50,000 years.

See also Wright et al. (2018).

Torres Strait Islanders

Nagle, van Oven et al. (2017) sequenced and compared 127 mitogenomes, including those of Papuans, Aboriginal peoples and Torres Strait Islanders. The research supported – as had long been suspected – a stronger genetic link with Papua New Guinea populations, although certain SNPs were restricted to either Papua New Guinea or the Torres Strait, suggesting isolation as a significant feature of much of the latter's history. Further, there was little evidence of pre-contact genetic mixing between Torres Strait Islander and Aboriginal populations.

Human genomic health research undertaken in Australian Indigenous populations

Metabolic disease

Type 2 diabetes

The Australian Institute of Health and Welfare (AIHW) estimates that type 2 diabetes (T2D) determines about 8 per cent of the Indigenous – non-Indigenous health gap in Australia (AIHW 2020b). High body mass index (BMI) and physical inactivity are key risk factors for diabetes in Indigenous populations, and TD2 rates are higher in remote areas and for those with poor socioeconomic status (Thurber et al. 2018).

Until 2015, genome-wide association studies (GWAS) were used to identify multiple SNPs/ genes associated with T2D and a high BMI in various population groups (Billings & Florez 2010). However, little significant research had taken place among Australian Indigenous populations until Anderson et al. (2015) focused on a cohort of 402 individuals from Western Desert Martu people and family groups, including those with diagnoses of T2D.

DNA was obtained from participants by saliva samples and corelated to height and weight measurements/BMI. GWAS and supplementary techniques were used to compare millions of identified SNPs with those found in the 1000 Genomes Project reference genome database, including SNPs genotyped as associated with BMI/T2D from previous studies.

By this method, and despite the out-of-Africa dispersal of modern humanity c. 100,000 years ago, the Martu cohort was found to share SNPs in gene loci and high BMI/TD2 with populations worldwide, including those associated with the strongest gene-by-environment interaction for BMI in African-Americans, suggesting the ancient nature of these gene functions.

Additional, novel SNPs were also found in the same loci, including the region of genes BCL9 and KCNJ6. These genes transcribe proteins that through complicated pathways stimulate and regulate insulin secretion in response to food intake. Significantly, because these SNPs were in the same loci associated with BMI/T2D in other populations, international research efforts were likely to be of ongoing relevance in understanding BMI/T2D development in the Martu, with likely ramifications for other Australian Indigenous populations.

Sorenson et al. (2016) proposed that Flaviviridae-family viral infections might be T2D risk factors among Aboriginal peoples. Their hypothesis is based on several findings:

- Among the Flaviviridae-family viral family, hepatitis C (HCV) is already acknowledged as a risk factor for T2D, including by immunological inflammation responses that can affect liver

and other metabolic functions. Yet genomic research shows that HCV and other flaviviruses share similar ribonucleic acid (RNA) variations in the same loci as HCV and could be causing similar inflammation responses as HCV.

- Other flaviviruses – Murray Valley encephalitis virus (MVEV), Kunjin virus, Alfuy virus, Kokobera virus, Stratford virus and Edge Hill virus – have been isolated from mosquitoes throughout Australia and the Torres Strait. They are endemic. One study reported that 50 per cent of an Aboriginal community had MVEV antigens (Australian Government 2013b). But while these viruses can cause human disease, the majority of infections are asymptomatic or mild, whereby they tend to 'fly under the radar' of researchers.

The researchers argue for further genomic-viral research to test their hypothesis, with a focus on Aboriginal people to see if they might be responding differently to exposure to Flaviviridae-family viral infections.

Kidney disease

Albumin is a protein found in the blood. A healthy kidney does not let albumin pass from the blood into the urine, but a damaged kidney does (a condition called 'albuminuria'). However, when it occurs, this 'leakage' enables kidney disease and/or damage to be detected by measuring the albumin-creatinine ratio (ACR) in urine samples (Kidney Health Australia n.d.).

Based on ACR results, the 2012–13 Australian Aboriginal and Torres Strait Islander Health Survey (ABS 2014) suggested 18 per cent of Indigenous people in Australia had various – but mostly early – stages of kidney disease (AIHW 2020c:57). Of concern, almost nine in ten did not have a diagnosis, which suggests, as with diabetes, the primary care and broader health system challenge in this context (AIHW 2020c:57). In part, the low detection rates are because the onset of kidney disease tends to be at an earlier age in Indigenous peoples, with rates steadily increasing from the age of 18, compared with rates beginning to climb from 55 years for non-Indigenous people (AIHW 2020c:57).

Further, kidney disease in Indigenous peoples is significantly associated with T2D, high blood pressure/hypertension and obesity (high BMI) (Thomson et al. 2019), which are all found at higher rates in the Indigenous population. Glomerulonephritis – kidneys affected by an autoimmune response to group A streptococcal (GAS) infection – also significantly contributes to overall kidney disease rates (AIHW 2011).

Prior to 2010, McDonald et al. (2002) confirmed an association between albuminuria and SNPs associated with a 'p53' gene polymorphism. The p53 gene remains inactive within cell nuclei for most of a cell's life, becoming active when the cell ceases to function effectively, including from damage to its DNA that can lead to tumours. At this point, p53 not only causes a cell to stop reproducing, it precipitates its self-destruction (apoptosis) in order to be removed as waste products. Existing research demonstrated that p53 SNPs was associated in higher ACR results in individuals, suggesting a build-up of cells that otherwise should have been cleared from the kidney, affecting functioning.

The research involved about 200 remote East Arnhem Land Indigenous people. In addition to confirming the above p53 association, the research also reported on a tentative association between high blood pressure and SNPs for the gene responsible for angiotensin converting enzyme (ACE) production. ACE causes the muscles around the blood vessels to constrict, causing high-blood pressure. When released chronically, ACE is associated with hypertension that can lead to kidney

disease and other chronic conditions but, once detected, is amenable to suppression by medication to lower blood pressure into healthier ranges (Ogbru 2019).

Based on the above, Duffy et al. (2016) further explored the genetics of kidney disease with reference to p53 and ACE gene SNPs. Their research involved the genomic sequencing of just over 350 individuals assessed as at risk of kidney disease and diabetes, including by ACR levels in urine, kidney filtration rate, blood pressure and plasma glucose. They not only confirmed the association as per the 2002 research (McDonald et al. 2002), but also demonstrated significant heritability of the two SNPs, suggesting significant genetic contributions to the high prevalence of chronic diseases observed in the cohort.

Tang et al. (2018) further examined the role of SNPs in genes associated with metabolism functions and higher rates of diabetes, renal disease and associated conditions. In their study, by whole exome sequencing 72 Aboriginal exomes and comparing them to reference exomes, the researchers found functional variants in gene sets/pathways that connect bile acid regulation with lipoprotein, lipid and glucose metabolism. In addition, functional variants to the asrA gene associated with a condition called arylsulfatase A pseudodeficiency and reported at high rates in this population is associated with T2D and cardiovascular disease (CVD) and kidney disease in non-diabetic individuals, with implications for the wider Aboriginal population.

There are more than 200 genetic changes that cause or are associated with either renal disease or renal developmental abnormalities (Thomson et al. 2019). Among these, in many populations, apolipoprotein L1 (APOL1) gene alleles (variations) are associated with kidney disease risk, and there was a presumption this might be found in Aboriginal populations because of the high reported rates of the condition (AIHW 2019). Among the Tiwi Islanders, the problem is so severe that the 3000-strong island community requires its own dialysis unit and renal failure is the most common cause of death (Thomson et al. 2019). As part of a health screening program, high ACR was assessed in a representative sample of 200 Tiwi Islanders, with their genomes then sequenced as a part of Phase III of the International HapMap Project (Thomson et al. 2019).

The HapMap Project confirmed that – in common with other Aboriginal Nations in Australia that have lived on their Country for tens of millennia – the Tiwi are, in relative terms, genetically distinct (Manolio & Collins 2009). Hoy et al. (2017) further examined this database and determined that the above APOL1 risk alleles was not an indicator of risk in the Tiwi. Based on this and other evidence, it is now estimated that APOL1 renal risk variants G1 and G2 arose in sub-Saharan Africans about 5000 to 10,000 years ago, well after the out-of-Africa migration of modern humans, including Aboriginal peoples. The research was useful in ruling out a line of enquiry.

Thomson et al. (2019) continued investigations into the genetic determinants of kidney disease in Aboriginal people with reference to the HapMap Project's Tiwi Islander reference genomes, and by comparing these to reference databases for 11 other populations (including African Maasai, Luhya and Yoruba people, Mexicans, Han and United States-based Chinese and Japanese groups). By this, eight SNPs were identified that were, nominally at least, associated with high ACR from the urine tests carried out in field.

Focusing on these eight SNPs, further investigation took place by sequencing an additional 497 Tiwi Islanders with a focus on relevant loci. By this, four SNPs were significantly associated with high ACR. In particular, one of these (SNP rs4016189 located near the CRIM1 gene) was not associated with other conditions such as diabetes, high blood pressure and other kidney disease associations, suggesting a unique-to-the-Tiwi SNP associated with kidney disease.

Rheumatic heart disease

RHD kills Aboriginal people in Australia at more than 20 times the rate of the non-Indigenous population (AIHW 2019). Acute rheumatic fever (ARF) is an autoimmune response to the GAS bacterial infection and is most common in children aged 5 to 14 years. RHD is heart valve damage resulting from heart inflammation as a complication of ARF, and usually after repeat exposure (Sika-Paotonu et al. 2017).

In autoimmune diseases, the body's killer T-cells attack the cells of vital bodily tissues, damaging the tissues and causing disease, so tissues cease to do their work. Killer T-cells have receptors that enable them to detect protein signals on infected or damaged cells (known as antigens) and that triggers them to attack. In this context, it has been proposed that GAS infected cells might be generating antigens that are very similar to the proteins on the surface of heart cell tissues. The killer T-cells, otherwise doing their job, then come to recognise the GAS antigens on cells as signals to attack. But here the problem arises – as in RHD, they do not distinguish between the GAS antigens on infected cells and the heart tissue cell proteins as signals to attack, and so the heart tissues become 'collateral damage'.

Gray et al. (2017) tested whether this apparent inability of the killer T-cells to distinguish between the above cells in Aboriginal people with RHD was associated with either or both particular GAS strains found in Northern Territory communities with high rates of RHD (which might be generating particular antigens) and any candidate genetic variations that might be enabling these proteins to mimic heart cells tissues for the killer T-cells.

The methodology used collated the GWAS of about 1250 Aboriginal genomes, over which about 400 were from persons with RHD. SNPs were a focus of attention, and by association those in the human leukocyte (white blood cell) antigen (HLA) generating loci of the genomes of people with RHD were implicated. Fine mapping of HLA loci revealed the HLA-DQA1 position to be particularly associated with RHD. But other risk and protective loci were also discovered. The researchers also examined the proteins being produced by the two strains of GAS found in the communities. They concluded that both genetic vulnerability and GAS protein mimicry were likely at play, with differences in combination of risk and protective SNPs across the population accounting for some of risk-variance within Aboriginal groups to RHD. Further research is necessary to better understand this complex set of findings.

Blood transfusion practice

Because of higher rates of CVD and kidney disease in the Aboriginal population, there is also greater dependency on medical treatments requiring the transfusion of blood. A person's genome holds the information for producing any of the 320 or so different proteins (antigens) that, in combination, have been identified as 'coating' human red blood cells (Brown 2002).

Different antigen-combinations in these 'coats' are classified by the International Society of Blood Transfusion into 36 blood groups (Mitra, Mishra & Rath 2014). Further, within these groups, differences in the precise antigen combinations are known. Understanding and being able to predict blood group variation in patient cohorts is particularly important in blood transfusion practice, as a patient's immune system will attack red blood cells it 'reads' as being from different blood groups, by virtue of differences in the antigens coating the cells. Likewise, it can be critical for the effective treatment of foetal and infant conditions that can occur when a mother has a different blood group.

Population groups and cohorts tend to be of similar blood groups or share variations that occur within blood groups (Cooling 2015). Nonetheless, while blood sample-based analysis and other research stretching back to the 1940s broadly identified Aboriginal blood groups and some variations, little broad surveying of possible potential blood group variations had occurred to support better Indigenous health outcomes at the population level, particularly those involving transplants or transfusions.

But now genomics has made it possible to predict a person's blood group by analysis of genes and loci that are associated with the antigen coats of red blood cells. By this approach, Schoeman et al. (2019:17) aimed to close some of the above knowledge gaps in the Aboriginal population by comparing the abovementioned 72 already-sequenced genomes from Western Desert Martu peoples to 'global population' reference sequences – including those of the International Society of Blood Transfusion – to identify antigen-related gene variations.

By this method, it was possible to predict potential antigen variations across all 36 blood groups as they might be expressed in Australian Indigenous populations. The outcome of the research was that within 21 of the 36 International Society of Blood Transfusion's blood groups, the variations predicted to be encountered were comparable to global populations. However, within 13 of the 36 blood groups, 12 or so novel variations and four rare variants with potential clinical significance in Aboriginal peoples were identified.

Severe and pandemic influenza

Indigenous populations in Australia, Aotearoa New Zealand and North America are at substantially higher risk of hospitalisation and morbidity from influenza infection than of their non-Indigenous counterparts (Gall et al. 2020). Such susceptibility is evident with other novel and highly contagious viruses too. In recent Australian history, Indigenous peoples accounted for 16 per cent of patients hospitalised with pandemic H1N1 2009 influenza (swine flu) and just under 10 per cent of those admitted to intensive care units, despite comprising about 3 per cent of the Australian population (Flint et al. 2010). At the time of writing of this report, Australian Indigenous peoples also face heightened risks from the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for the worldwide coronavirus disease (COVID-19) pandemic.

Understanding the genetic contributions to the capacity of different populations to respond to influenza and other viruses (and to pandemics, in particular) is important in shaping specific responses for various cohorts – for example, the relative importance of self-isolation within a wider package of responses.

There are many reasons why influenza, COVID and associated pandemics represent greater risk to Indigenous, compared with non-Indigenous, populations in Australia. Not the least of these are high rates of households living in overcrowded and hygiene-challenged conditions, where pathogens can spread relatively easily. Further, the impact of viruses, such as influenza, on those with pre-existing chronic conditions is greater and – as highlighted in relation to diabetes and renal disease in this section – morbidity from these is significantly higher among the Indigenous, compared with the non-Indigenous, populations in Australia.

In this context, while pre-emptive vaccination is clearly of significant benefit, and vaccination campaigns among Indigenous Australians have been a major focus of policy makers in the past decade, such focus can confer little protection against newly emerged unpredicted influenza viruses and other respiratory viruses like COVID-19, until widespread vaccination. Ultimately, the capacity to

clear, for example, the influenza virus and recover from infection depends on the ability of an individual's/cohort's immune system to respond effectively, and researchers have shown that this can have genetic determinants (Chen et al. 2018).

Key to immune responses are killer T white blood cells. These kill cancer cells, infected cells and/or otherwise damaged cells while also releasing anti-viral and bacterial agents. Killer T-cells are covered in receptors that recognise antigens in the coats of infected cells and respond by binding to them to kill them. Against influenza, killer T-cells with CD8 protein in their coats are particularly effective at binding to infected cells and are referred to as CD8+T cells (Wissinger n.d.). And key to the development and functioning of CD8+T cells is another protein referred to in short as 'HLA'.

Clemens et al. (2016) investigated the genetics behind CD8+T cells in 82 sequenced Aboriginal genomes in comparison to reference genomes. The research revealed two variations around HLA-producing genes that impacted the cohorts and, by extension, the ability of Aboriginal people in general to produce CD8+T cells and thereby immunologically respond more effectively to influenza and related viruses.

The difference was broadly explained as follows. The HLA-producing genes in non-Indigenous populations have adapted to relatively constant exposure to influenza viruses over time. By this, CD8+T cells represent a positive adaptation specifically in response to those influenza that remain relatively constant despite the continuing mutation of the influenza virus into new forms. In contrast, for much of the Indigenous population, that adaptation is yet to occur/is ongoing because of their relatively recent (i.e. post-1788) exposure to influenza.

This is critical information and underscores the need for potentially Indigenous-specific responses in vaccine development among other non-medical responses to coronavirus-related pandemics, including Covid-19.

Rare diseases and cancers

There are thought to be at least 6000 rare diseases (Bilkey et al. 2019), which are defined variously but indicate a disease affecting only a small minority of people within a given cohort, and sometimes for which there is no market incentive to develop treatments (Dawkins et al. 2018). However, as a combined disease group, they affect up to 6–8 per cent of the population, and people could wait for decades for a diagnosis within previous diagnostic procedures. A game changer in that regard is that many rare diseases have genetic causes and corresponding new diagnostic pathways (Boycott et al. 2017).

In Australia rare diseases detected in the Indigenous population by genomic sequencing include Silver Russel disease (Poulton et al. 2018), which occurs in approximately one in every 50,000 to 100,000 births and is associated with dwarfism and other impacts of Marfan syndrome (MFS) – a genetic disorder that affects the connective tissue. Those with the condition tend to be tall and thin, with long arms, legs, fingers and toes. They also typically have flexible joints and scoliosis. About 75 per cent of the time, MFS is inherited from a parent with the condition.

Machado-Joseph disease: in the 1960s clinical presentations of ataxia (conditions characterised by lack of muscle control, of which there about 30 forms (NINDS 2010) were reported in Aboriginal families at Angurugu, on Groote Eylandt, and at Yirrkala, in Arnhem Land. Initially suspected of being caused by manganese poisoning from nearby mines, a diagnosis of Machado-Joseph disease (MJD) was confirmed in 1996 (Kaplan 2016). MJD symptoms include progressive lack of coordination in the

arms and legs, a staggering lurching gait that can be mistaken for drunkenness, and twisting and twitching of the face, body and limbs (NINDS 2010).

Life expectancy ranges from the mid-30s for those with the most severe forms to a nearly normal life expectancy for those with mild, late onset forms (NINDS 2010). MJD is presently incurable, but some symptoms of the disease can be treated. For example, antispasmodic drugs can help reduce twitching and jerking movements. Speech problems and trouble swallowing can be treated with medication and speech therapy. Physiotherapy can help patients cope with disability associated with gait problems. Physical aids, such as walkers and wheelchairs, can assist with everyday activities (NINDS 2019).

MJD has genetic origins. The ATXN3 gene provides instructions for making an enzyme that helps destroy and get rid of excess or damaged proteins in the cells (Genetics Home Reference 2020). In a healthy cohort, key parts of the ATXN3 gene will be repeated (short tandem repeats or STRs) between 12 to 44 times along its DNA strand. But when it is repeated up to 84 times, MJD results. Indeed, there is an association between the number of repeats and the earlier onset and increasing severity of MJD (GeneCards n.d.).

The prevalence of MJD is highest among people of Portuguese descent but occurs worldwide. The name 'Machado-Joseph' reflects two variations within the overall condition. The Joseph lineage is found worldwide, with its origins in Asia 6000 to 7000 years ago, while the Machado lineage is more recent in origin and largely confined to Portugal (Martins et al. 2012). Understanding the lineage of an MJD presentation is an important part of diagnosis, prognosis and treatment. And the possibility of Machado lineage via Portuguese interactions with the Macassan people of Indonesia was initially proposed to explain the presence of MJD in Aboriginal populations (Martins et al. 2012). The Macassans are known to have traded and otherwise interacted with northern Australian Aboriginal populations (Macknight 1972).

Martins et al. (2012) sought to test the above hypothesis, and otherwise establish which MJD variation was presenting. The research involved comparing STRs (as above) in the ATNX3 gene in the genomes of two Aboriginal families – one from Groote Eylandt and one Arnhem Land – with families with MJD worldwide, including those sequenced in previous studies. They found that the two Aboriginal families shared similar STRs to the Joseph lineage, and relevant with that of nine families from Taiwan, India and Japan. The researchers concluded either a common Asian origin of the mutation among Asian and Aboriginal peoples dating to c. 6000 to 7000 years ago – one with scant support from any other area – or an independent mutation entirely separate from the Joseph lineage. Regardless, the finding did not support a Portuguese link.

Vulvular cancer: vulvar cancer can occur in any part of the external female genitals. It is associated with precursor vulvar lesions (VIN). About 300 Australian women are diagnosed with vulvar cancer each year (Cancer Council n.d.). Of relevance here, a cluster of vulvar cancer has been identified in young Aboriginal women living in remote communities in Arnhem Land.

Vulvar cancer is a serious condition that requires a range of specialist treatments, including surgery, chemotherapy and radiation, that are only available in major metropolitan hospitals (McGrath & Rawson 2013). For the Arnhem Land women, in addition to physical/health concerns, the psychosocial impacts of treatment can be significant, involving periods of relocation, distance stress on family and community connections, the potential of cultural distress, loneliness and so on (McGrath & Rawson 2013).

Because the cohort of Aboriginal women was relatively small and isolated from other populations, a genetic origin by SNP or STR variant and autozygosity was proposed as an explanation. This describes DNA sequences that are identical (homozygous) among individuals in a cohort as a result of inheritance from shared ancestors (e.g. through the mating of cousins with a shared grandparent). Understanding if autozygosity was associated with the cancer cluster could help prevent future cases, as well as, potentially, having treatment implications. McWhirter et al. (2014) explored this by genomic sequencing of 30 women with cancer or its precursor VIN, and 61 'control' women of a similar age and from the same communities but without cancer or VIN. In particular, the researchers looked for evidence of homozygosity in various implicated loci. If such were found to be shared among the women with cancer or VIN, genome-wide homozygosity among them was significantly likely, and in turn this would support the above proposal.

The researchers found, however, no evidence for elevated homozygosity among the cohort of women with cancer or VIN compared to the control group. They concluded that while the clustering of cases still suggested a potential genetic origin, alternative explanations to autozygosity should be explored.

Further, the researchers noted an association between a previous diagnosis of cervical intraepithelial neoplasia (CIN – precancerous changes to the skin of the cervix) and the later development of VIN and vulvar cancer. The research then had value in not only eliminating a potential but otherwise 'dead-end' cause from consideration, but also because CIN – caused by the human papilloma virus – is treatable in many cases and an HPV vaccine is available.

Aotearoa New Zealand Māori and Polynesian peoples

Archaeogenetics

The arrival of the Māori in Aotearoa New Zealand c. 1200 AD provides as good a bookend as any to the vast out-of-Africa migration event that began c. 100,000 years ago and discussed above.

Linguists have long identified an Austronesian language group that includes the Aboriginal peoples in Taiwan, Island South East Asia, Micronesia, coastal New Guinea, Island Melanesia Polynesia and Aotearoa New Zealand and that suggests these populations have a shared origin (Hudjashov et al. 2018). This was also supported by archaeological evidence of the ancient Lapita culture found across a number of far-apart islands with what are believed to be antecedents in Island South East Asia (Clark, Anderson & Vunidilo 2001). And since the 1990s, genetic research has added substantially to this picture.

In particular, the research project that identified a so-called 'Polynesian motif' (three signature SNPs that comprise mtDNA haplogroup B4a1a1a (Knapp et al. 2012)) in the HVR 1 region of the mtDNA in populations stretching from Taiwan to Polynesia (Bandelt et al. 1995; Lum et al. 1998; Murray-McIntosh et al. 1998; Hagelberg et al. 1999; Friedlaender et al. 2002). Further, phylogenetic trees suggest an 'out-of-Taiwan' model of migration across South East Asia and the northern coastal area of Papua New Guinea, and onward into the Pacific (Klamer 2019). The model was further supported by research that identified only a limited number of mtDNA haplotypes present in far-travelled Polynesian populations, contrasting with more diverse haplotypes the more one retraced back the proposed migration route (O'Connell & Allen 2004).

Out of Taiwan

Significant research milestones in the development of this model include Trejaut et al. (2005), who sequenced 640 Taiwanese Aboriginal mitogenomes from nine tribes, including those of the Pacific-

facing east coast regions of Taiwan. The researchers identified significant differences in the mtDNA haplogroups between the Aboriginal and subsequently arrived Han populations of Taiwan. Second, they identified common haplogroups – and B4a1a1a (see above) – shared with Polynesian populations and that supported a line of matriarchal descent between the two.

Pierson et al. (2006) sequenced 19 mitogenomes and accessed others from existing datasets to analyse 137 mitogenomes from Oceania, Australia, Island South East Asia and Taiwan. By this methodology, they constructed a migration model based on a phylogenetic tree based on the haplogroup B4a1a1a variation that is still broadly accepted today (Figure A.4).

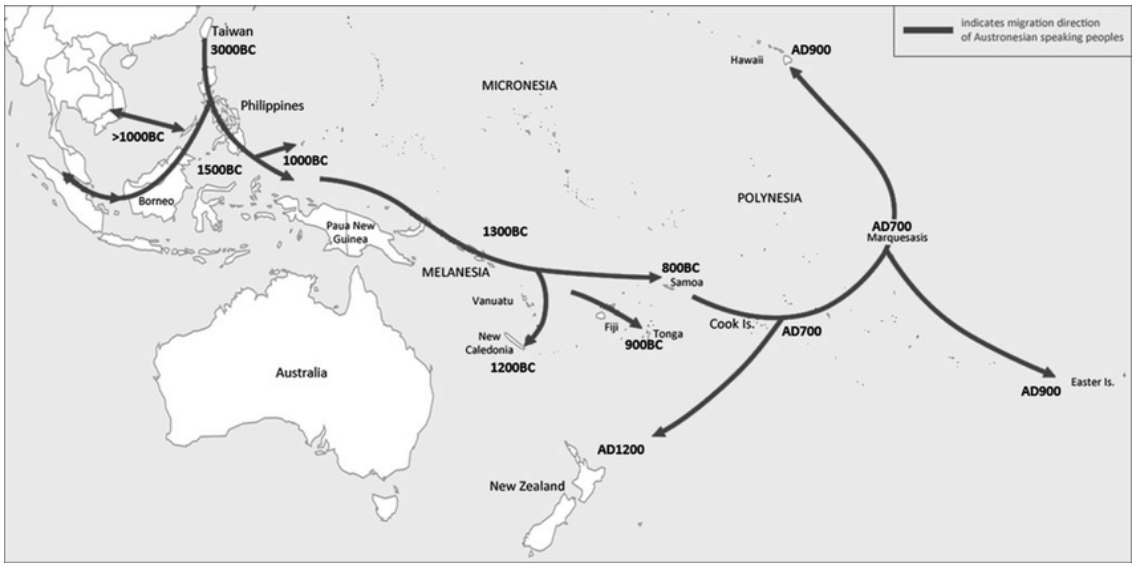


Figure A.4: Pacific migration route (Pierson et al. 2006)

To Aotearoa

Knapp et al. (2012) genomically sequenced four Māori burials in the Wairau Bay area dated c. 1285–1300 AD. The research, in part, was intended to test a model whereby a single ancestor population based on the Society Islands (an archipelago in present-day French Polynesia that includes Tahiti) had rapidly expanded across the entire Eastern Pacific – including Aotearoa New Zealand – in a period of about 100 years around 1200 AD.

The researchers found that while all four burials had two of the three unique additional elements of the Māori 'mtDNA signature' in addition to the Polynesian motif (above), there was nonetheless enough variation to suggest a more complex picture. Indeed, three of the four remains were not recently maternally related and belonged to different haplotypes (B4a1a1a and B4a1a1a3), indicating that there was likely to be significant mtDNA variation within the founding population of Aotearoa even if that variation was otherwise within the B4a1a1a haplogroup. In other words, the exact lines of descent were likely to be quite complex. A further important discovery was that one of the burials was found to have mutations associated with insulin resistance in the contemporary population and showed skeletal evidence of gout. Both conditions are discussed in the next section.

Benton et al. (2012) sequenced 20 diverse Māori genomes with lineages that excluded admixture with pakeha (non-Indigenous New Zealanders). The researchers reported a relative lack of variation among the Māori mtDNA haplotypes, suggestive of a relatively recently arrived population but that was then genetically isolated from other populations. This finding supported archaeological and other research that dates the arrival of the Māori on Aotearoa to c. 1200 AD. In the course of the

study, the researchers identified a unique Māori 'mtDNA signature' of six SNPs, including the three of the so-called 'Polynesian motif' (see below).

In closing, and as reported in July 2020, Ioannidis et al. (2020) tested models that proposed Indigenous South American populations had helped settle far-eastern Polynesia, including Rapa Nui – Easter Island (Wade 2020). The researchers conducted GWAS on 807 individuals from 17 island populations and 15 Pacific coast Native American groups. They reported conclusive genetic evidence for Polynesian – Native American admixture, with a group most closely related to the contemporary Indigenous peoples of Colombia around c. 1200.

Overview of human genomic health research undertaken in Māori and Polynesian populations

Metabolic disease

T2D is reported at about double the rate in Māori compared to pakeha in Aotearoa New Zealand, and renal failure at three times the rate (Ministry of Health 2018a). There is an association between the two. T2D can damage the smaller blood vessels in the body, affecting circulation. This can specifically impact kidney functioning as these organs rely on small blood vessel networks as the sites of their blood clearing/ filtering work and by which excess water and waste products are eventually excreted. Effects can include water retention, and uric acid retention leading to gout (National Kidney Foundation n.d.), chronic kidney disease and potentially kidney failure.

Obesity

The 2018–19 New Zealand Health Survey found that around one in three Aotearoa New Zealand adults were deemed obese, but that prevalence varied, applying to 66.5 per cent of Polynesian, 48.2 per cent of Māori and about 30 per cent of pakeha cohorts.

As in several developed countries, a 'thrifty gene' hypothesis has been proposed as an explanation for obesity and other metabolic disease states. By this, in populations believed to have experienced 'feast or famine' as a relatively constant condition, natural selection favoured individuals whose gene variants resulted in the storage of energy as fat in the 'good times' (in anticipation of being used in the not-so-good times) over individuals whose genes did not. In this case, what is presumed to be the long periods of cold, stress and starvation endured by Polynesian populations as they travelled the Pacific and established populations across hundreds of islands. The thrifty gene model has also been proposed to explain population susceptibilities to T2D among the Māori (Cadzow et al. 2016).

As noted above, Benton et al. (2012) identified a unique Māori 'mitochondrial genetic signature' with 6 SNPs. We take the discussion up here by noting that one of these included a 'thrifty gene [SNP]' candidate that also correlated with earlier research findings (Ayub et al. 2014). Myles et al. (2011) investigated this candidate in Māori and Tongan cohorts. They reported the association to be present among Tongan, but not Māori, populations, highlighting the need to approach genetic research across Polynesian populations at a regional/island group level. Cadzow et al. (2016) confirmed this finding.

Type 2 diabetes

Krishnan et al. (2018) undertook the Genetics of Gout, Diabetes and Kidney Disease in Aotearoa New Zealand Study to try to understand genetic contributions to the study's eponymous diseases with particular reference to a STR variant at CREBRF rs373863828, whereby a piece of genetic code associated with metabolism is repeated multiple times along its DNA strand, and that had been

observed in significant numbers of Samoan and Tongan Polynesians. But counterintuitively, perhaps, the STR was associated with both a 1.3 x tendency for increased BMI and a 1.6 x reduced risk of T2D (Loos 2016).

The researchers included several Aotearoa-New Zealand Polynesian resident populations, including Māori, Samoan, Tongan, Niuean and Pukapukan cohorts. Among these, the STR was most prevalent among the Samoan and Pukapukan cohorts, but also present in the Māori cohort. And it was confirmed to be associated with an increased BMI risk and decreased risk of T2D. Further, the more times the piece of genetic code was repeated along its DNA strand, the stronger the associations. There was, however, no association with the prevalence of gout in the Polynesian cohorts studied.

The research helped explain some of the variance in rates and presentation of obesity with and without T2D among Māori cohorts. It confirmed a potential for new treatments for both conditions targeting metabolic processes in particular ways. It underscored the importance of genetic testing of Polynesian persons, including Māori, presenting with T2D and/or obesity to understand the specific genetic contributions to their condition.

Rheumatic heart disease

Just as among Indigenous peoples in Australia (see above), the Polynesian, including Māori, population of Aotearoa New Zealand reports a significantly higher burden of RHD than pakeha, with a death rate five times higher (Ministry of Health 2018b). Three SNPs (at the IL-6, IL1RN and CTLA4 genes) in other world populations have been associated with ARF-caused RHD. For these, new medications have been developed to help prevent the onset of RHD.

Azevedo et al. (2016) investigated the presence of these three SNPs in sample of 204 Polynesians, including Māori, with RHD along with 116 control counterparts. Part of the research involved each participant self-reporting the likelihood of ARF/RHD in their eight great-grandparents. Of the three potential candidate SNPs, one was found to be associated with susceptibility to the development of RHD in Polynesians, including Māori. Another was found to influence the severity of the RHD heart and valve damage – in general, resulting in about 2.4 times more damage than in those people without the SNP. One SNP was not associated with either susceptibility to, or severity of, RHD. The research confirmed the promise of new medications to the prevention of, and severity of, RHD in Polynesians, including Māori.

Gout 1 – focus on uric acid transporters

Uric acid is a metabolic waste product that is carried in the blood to the kidneys for excretion. Gout is a painful arthritic condition whereby excess uric acid remains in the blood, precipitates out, crystalises around the joints, and triggers an autoimmune inflammation response (National Kidney Foundation n.d.). Polynesian populations, including Māori, have among the highest rates of gout in the world, with between 6 per cent of Māori and 8 per cent of pacific Polynesian populations with the condition (NZ Herald 2017) compared to 1–2 per cent in the general population (Thompson 2018).

In addition to behavioural factors (diet), there are genetic determinants of gout. In the kidneys and other sites, uric acid and other waste products are filtered from the blood by 'transporters' made of protein for excretion. Two types of transporter have been associated with gout risk. Gene ABCG2 encodes one of these uric acid transporter proteins. Phipps-Green et al. (2010) investigated SNPs in this in Polynesian (including Māori) and pakeha. The researchers found a strong association between the SNP and gout in Western Polynesian participants, less so in pakeha, but no association with gout

in Māori. The research highlighted the need for island and/or region-specific genetic variation among Pacific populations, and the need to research at that level (more below.)

Following the above, Flynn et al. (2013) further investigated other potential gout-risk associated SNPs in 12 loci in Polynesian peoples, including Māori. The researchers sequenced just over 1000 genomes from people with gout and about 1150 control genomes from the following populations: Eastern Polynesian; Aotearoa New Zealand and Cook Island Māori; Western Polynesian (i.e. Tongan, Samoan and Niuean); a mixed eastern and western Polynesian ancestry group; and European Caucasian. The researchers confirmed transporter-making gene SNPs shared by European and Polynesian populations and associated with gout in both cohorts. Second, they found a previously unrecorded transporter-making gene SNP associated with gout in Polynesians, but not associated with gout in European Caucasians. But, as above, there was significant variance in the strength of association in the Polynesian cohorts.

This research, along with the Phipps-Green et al. (2010) study, underscores the complexity involved in understanding specific genetic contributions to gout within Polynesian population groups, suggesting multiple, perhaps compounding, genetic pathways to gout are operative and require further research.

Gout 2 – focus on Dyslipidaemia

Gout is also associated with a high amount of free-floating fats (lipids) in the blood, a condition referred to as 'dyslipidaemia' or the more commonly well-known condition of 'high cholesterol'. Fats are insoluble in water, including water-based blood plasma. Because of this, lipids are enclosed within 'protein capsules' to be carried in the blood to sites, including for excretion. These protein capsules are, in turn, manufactured according to instructions encoded genes, and that can be the subject of SNPs.

When, as a result of gene variation, the body does not manufacture enough, or the right kinds, of protein capsules, or the capsules produced are defective, the lipids tend to float freely in the blood, causing dyslipidaemia. Such free-floating fats can be deposited in arteries and cause CVD. But in relation to gout, any association between dyslipidaemia and the precipitation of uric acid from the blood is unclear. And there is a possibility that dyslipidaemia be an independent (non-uric acid related) cause of gout.

A small study by Cardno & Owen (2014) identified (1) a protein capsule-making gene SNP associated with increased risk of gout (hereon 'increased risk SNP') and (2) another associated with decreased risk (hereon 'decreased risk SNP'). Rasheed, Phipps-Green et al. (2016) investigated whether these SNPs were operative in Polynesian, including Māori, populations of Aotearoa New Zealand. In addition to sampling about 450 European and almost 1000 Polynesian, including Māori, Auckland area-based individuals, the research included – in total, by utilising existing research – the genetic data of about 2700 people with gout and a control cohort of 2500 people without gout – with people of pakeha and Māori ancestry in each cohort. For all, the decreased and increased risk SNP sequences were measured against reported gout and two conditions associated with gout – high BMI and high blood cholesterol. The researchers confirmed the association of both the increased and decreased risk SNPs with the presence of gout in the Polynesian, including Māori, and pakeha cohorts. However, the association of the increased risk SNP was stronger in the Polynesian, including Māori, cohort. Further, the effect of the decreased risk sequence was noted only in males from both Polynesian, including Māori, and pakeha cohorts. While further investigation is needed, the research suggested the potential for dyslipidaemia-focused approaches that could be applied to the

management of gout in both Polynesian, including Māori, and pakeha populations, but with significantly greater population-level benefit to the former.

Inflammation response

The joint inflammation associated with gout follows an immune response to the presence of uric acid crystals around the joints. These are perceived as foreign to the body – akin to a virus. The immune response is triggered by mitochondria in the body's cells through several complex pathways. Related to this, among European and Han Chinese cohorts, increased gout risk has been associated with SNPs in the genes for receptors on the surface of white blood cells that cause the immune system's 'reading' of uric acid crystals as invaders. Rasheed, McKinney et al. (2016) aimed to determine whether the above SNP and association was also evident in Polynesian, including Māori, populations. Using data from various sources and drawing on existing research, about 2250 people with gout and almost 14,000 controls overall (including just under 650 Polynesian, including Māori, with gout and 920 counterpart controls) were included in the study. The research team determined that while the SNP is associated with increased prevalence of gout in European populations, it is associated with a decreased prevalence of gout in Polynesian, including Māori, populations. The research highlighted the variance between population groups and the complexity involved in developing genetic-based responses to gout in Polynesian, including Māori, populations.

International research suggested the more repeats of the genetic sequence in the mitochondria responsible for triggering inflammation responses, the lower the risk of gout (Tseng et al. 2018). Research undertaken by Gosling et al. (2018) tested this in Aotearoa New Zealand population cohorts.

The cumulative gout-specific research confirms the role of the particular SNPs in gout, but – more broadly – highlights the population variance possible when considering genetic contributions to various conditions, including gout, and the importance of Indigenous-specific genetic sequencing to understand the particular genetic determinants functional or non-functional, or that operate in different ways, when compared with non-Indigenous populations.

Transfusion practice

When a blood transfusion occurs, the body can react as if invaded, depending on how it 'reads' the blood using antigens on the blood cells. If perceived as an invading substance, transfused blood can be attacked by the immune system (alloimmunisation). This can have implications across several areas where blood transfusion may be required. Platelets are present in the blood stream and cause blood to clot. Knowledge of a person's platelet antigen genetic coding (and any SNPs) can help medical staff understand any risks blood transfusions, in addition to the management of pregnancies and other benefits.

Edinur et al. (2013a, 2013b) published research into the platelet antigens of Polynesian, including Māori, populations. They detected different prevalences of recognised platelet antigen-making genes in these, contributing towards understanding the different risk profiles for platelet-specific alloimmunisation.

Biliary atresia

Upon being eaten, the fats in food pass from the stomach to the small upper intestine to be digested. Connected to the small intestine is the gallbladder, from which bile is injected to break the fat down into molecular size pieces as the first stage of the fat digestion process. This emulsification significantly expands the total surface area of the fat intake, enabling enzymes to rapidly and

efficiently convert the fat molecules to forms of energy the body can use (InformedHealth.org 2016). Bile, therefore, plays a critical intermediary role in fat digestion. Cells within the liver produce bile and these drain through a network of channels and ducts into the gallbladder, which holds and concentrates the bile in readiness for release into the small intestine after a meal.

Biliary atresia is a condition that usually starts in infancy. In this, the bile flow from liver to gallbladder is blocked. The trapped bile causes liver damage and scarring and this, in turn, can lead to liver failure and death. An operation providing an alternative bile channel from the liver to small intestine is possible but associated with complications. Eighty-five per cent of those with biliary atresia will need a liver transplant before the age of 20 years; the remaining 15 per cent manage the disease (Cincinnati Children's 2020).

Higher rates of biliary atresia in East Asian and Polynesian groups, including Māori, and differences in response to treatment in African Americans (compared to European Americans), suggest genetic contributions to the disease (Muraji, Tanaka & Ieiri 2018). And, of interest, one particular Māori iwi ('tribe' or 'Nation') records the condition at a population rate of about one in 900. This compares to about one in 6000 among other Māori, and about one in about 22,000 in the pakeha (European Aotearoa New Zealanders).

Cameron-Christie et al. (2018) sequenced the genomes of 12 individuals from this iwi with biliary atresia, along with those of their fathers, mothers and siblings. This was combined with cohort genealogical research back seven generations. The researchers determined all 12 with biliary atresia and their relatives were within one pedigree or line of genetic transmission. However, the research was otherwise inconclusive. Within the lineage, no single SNP could be connected to biliary atresia. Nor was there homozygosity (shared sequences of genetic material) within members of the pedigree that might otherwise suggest genetic transmission within a limited population size. The researchers, however, did not necessarily rule out other genetic possibilities (to be the subject of further research) in combination with environmental factors.

Cancers

Retinal cancer

Cancer on the eye's retina (or retinoblastoma) is a rare form of cancer but is among the most common cancers in children. It is almost exclusively found in young children and is associated with the malignant development of immature retinal cells. As these cells mature (as the child ages) the risk of disease diminishes. Depending on the stage of detection, up to 70–80 per cent of infected eyes can be saved. Further, if the tumour is contained within the eye, about 95 per cent of treated patients will survive. If treated too late, the cancer can spread to the brain and cause death. The malignant development of the retinal cells is associated with a SNP. Pradhan et al. (2010) examined this gene sequence in 20 Aotearoa New Zealanders. Ten were European, four Māori, three Polynesian, two Asian and one of mixed ancestry. The SNP was detected in 75 per cent of the Māori sample compared with 40 per cent of the European. While the sample size was small, the research nonetheless suggested the potentially important role of genetic testing for detection and preventative interventions in predisposed individuals and particularly within Māori populations.

Rod-cone retinal dystrophies

The light-sensitive cells of the retina (called 'cones' and 'rods') are a critical part of sight. Rod-cone retinal dystrophies are a group of eye disorders whereby these cells deteriorate over time and impair vision. Blind spots in the central field of vision usually emerge in childhood, with most

patients legally blind by adulthood. Mutations in more than 30 genes are known to cause rod-cone dystrophy. Vincent et al. (2017) sequenced relevant parts of the genome of 16 Polynesian and Māori people with rod-cone retinal dystrophies to assess which of the 30 genes, if any, were operative. In seven of the 16 patients, a recognised SNP was identified. In the balance – more than 50 per cent of participants – novel SNPs were reported, including a homozygous stretch of gene shared by all nine patients. This suggested the SNP was ancestral to all – an example of the so-called 'founder effect' (the loss of genetic variation that occurs when a new population is established by a very small number of individuals).

Testicular cancer

Testicular cancer is among the most common forms of cancer in young men, with rates appearing to have significantly increased in the past 50 years (Khan & Protheroe 2007). The condition is associated with one or both testes failing to descend from the abdomen into the scrotum in infancy and childhood – referred to as cryptorchidism. Once cancer is detected, treatment is to remove affected teste. While the five-year survival rate is high, the cancer can spread and kill if otherwise untreated (American Cancer Society n.d.b). European ancestry and a family history of the cancer are risk factors and suggest a genetic contribution (Pomerantz & Freedman 2011). However – and puzzlingly – Māori men have higher testicular cancer rates than pakeha within Aotearoa New Zealand (Gurney et al. 2018). This research group have begun research into potential genetic explanations of this situation and describe their methodology for undertaking the research.

Neurotransmitter regulation

The brain largely comprises neurons – specialised nerve cells that transmit information among themselves and through the nervous system. Between the neurons are gaps called synapses, and messages are transmitted across them by hormones (chemicals) known as neurotransmitters. These include dopamine (which plays a role in how we feel pleasure) and serotonin (which is associated with feelings of happiness). The brain also uses an enzyme known as monoamine oxidase A (hereon MAO-A) to regulate these and other neurotransmitters by neutralising them in preparation for their removal from the nervous system and brain as waste products. The MAO-A gene contains several SNPs, including a variable number of repeat SNPs that influences the gene expression levels. Of note, the 3-repeat SNP and 5-repeat SNP variants result in a gene that produces 10 times less than the usual amount of MAO-A (referred to as the low activity SNP). In such, it is believed that the MAO-A is unable to neutralise enough neurotransmitters as required, resulting in their build-up around the neurons. There is also a high activity 3.5 or 4 repeats SNP variant, whereby significantly more MAO-A is produced.

Initial 1993 research involving a Dutch family, followed by 1995 experiments in mice, suggested the low activity SNP was associated with aggressive behaviour (McDermott et al. 2009). This finding was repeated in 2004–05 research involving rhesus monkeys, resulting in the low activity SNP being labelled the 'warrior gene' by a reporting science journalist (Merriman & Cameron 2007). Because of the implications (potentially even to the legal system – i.e. could a low activity SNP be a defence against charges involving anti-social behaviours and violence?), the findings attracted significant interest. However, three further and larger studies over 2002–06 within Caucasian European male cohorts largely disprove any association between the low activity SNP and aggressive behaviour in humans (Godar et al. 2016) – but they did report that the high activity SNP apparently provided something akin to a buffer between childhood abuse and antisocial and/or aggressive behaviours in adulthood in males, being associated with lower anti-social or aggressive responses in adulthood

despite similar childhood experiences. By extrapolation, then, the finding included an inference that the low activity SNP might also, in interaction with a human male's environment, be associated with behavioural change, but – and it must be stressed – not in isolation. As was noted by a commentator, 'in isolation the gene variant could predict nothing about aggression in male carriers' (Clukay et al. 2019).

Despite these caveats, unpublished research presented at an international genetics conference in 2006, and attracting significant media attention (Sydney Morning Herald 2006), not only claimed that high activity SNP presented strongly in male Māori population, but also borrowed the term 'warrior gene' from the animal-based research (discussed above) to describe the high activity SNP. Further, the conference presentation associated high activity SNP with alcohol and drug use, and violence among Māori males. See Box A.1 for the contemporaneous media report (Sydney Morning Herald 2006) extract that suggests the direction of the announcement and the reporting around it. Although the research behind the announcement has been long discredited (not least because it was based on an unrepresentative Māori male cohort of only 17-strong), the impact of the announcement continues to have ramifications in the Indigenous genome space. Further research has since revealed a range of SNP/variants in the MAO-A making gene across seven population groups, suggesting natural selection favouring one or another variant according to environment and experience: these are Pygmy, Aboriginal Taiwanese, Chinese, Japanese, Mexican and Russian cohorts (Zhang et al. 2013).

Eccles et al. (2012) published further research comparing MAO-A SNPs among the Māori by examining the prevalence of 13 MAO-A gene SNPs associated in a cohort of 47 unrelated Māori individuals, in comparison with other groups. They reported a relatively consistent presence of the 3-repeat, or low intensity, SNP in the Māori male and female population, with some evidence of position natural selection (i.e. the favouring by experience and environment) of the 3-repeat in Māori males. The study was intended as the basis for further research in the area and made no attempt to connect the low activity SNP to behaviours.

Box A.1: 'Warrior gene' blamed for Māori violence (extract)

Sydney Morning Herald, 9 August 2006

> New Zealand Māori carry a 'warrior' gene which makes them more prone to violence, criminal acts and risky behaviour, a scientist has controversially claimed. New Zealand researcher Dr Rod Lea and his colleagues have told an Australian genetics conference that Māori men have a 'striking over-representation' of monoamine oxidase – dubbed the warrior gene – which they say is strongly associated with aggressive behaviour.
>
> His says the unpublished studies prove that Māori have the highest prevalence of this strength gene, first discovered by American researchers but never linked to an ethnic group. This explains how Māori managed to migrate across the Pacific and survive as they have, said Dr Lea, a genetic epidemiologist at the New Zealand Institute of Environmental Science and Research. 'Maori, being very adventurous individuals as they crossed the Pacific, have carried this gene forward and it was partly responsible for them arriving in New Zealand and surviving,' he told AAP. But he said the presence of the gene also 'goes a long way to explaining some of the problems Maori have'. 'Obviously, this means they are going to be more aggressive and violent and more likely to get involved in risk-taking behaviour like gambling,' Dr Lea said ahead of his presentation to the International Congress of Human Genetics in Brisbane. 'It is controversial because it has implications suggesting links with criminality among Maori people,' he said. 'I think there is a link, it definitely predisposes people to be more likely to be criminals and engage in that type of behaviour as they grow older.'
>
> Dr Lea said he believed other, non-genetic factors might be at play as well. 'There are lots of lifestyle, upbringing-related exposures that could be relevant here so, obviously, the gene won't automatically make you a criminal.'… He said the same gene was linked to high rates of alcoholism and smoking among Māori…

The Indigenous peoples of the United States and Canada

Archaeogenetics

East Asian lineage and the Beringian model

Although the focus of this section is on genomic medical research relevant to the Indigenous populations of the United States and Canada, this requires contextualisation in an ancient migration story that starts in East Asia/Siberia and takes in North America, Central America, South America and surrounding islands.

Archaeological findings show groups of hunters living in North East Asia/Siberia around 25,000 years ago, during the last Ice Age (Pitulko et al. 2004). Further, a land bridge connected Siberia to Alaska across the Bering Strait to create a contiguous area from roughly Siberia to Alaska named 'Beringia' at that time. The Beringian 'model' is used to explain Indigenous American lineages. By this, Beringia was crossed by groups of ancient East Asian/Siberian hunters to reach the Americas before the melting ice sheets caused sea levels to rise (Wang et al. 2007), followed by their rapid spread across the two American continental land masses and beyond – into the Caribbean.

Mitochondrial DNA (mtDNA) research published as early as 1985 had proposed that the ancestry of all Indigenous Americans derived from a relatively small number of women in the maternal line, giving rise to many descendants today (Wallace, Garrison & Knowler 1985). Subsequent research to 2010 pointed to East Asian origins, based on genomic research that identified four mtDNA haplogroups (A, B, C and D) shared by almost all Indigenous American and East Asian female populations (and not other populations), suggesting all Indigenous Americans had East Asian origins (Silva et al. 2002; Achilli et al. 2008).

Other early research focused on Y chromosome paternal lines (Bergen et al. 1999). In 2002, findings from researching 550 Indigenous American and Siberian Y chromosomes resulted in the proposal of the 'first wave' model of migration, encompassing a journey from middle Siberia to the southernmost tip of South America (Bortolini et al. 2003), followed by a 'second wave' from eastern Siberia to North America to coalesce as some Arctic populations (Lell et al. 2002), as discussed below. And in 2003, following investigation into almost 2500 Y chromosomes covering 18 Native American, 28 Asian and five European populations, researchers found that just three Y-chromosome haplogroups, C, Q and R, accounted for 96 per cent of Indigenous American Y chromosomes: C and Q were proposed to represent early founding Y chromosome lineages, with R coming from admixture with European coloniser lineages after 1492 (Zegura et al. 2004). Some even proposed an East Asian 'Adams' to match the mitochondrial East Asian 'Eves' of the Indigenous Americas (Hutardo de Mendoza & Braginski 1999; Lell et al. 1997).

Investigating the emergent Beringian model further, Yang et al. (2010) used an Americas-wide range of ancient and contemporary Indigenous American genomes. Using fixation indices, they reported that the further a particular genome was located from the Beringia area (a) STRs among them had greater variance, while (b) intra-population group genetic diversity decreases. Both findings not only supported the East Asian/Siberian lineage ancestral origin and Beringia model, but supported it was the sole migration entry point to the Americas, providing almost no support for an alternative (either competing or complementary) Solutrean hypothesis. This is a model based upon similarities between the stone tools of the European Solutrean culture (about 21,000 to 17,000 years ago) and that of the Clovis culture (about 13,000 years ago) that are found roughly in the north west and coastal regions of the United States. The 'Solutrean hypothesis' was that populations culturally connected to the Solutreans migrated across high North Atlantic pack ice to North America. It has not been supported by archaeogenetics, such that a consensus position today is that of support only for the Beringian model, at least in broad terms.

There have been, however, findings that do not support the Beringian model as strongly. To understand these, it is important to understand that phylogenetic tree development is based on a defined population group that is genotyped and that data is used to calculate variance in allele probabilities (i.e. if two in 100 have an allele, the probability of the allele being shared within that population is one in 50) with interpopulation probabilities also estimated within fixation indices. But what defines a population group: language and culture, self-identification, contiguous location? Much of the previously discussed research is based on these. In contrast, Hunley, Gwin and Liberman (2016) used a program called STRUCTURE and defined population groups according to detailed haplogroup differentiation. By this method, they analysed 645 Indigenous American STR genotypes from about 1050 individuals/63 previously defined population groups. Among other things, they reported that language and culturally defined populations do not necessarily match haplogroups, and inconsistencies in the data generated to support the Beringian model. They

proposed that the data to date used to support the Beringian model may have more to do with admixture with European coloniser lineages after 1492 than previously thought. (But also note that most of the research reviewed here uses methods to minimise the risk of such distortion.)

Eurasian lineage

Prior to 2010, and in addition to the four mtDNA haplogroups discussed above, researchers had also identified the presence of mtDNA haplogroup X in the Indigenous Americas, primarily in North America, and proposed an ancient association with Caucasian-European populations where haplogroup X is also found (Brown et al. 1998). Research by Raghavan et al. (2014) compared Indigenous American datasets to the sequenced genomes of a male child dating to around 24,000 years ago, and a second dating to 17,000 years ago, found at Mal'ta in central Siberia. They reported both genomes:

- were members of a Y chromosomal haplogroup shared by both modern western Eurasian populations and Indigenous American lineages
- were members of mtDNA haplogroup X found in western Eurasian and European populations (and not a member of the A, B, C or D haplogroup)
- that between 14–38 per cent of Indigenous American genetic ancestry was from this X mtDNA lineage.

In other words, the older child was related to varying degrees to Indigenous American, western Eurasian and European populations, but not to East Asian populations. Further, the second child's 5000-year younger genome demonstrated lineage continuity for at least 5000 years at the Mal'ta location and, again, without East Asian admixture. The model proposed by the researchers to account for this was that the mtDNA haplogroup X indicated a distinct Eurasian source of Indigenous American ancestry in addition to the East Asian. Further, Eurasian–East Asian admixture had occurred within North East Asia/Siberia prior to the first wave of migration across Beringia that was the source of most Indigenous America's ancestor populations. Finally, because mtDNA haplogroup X is also found in some European populations, researchers proposed some Eurasian–European admixture in ancient times. In other words, both Indigenous American and some European populations shared roughly the same Eurasian ancestry. The researchers also used the model to explain the presence of some ostensibly anomalous European 'genetic signatures' in Indigenous American populations that had, until then, been proposed as from admixture with European coloniser lineages after 1492.

Grugni et al. (2019) aimed to consider (among other questions) Indigenous American's Eurasian inheritance by paternal lines by analysing 154 Q haplogroup Y-chromosomes from the Americas (discussed above) and then constructing phylogenetic trees with reference to other datasets. This supported a Eurasian lineage for Indigenous Americans evidenced by, in particular, ancestry in haplogroup Q-M1107, with one sub-branch (Q-Z780) found only in the Americas and another (Q-M930) found in the Americas (as further sub-branches Q-M3) and the northwest European Q-L804. The researchers modelled the arrival of the 'first wave' ancestor populations into North America, followed by a major expansion of the male population and the establishment of the two signature North American Q haplogroups (Q-Z780 and Q-M3). By 15,000 years ago, variations on these had reached Central America, followed by further coalescing of Q haplogroups and 'tribalisation' in that continent.

Australasian lineage

While shedding significant light on Ancient Americas' genetic history, none of the above accounted for archaeological discoveries of ancient and puzzlingly 'Australasian'- type skulls in Central America, and Australasian 'genetic signatures' found in Central and South American populations, and particularly evident in the Shuri Amazonian population but not found in North American lineages, suggesting a possible Australasian signal had somehow been inserted into migrating populations at roughly Central America. Moreno-Mayar, Vinner et al. (2018) investigated this with archaeogenetics. They sequenced 15 ancient (10,000 to 500 year old) genomes from across the Americas and undertook multiple comparisons with contemporary Indigenous American genomes. They also included an Andaman Islander genome as a proxy for Australasian ancestry. They then modelled a phylogenetic tree that best accounted for their findings (Figure A.5).

In short, the team proposed that:

- the Australasian–East Asian admixture occurred around 25,000 year ago in East Asia/Siberia in parallel to the Eurasian–East Asian lineage admixture
- the Australasian–East Asian lineage undertook what is in effect a 'second wave' of migration into North America, Central America and then South America but leaving little – at least as yet discovered – traces in North America or to be explained by their replacement over time
- that about 10,400 years ago, admixture of the foundational Eurasian–East Asian lineage and the second Australasian trait lineage occurred in Central America.

(Note that the model proposed is also supported by Skoglund et al. 2015).

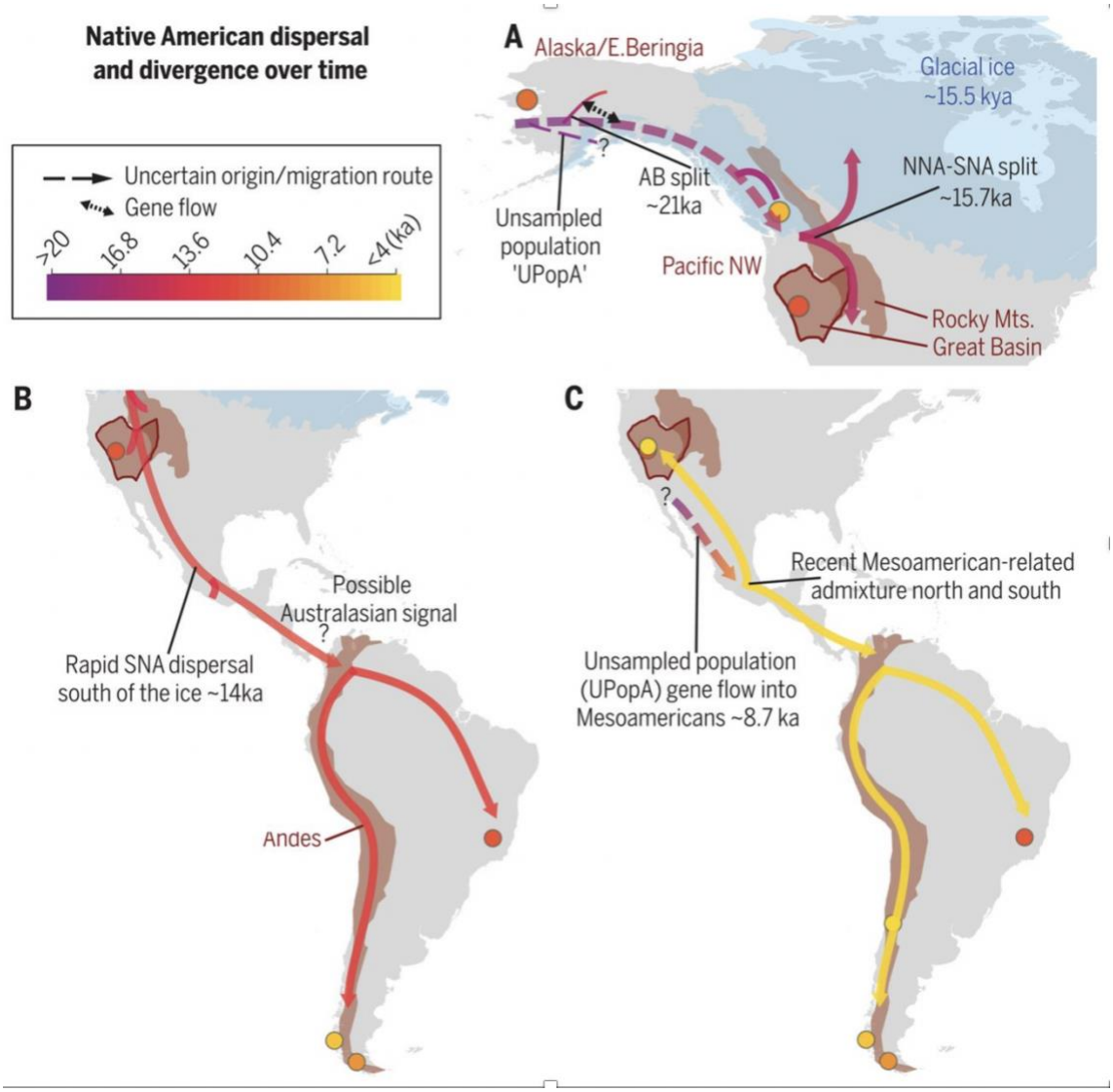


Figure A.5: Native American dispersal and divergence over time (Moreno-Mayar, Vinner et al. 2018)

The Beringian standstill and the AB and ANA lineages

Research published in 2007 included the modelling of a Beringian 'standstill' during the first wave of migration (Tamm et al. 2007). This had involved the analysis of 623 mtDNAs, including from 20 American populations and 26 Asian populations. Phylogenetic analysis of the results identified particular sub-haplogroups within the A, B, C and D mtDNA haplogroups that were widely present in Americas but not East Asian/Siberian populations. The model proposed to account for this was that the migrating first wave had been paused for a significant period while in Beringia, allowing for the coalescing of the sub-haplogroups prior to their rapid dispersal throughout the Americas (Schroeder et al. 2007; Tamm et al. 2007; Kitchen, Miyamoto & Mulligan 2008; Mulligan, Kitchen & Miyamoto 2008).

Research along similar lines by Estrada-Mena et al. (2010) focused on the O blood group shared by nearly all Indigenous Americans. The team identified shared haplotypes within Central and South American populations only including a unique mutation – named O1v\G542A – that was not reported elsewhere.

Further research by Villanea et al. (2013) extended the scope of O1v\G542A research to North American populations – the Haida from the Pacific Northwest, Californian populations and Na-Dene speakers from the Arctic. The cumulative findings of the above – that O1v\G542A is found in all so-far-studied American (but not other) populations – support a standstill time in Beringia during which O1v\G542A coalesced as a genetic signature prior to dispersal.

Research by Raghavan et al. (2015) sequenced 31 contemporary Indigenous American, Siberian and other population genomes for comparison with 23 ancient (200 to 600 years old) North and South American genomes. By dating the emergence of the abovementioned distinctly Indigenous American mtDNA haplogroups (A, B, C, D and X), the researchers estimated the Beringian standstill at 25,000 to 17,500–14,600 years ago – around 8000 years before migration into the American continents resumed.

Significant detail was added to this part of the model by Moreno-Mayar, Potter et al. (2018), who sequenced the genome of an infant who had died in Alaska about 11,500 years ago and compared this with a dataset of ancient Indigenous Americas genomes (including from the above research), as well as 167 genomes from worldwide populations. By this, during the standstill in ice-locked Beringia, they modelled the emergence of a now apparently non-existent Ancient Beringian (AB) lineage and an Ancestral Native American (ANA) lineage.

The NNA and SNA lineages

The ANA pathway into the Americas was investigated in a 2008 study that reported the presence of mtDNA sub-haplogroup D4h3 almost exclusively along the path of the first ice corridor that opened along the Pacific coast and that connected Beringia to the rest of North America; indeed, the presence of the D4h3 suggested such was the primary migration path into the Americas (Fagundes et al. 2008). Research published in 2009 further examined the presence of mtDNA sub-haplogroups D4h3 and X2a in Indigenous American populations to model two roughly simultaneous paths of migration from Beringia along emerging ice-free corridors. In addition to the above on d4h3, sub-haplogroup X2a entered through the ice-free corridor between the Laurentide and Cordilleran ice sheets away from the coast (Perego et al. 2009). This finding was later supported by Grugni et al. (2019, as above).

Moreno-Mayar, Potter et al. (2018) modelled the ANA lineage, once south of the ice sheets, had relatively quickly split into (a) northern Native American (NNA) and (b) southern Native American (SNA) lineages. In broad terms, the NNA lineage is considered ancestral to contemporary Indigenous northern American populations above Mexico, including Algonquian, Na-Dené, Salishan and Tsimshian speakers from Canada, whereas the SNA includes all Mexican, Central American and South American Indigenous peoples, with some admixed with the Australasian lineage (as above) (Scheib et al. 2018).

The researchers also modelled that the NNA lineage moved back into the Alaskan region and replaced or absorbed the AB lineage about 9000 years ago, leaving, in effect, only the NNA and SNA lineages present among contemporary Indigenous Americans.

Research by Llamas et al. (2016) involved sequencing 92 mtDNA genomes from ancient Indigenous American remains (8600 to 500 years old) and temporally calibrating the peopling of the Americas by use of the so-called mtDNA 'molecular clock'. Such a technique has been subject to criticism (Llamas et al. 2016) but otherwise, in broad terms, the research supported much of what is otherwise modelled above:

- divergence of proto-Americans from East Asian populations about 25,000 years ago
- founding ANA lineage formed in the Beringian standstill by 18,400 years ago
- population expansion into the Americas around 16,000 years ago and split into NNA and SNA lineages.

NNA lineage and the peoples of the Arctic

For the NNA lineage, Moreno-Mayar, Vinner et al. (2018, above) modelled that its radiation across North America was rapid (taking a few centuries). However, the broad brush NNA/SNA model does not account for all North American Indigenous diversity, and particularly Arctic peoples.

Research by Reich et al. (2012) followed the genotyping of extant samples from 52 diverse Americas populations (493 individuals), 17 Siberian groups (245 individuals) and 57 other populations (1613 individuals) to identify SNPs. Further, by use of fixation indices, the team modelled that many of the Arctic's Indigenous peoples derived ancestry from two additional lineage migrations (4500 and 2000 years ago (Scheib et al. 2018)), presumably across Bering Sea ice (i.e. at a later time than the Beringian land waves discussed above), that were, respectively, among the ancestors of today's speakers of Eskimo-Aleut languages in the Arctic and the Na-Dene-speaking Chipewyan from Canada. The research suggested three waves of migration had taken place to populate the Americas.

The above echoed findings by Dulik et al. (2012), who analysed Y-chromosomal haplogroup data from Inuvialuit, Gwich'in and Tlicho populations living in the Northwest Territories of Canada (Figure A.6). They reported, based on Y-chromosome haplogroup variation, that Canadian Eskimoan- and Athapaskan-speaking populations were respectively the result of two population expansions that occurred after the 'first wave' migration of people into the Americas. Broadly, the study also demonstrated that Y-chromosomal diversity among the Arctic peoples was greater than previously recognised.

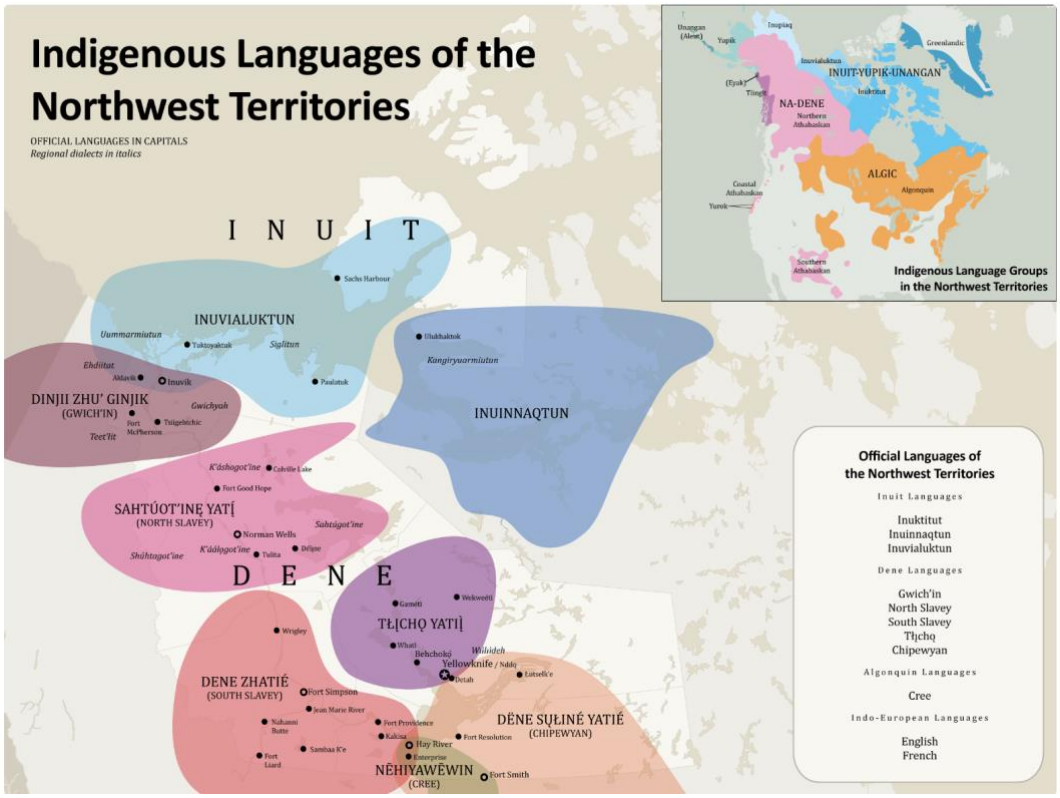


Figure A.6: Language groups of the Canadian Northwest, 2013

Further, Achilli et al. (2013) sequenced 41 mtDNA to focus on the phylogenetic relationships within and between the B2a and A2a mtDNA haplogroups. They reported that while most mtDNA haplogroups across the Americas (i.e. as mentioned, broadly A, B, C, D and X including B2a) stems from a 'first wave' of migration from Siberia to Beringia. This was accompanied or followed by a 'second wave' marked by haplogroups X2a and C4c, with admixture evident in all North American populations. Much later, the ancestral A2a haplogroup spread from Alaska, undertaking both (a) a westward migration back to Asia and (b) an eastward expansion into the circumpolar regions of Canada. In other words, the first wave left the greatest genetic mark in terms of the NNA lineage, but was reshaped by additional waves of migration, tribalisation and so on. This model was further supported by Moreno-Mayar, Potter et al. (2018, discussed above).

Scheib et al. (2018) included investigations into the mtDNA and Y-chromosome haplogroups of the NNA lineage populations of Algonquian speakers in southern Ontario with reference to ancient and modern genomes from the area. They reported both the ancient and modern populations were of the NNA lineage, but there was significantly more admixture with the Indigenous Arctic lineages in later samples, also found in Pacific Northwest populations. This was also proposed to support the above models, with NNA admixture only possible temporally with the more recent migration waves.

The SNA lineages

SNA research also reveals a complex picture. The admixture with Australasian lineages has already been discussed. But Moreno-Mayar, Vinner et al. (2018, above) identified that a further hitherto unsampled wave of migration roughly from the direction of the Beringian entry point and into central and South America occurred around 8700 years ago. There is also significant support for a model by which a single first wave of SNA migration into Central America and South America occurred with subsequent back migrations from Central America into North America.

Sandoval et al. (2012) involved the analysis of 197 Indigenous Mexican Y chromosomes from 11 populations and 1044 from 44 Indigenous American populations. They reported that the majority of Indigenous Americans from Central America down shared Y-chromosome haplogroup Q-M3 with a transition zone between Central America and North America that was not so differentiated. On this basis, they modelled (a) a single wave of SNA migration into Central America and South America, and (b) subsequent back migrations from Central America into North America.

Rasmussen et al. (2014) sequenced a male child's genome found in western Montana among, and contemporaneous with, 'Clovis' stone tools and artefacts dated to around 12,500 years ago. The researchers, first, found the child was unambiguously a member of the 'D' mtDNA haplogroup, connecting him to the founding East Asian-Eurasian lineage. But Y-chromosome haplogroup analysis determined the child was more representative of the SNA than NAA lineages. Hypotheses were proposed to explain this, including that:

- the child's lineage dates from before the ANA split into the SNA–NNA lineage fully occurred but so that the child was closer to the SNA population than the NNA
- the SNA lineage's generally southern trajectory had nonetheless radiated back into North America at some point prior to the child's burial.

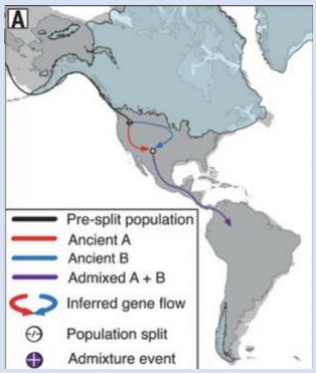
In either case, over time the SNA lineage was subsequently replaced by people of NNA lineage – at least at the Clovis site location of the child's burial.

Regardless of hypothesis, however, 2015 research by Skoglund et al. reported the Clovis child, while part of the SNA lineage, did not share in the Australasian lineage ancestry found in SNA groups in central and South America.

Scheib et al. (2018, discussed above) further investigated the relationship between the SNA and NNA lineages. For the SNA, ancient genomes mainly from the North American west coast (the Californian Channel Islands) were sequenced, or sequences accessed. The genomes were then compared to other relevant datasets to provide context. The researchers reported:

- the ancient Californian island genomes were largely of the SNA lineage
- within the SNA lineage, the genomes from San Nicolas Island had come from a split of the SNA lineage into two populations the researchers called ANC-A and ANC-B but that despite the initial split, the ANC-A and ANC-B groups had later admixed
- the ANC-A lineage was ancestral to the Indigenous groups of South America
- the ANC-B lineage was found at greater levels among Californian Islander groups and Central Americans, Andean and Amazonian Indigenous populations.

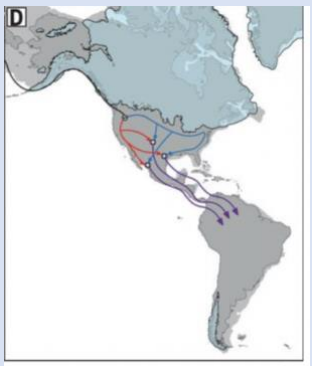
The researchers proposed four possible models to explain the contribution of both the ANC-A and ANC-B branches of the SNA lineage to the Central American and South American populations (Figure A.7).



(a) an admixture event in North America prior to the peopling of South America

(b) ANC-B–related ancestral population(s) dispersing into South America first, followed by a dispersal of ANC-A-related population(s) and admixture of the two branches occurring in South America

(i) The same model as (b) but reversing the ANC-A and ANC-B roles.



(j) multiple admixture events occurring in North America, with multiple dispersals into South America

Figure A.7: Dispersal models that are consistent with the results of the study (Scheib et al. 2018)

Natural selection and tribalisation

Some of the research discussed so far has included reference to the 'tribalisation' by natural selection and relative isolation of peoples as effectively the last phase of the Americas migration process. Indeed, genetic continuity and connection to place is evident for millennia in some cases. Lindo et al. (2017) sequenced (a) an ancient (10,300 years ago) genome from southeast Alaska and (b) three ancient (6075 to 1750 years ago) genomes from British Columbia and compared them with contemporary representatives of these populations. They reported that these were of a continuous lineage dating back 10,300 years.

Natural selection is particularly prevalent among South American groups (e.g. Andean populations who have genetic adaptations to living at high altitude) (Pickrell et al. 2009; Bigham et al. 2010; Schlebusch et al. 2015; Mychaleckyj et al. 2017). But until recently, only limited focused research in this area had been undertaken in North American populations despite such research having the potential to (a) support their ancient connections to their lands and waters, as well as their status as peoples/ nations; (b) assess the impact of colonisation on Indigenous American health; (c) support Indigenous American health in general at the level of peoples or nations; and (d) forensic uses discussed in the next sections of this report.

Research by Fumagelli et al. (2015) on Greenland Inuit looked for evidence of genetic adaption over the generations to exposure to freezing conditions and a specialised fish-based diet rich in protein and fatty acids, particularly omega-3 polyunsaturated fatty acids (PUFA). By genomic sequencing and comparison with other populations, positive natural selection for beneficial genetic variants in fat metabolism were identified. These both promoted the production of heat-generating 'brown' fat cells and helped the body cope with large amounts of PUFA. The same genes also affected height (the population are generally shorter) and weight (heavier), as well as supporting a protective effect on cholesterol and triglyceride levels.

Lindo et al. (2016) sequenced 50 exomes from ancient (up to about 6200 years old) and contemporary individuals from the lineage of the Tsimshian of British Columbia, Pacific Northwest. By phylogenetic modelling, they identified an almost 60 per cent collapse in this population's size at time of European contact. The researchers identified unique markers of immunological adaption to local environmental pathogens in the ancient exomes that decreased in modern populations, coincident with colonisation. They proposed that the environment had been so changed by the colonisers – including by introduction of new diseases – such that the same unique markers became subject to negative selection (i.e. people with them died because they otherwise offered no immunological protection to new pathogens).

Reynolds et al. (2019) collected genomes from northern Alaskan groups (for evidence for environmental adaptations to cold and high-latitude environments as per above) and south-eastern United States and central Mexico populations (both to assess immunological adaptations, and as per above). They reported in the Alaskan population, evidence for genetic adaptation to cold, little sunlight for parts of the year and an almost entirely meat-based diet. This included in relation to genes that influence blood thickness, fat storage, metabolic pathways and skin pigmentation. In the history of the south-eastern United States population, numerous reports of introduced disease epidemics, including smallpox, are reported post-contact. The research suggested that these may have also created significant selective pressures similar to that discussed above and influencing a greater population immunity to these introduced diseases. The Mexican population demonstrated

selection on the mucin gene MUC19 – primarily involved in the immune response to parasitic infection but also associated with decreased vulnerability to smallpox virus. Ultimately, these results were inconclusive, but nonetheless suggestive of natural selection in response to exposure to smallpox.

The population after European contact, 1492

As suggested, contact had significantly negative effects on Indigenous American health and populations levels. O'Fallon & Fehren-Schmitz (2011) used a large dataset, including 63 ancient (up to 3000 years old) and 197 contemporary mtDNA within the five signature Indigenous American mtDNA haplogroups (i.e. A, B, C, D and X). By undertaking further mtDNA 'clock'-based analysis, they approximated the population sizes of Indigenous Americans prior to and after contact. Their reconstruction suggested that *all* so-far-studied Indigenous American populations suffered roughly 50 per cent contraction in female population size about 500 years ago, coincident with colonisation, and otherwise resonant with historical reports.

Such is also supported by research populations groups, including research among the Tsimshian of the Pacific Northwest by Lindo et al. (2018). The researchers compared exome sequences from 24 modern and 24 ancient (pre-contact) members of this group. They reported a dramatic population decline following contact, but within around ten generations of admixture and natural selection, modern individuals had lost potentially damaging variants found among the ancient populations that were maladapted to post-colonisation conditions. However, the researchers reported that the population had otherwise been on a steady decline in size for several thousand years before contact, and therefore cautioned against 'one size fits all' Americas-wide population histories, including post-contact ones.

In closing this section, American colonisation brought European (Spanish then Western European), African and Native American populations into admixture for the first time. Building on some pre-2010 studies (Buroker et al. 1997), Jordan, Rishishwar & Conley (2019) investigated the extent of Native American ancestry in Western European, Spanish and African descendant populations present in the United States. They found that history was effectively written in the genes of these three population groups as follows:

- The Western European descendant group shows the lowest levels of Native American admixture consistent with a large, ongoing and constant influx of European immigrants to the United States, along with social and legal prohibitions against mixed-race relationships. However, there was significant variation within the admixture pattern, suggesting, as had occurred along the Australian frontier, mixed-race children were being born to European and different Indigenous American groups as the United States frontier moved westward and the reach of colonial social norms and laws declined.
- The African descendant group demonstrated a relatively low but consistent admixture across the United States. The researchers identified this as signifying the admixture occurring in relative isolation – in the antebellum south prior to the Civil War – followed by dispersal across the United States.
- Spanish descendant populations showed the highest rates of admixture and the highest rates of variation in the admixture. In particular, the descendants of the early Spanish coloniser populations – known as Nuevomexicanos (who migrated 1598 to 1848 and who occupied southern areas, such as Texas and New Mexico, of what would become the United States) – were clearly distinguishable by the higher rates of admixture with Native

Americans from those who arrived post-1848. This was anomalous with historic Nuevomexicano claims that denied admixture had occurred to any significant degree.

Forensic genomic research

Indigenous American (United States) and Canadian genetic signatures

Previous to 2010, and as might otherwise be expected as per the previous section, forensically diagnostic (or distinguishing) STRs had been reported and used to support the identification of Indigenous American genomes, with relatively limited risk of confusion with geographically distant (at least in origin) northeast Siberian genomes (Phillips et al. 2008). Further, while many of the signature Indigenous American mtDNA haplogroups (A, B, C, D, X) are shared with east Asian groups, evidence suggests it is possible to distinguish population variations (i.e. sub-haplogroups) (Starikovskaya et al. 2005). This is important not only to archaeogenetics but also to forensic science – for example, in relation to identifying remains found on World War II combat zones where such might have Japanese (East Asian) or Indigenous American mtDNA (Wood et al. 2019).

In such cases, or others where mtDNA might be significantly degraded, there might only be a limited number of variation points to measure. MtDNA haplogroup B2 has no established diagnostic variants in the mtDNA control area (see above) from its parental B4 Indigenous American and closely related B4b haplogroups found in Asia. In response, Wood et al. (2019) sequenced 56 B2 and B4 mtDNA genomes (mitogenomes) from East Asian and Indigenous American individuals. Haplogroups were estimated based on HV1 and 2, the control region, and full mitogenome. The researchers determined Indigenous American B2 haplotypes were distinguishable solely based on CR data in 82 per cent of samples, though the remaining samples required full mitogenome data for haplogroup B2 designation. Overall, half of the samples required full mitogenome data in order to make forensically reliable distinctions.

For SNP and STR variants, the flanking region (base pairs extending on either side of the STR/SNP) have been described for major population groups, but not for more isolated populations such as the Yavapai (people of the sun), a Native American tribe located mostly in northern Arizona. To remedy this, genomes representative of the nation was analysed by Wendt et al. (2017) using a commercial massive parallel ('next generation') sequencing machine. Seven SNPs exhibited flanking region variation such to provide a Yavapi genetic signature and support positive identification.

Random match probabilities and datasets

Among the ongoing legacies of colonisation are social determinants and structural (including institutional) racism, which lead to disproportionate exposure to the criminal justice system and significantly higher incarceration rates when compared to their non-Indigenous counterparts. These include the ability of Indigenous plaintiffs to receive fair trials, particularly in the face of DNA evidence gathered at crime scenes to help prove connection of suspects to a crime. Indeed, matches provide compelling evidence of involvement because the odds of such occurring randomly are estimated in terms of millions or billions to one (Kaye 2016). These, often inconceivably tiny, odds of a random match are referred to as random match probabilities (RMP).

The accuracy of RMPs within Indigenous populations is critical to fair trials, as much as between Indigenous and general population contexts. This can be problematic because Indigenous populations can have lower genetic diversity than other populations, with more shared ancestors who might have spent generations in regional isolation (McEvoy et al. 2010). Within such

populations, the likelihood ratio (LR) for two individuals sharing an STR might be quite different from that in the wider population, and RMPs considerably lower.

Thirteen key STRs are required to be identified for any DNA profile entry into the national level of the United States DNA database, referred to as CODIS – the Combined DNA Index System, the FBI's program around criminal justice DNA databases (U.S. Government n.d.). These STRs are highly informative and particularly suited for direct comparisons (i.e. single source and mixtures) and indirect profile comparisons of related individuals (i.e. kinship). And by using these STRs, RMPs of one in 100 trillion can be attained (Bieber et al. 2016). These estimates are based on databases that comprise major United States population groups, including Caucasians, African Americans, Hispanics and Asian Americans, and which exhibit genotype frequencies that are different from those in Native American populations. However, distinguishing between Indigenous American groups has proven to be difficult (Kanthaswamy 2019).

Representative genomic information was, and still is, required in CODIS from many tribes in North America, as identified by Kanthaswamy & Smith (2014) and McCulloh et al. (2016). In the latter, the researchers used CODIS in relation to 10 non-represented tribal groups and determined an unacceptably high risk of misidentification for these groups. Ng et al. (2016) then addressed some of these gaps by producing STR genotypic data for 533 individuals representing 31 Native American tribal populations derived from eight geographically diverse regions in North America.

Genomic medicine and the Indigenous peoples of North America above Mexico

Mental health and substance use

As with the Māori and Indigenous Australians, Indigenous Americans have reported disproportionately higher rates of alcohol dependence and substance use. A focus of genomic research in the United States has been alcohol dependence and substance use among Indigenous Americans. In particular, a longitudinal study led by Ehlers that commenced in 1994 has focused on the genetic risk and protective factors to such issues in 3000 Native Americans living on eight contiguous reservations in the San Diego county and is referred to in several contexts below. Early focus included genetically determined alcohol metabolism (Wall et al. 1996). Ehlers and Gizer's (2013) literature review provide a useful overview of research until that date. It reported that while studies in non-Indigenous American populations have reported that up to 50 per cent of alcohol dependence risk is inheritable, few studies had focused on Native Americans up until that point. From extant literature, they concluded that substance dependence has a similar genetic risk component in Native Americans to other American populations, and:

> The high rates of substance dependence seen in some tribes is likely a combination of a lack of genetic protective factors (metabolizing enzyme variants) combined with genetically mediated risk factors (externalizing traits, consumption drive, drug sensitivity/tolerance) that combine with key environmental factors (trauma exposure, early age of onset of use, environmental hardship/contingencies) to produce increased risk for the disorder. (Ehlers & Gizer 2013:154)

Studies of interest include those through the following lenses.

Brain 'alpha wave' variations

Electroencephalography (EEG) is a method of monitoring brain electrical activity, usually with electrodes placed on the scalp. The activity registers as frequencies or waves. Alpha waves (in the frequency range of 8–12 Hz) are the most commonly measured in adult humans and are associated

with a state of rest, including REM sleep. Other wave types are 'infra low' (less than 0.5 Hz), 'delta' (0.5 to 3 Hz), 'theta' (3 to 8 Hz), 'beta' (12 to 38 Hz) and 'gamma' (38 to 42Hz).

Of relevance to this section, states of 'high alpha' are recognised (11 – 16 Hz), and 'low alpha' includes the absence of alpha waves and presence of other waves – usually theta or beta waves. Brain wave-based diagnostics include those for epilepsy, sleep disorders, depth of anaesthesia, coma, encephalopathies (disorders of the brain including degenerative conditions) and brain death. And the disordering of alpha wave states is associated with major sleep disorders, chronic fatigue syndrome, bi-polar disorders and major depression and is the subject of ongoing research.

To date, while many research efforts have focused on European-Caucasian populations, a significant number have focused on Indigenous Americans, including in relation to higher rates of alcohol dependence reported among some United States Native American populations that are also associated with higher rates of low alpha in these groups.

As an example of non-genomic studies to provide context, Ehlers et al. (2015) recruited more than 750 members of a Native American community and completed diagnostic interviews and a number of psychometric assessments. EEGs were also collected, including approximations of response to events to be able to match the former results to these and determine any relationships. Individuals with 'low alpha' were also found to have decreased energy in some responses to stimulus, but no association with personality variables, alcohol dependence and anxiety. Yet there was a suggestion that low alpha individuals were drinking more, yet reacting less to (i.e. tolerating), alcohol – suggesting a potentially increased risk for alcohol dependence.

As for specifically genomic associations, Ehlers et al. (2010:5) recruited 410 individuals from families from the longitudinal study discussed above (Tonigan et al. 2013), with about 60 per cent of the sample reported as having a lifetime Diagnostic and Statistical Manual of Mental Disorders (DSM) III-R defined dependence on alcohol, 32 per cent with dependence on cannabis and around 10 per cent with DSM-defined 'antisocial personality disorder'. EEGs were collected, as well as genotypes for STR analysis, with further reference to other datasets. The researchers reported a high degree of inheritability of associated STRs across several chromosomes, and, in particular, regions of chromosome 4 and 6, that they associated with alcohol dependence. In discussing their findings, the researchers stressed the importance of not generalising these results to other Native Americans.

In Peng et al. (2017), 850 Native Americans from a tribal group (including many mixed-race members) were recruited and their EEGs assessed for alpha, low alpha and high alpha variance. Of these, 692 were also whole genome-sequenced for analysis and comparison with other datasets. Among the most significant findings was association between alpha wave voltage and variation in the genes responsible for:

- Some acid-sensing ion channels (ASIC) in the brain and nervous system. There are several types of ASIC. In sum, these are associated with neurotransmission, with some associated with pain and central nervous system diseases. ASIC 2 is associated with defensive responses that could include fear and panic, and particular variance was noticed in the gene responsible for ASIC 2 production.
- Variation in the GPR158 gene associated with the regulation of neuronal excitability and associated with a propensity to panic disorders in a German population.
- LINGO 2 – a gene associated with Parkinson's disease and bodily tremors.

However, the TIA1 gene was the only candidate with high association to low alpha. TIA1 is, through complex neuro-transmission-related pathways, associated with the stress (fight or flight) response.

In sum, the researchers observed variation among a range of genes responsible for the brain's experience of stress or stimulation, and to a higher degree in the Native American sample population when compared with European populations. They hypothesised that low alpha may in fact be a basal state and the genetic foundation for alpha and high alpha determined by causal variants in European populations.

Stimulant use

Ehlers et al. (2011) investigated the reported high rates of amphetamine and cocaine usage by Native Americans among the abovementioned longitudinal study participants. The study simply aimed to map loci linked to stimulant dependence, heavy use and cravings. To do so, just over 380 members of families characterised as 'multiplex' (meaning, in this context, that more than one sibling had a substance use challenge) were recruited.

The researchers first administered a psychometric assessment – *Semi-Structured Assessment for the Genetics of Alcoholism* – to the participants to support DSM-III-R diagnosis of the following phenotypes: (1) stimulant (amphetamine or cocaine) dependence diagnosis; (2) stimulant 'craving' defined as endorsing the question, 'In situations where you couldn't use stimulants, did you ever have such a strong desire for it that you couldn't think of anything else?'; and (3) a measure of a period of heavy use of stimulants defined as endorsing, 'Was there ever a period of a month or more when a great deal of your time was spent using stimulants, getting stimulants, or getting over its effects?'

Of the 381 participants, 212 met criteria for amphetamine dependence, 17 met criteria for cocaine dependence, and 51 met criteria for both cocaine and amphetamine dependence, for a total number of participants with either diagnosis of 280. These were genotyped and compared with a control group. The researchers located at least three areas of the genome that may harbor genes that modulate levels of addiction to stimulants. This included a site on chromosome 15 – at q25.3-26.1 – that a range of previous studies had associated with alcohol, cannabis and cocaine use. The researchers concluded a group of genes may eventually be found on human chromosome 15 that are important for substance dependence and that research should continue at this loci. Among several qualifications, the researchers cautioned that the findings of this study may not generalise to other Native Americans or represent all Native American Indians of the tribes studied.

Cannabis dependence

Studies of impulsivity in Native Americans commenced with Ehlers et al. (2007) who, following research in European populations (Haughey et al. 2008), investigated the association of impulsivity with the CNR1 gene that encodes one of two receptors of cannabinoid – the psychoactive ingredients of marijuana – found to be involved in the central nervous system effects. These included the alterations in mood and cognition experienced by users of marijuana. Their aim was to determine if a significant association could be detected between the triplet repeat STR, as well as 5 SNPs in or near the CNR1 receptor gene and impulsivity in the longitudinal study participants. Impulsivity was assessed using psychometric assessment and blood samples were collected for sequencing from about 250 individuals. The researchers found that impulsivity was significantly associated with the 6-repeat allele of the triplet repeat polymorphism, as well as four SNPs in or near the CNR1 receptor gene, suggesting it was significantly associated with impulsivity in the

sample (Ehlers et al. 2007). However, these and other studies of the time were not able to reach standards of genome wide significance that later emerged.

Gizer et al. (2018) continued this line of research in a Native American community, consisting of 697 participants within family groups, and 1832 predominantly European ancestry participants within nuclear families. Participants in both samples were assessed for DSM-IV lifetime cannabis dependence, with 168 and 241 participants respectively being so diagnosed. Using a whole genome approach focusing on low frequency variations, the researchers identified cannabis dependence-associated candidates in the C1orf110 gene (about which little is conclusively known) and variation potentially involved in the regulation of MEF2B and PCCB expression. The former plays an important role in nerve synapse formation, particularly in the hippocampus. Variations in the gene are associated with memory disruption, among other effects. The latter is a gene previously associated with schizophrenia.

Impulsivity

Impulsivity is a multi-faceted construct developed around persons who tend to act suddenly, in an unplanned manner, without consideration for the consequences of such behaviour. Several psychiatric disorders in DSM-5 include impulsivity as a criterion, such as substance abuse (including use of cannabis), borderline personality disorder, pathological gambling, pyromania and kleptomania. Among Indigenous Australians, impulsivity has been proposed as one explanation for high rates of child and youth suicide when compared to non-Indigenous Australians. A limited number of studies suggest externalising disorders featuring 'behavioural under-control' and 'disinhibited personality', including disruptive behaviour disorders, attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder and conduct disorder, may share a genetic vulnerability. Quantitative genetic studies have also demonstrated that about 30–50 per cent of the variance in these impulsivity-related constructs is heritable, yet the specific genetic variants that contribute to impulsivity-related traits remain largely unknown (Ehlers et al. 2016).

Ehlers et al. (2016) further investigated genetic contributions to impulsivity in an American Indian sample from the abovementioned longitudinal study (Tonigan et al. 2013). In all, the study included about 650 individuals from 150 family groups. Impulsivity was assessed through several psychometric assessments. GWAS then revealed two significant findings that were positively associated with impulsivity:

- A variant on chromosome 2 located in a cluster of genes that encode for a family of proteins primarily excreted by the pancreas, and that are associated with the regeneration of cells in the so-called 'islets of Langerhans' without the pancreas, that are responsible for maintaining blood glucose levels. Dysfunctional cells in the islets are associated with types 1 and 2 diabetes. However, the cluster of genes is also associated with the central nervous system and the neurological development of the foetal brain referred to as neuronal sprouting (i.e. growth of brain neurons across the life cycle) and synaptogenesis (associated formation of synapses across neurons) in the adult brain.
- A variant to the NEIL3 gene area. NEIL3 belongs to a class of substances that help repair DNA strands but, like the above, they too play an important role in neurogenesis in the foetal brain, as well as a continued role in neurogenesis in the hippocampus of the adult brain.

The researchers caution that these potentially important findings to understanding the genetic determinants associated with the development of substance use disorders may not generalise to

other Native American communities, or represent all Native Americans within this population, among several other potential limitations.

Patterns of nicotine use

Quantitative genetics provides a useful research context for the study of nicotine use, which varies over the life course and represents an interaction between genetic influences and environment. Studies have determined a few genes and alleles associated with pattern of nicotine use in European populations. Using twins and families to assess inheritable traits, these studies had resulted in estimates that genetic factors account for 44 per cent of variance (i.e. within the population) in commencement of smoking; 50 per cent of smoking quantity (cigarettes per day or CPD); and between 33–75 per cent in the development of nicotine dependence, as defined (Vink et al. 2005; MacKillop et al. 2010; Agrawal & Lynskey 2008; Agarwal et al. 2012).

When comparing whole population groups, smoking rates in the United States are highest among American Indian and Alaska Native populations (although regional and other intra-population variation exists) (Espey et al. 2014). Despite this, relatively little focus has been on the genetic contributions to this situation and whether these populations share the same genetic risks as European populations.

To help address these questions, Otto et al. (2016) recruited 775 Native American participants aged 18 and 82 years, from 161 family groups from the abovementioned longitudinal study (Tonigan et al. 2013). It included people of mixed (European–Native American) race ancestry. From these, 288 individuals were selected. The sample was first assessed for CPD and nicotine dependence as defined by DSM-IV. Blood samples were then sequenced at significant coverage depths, with a focus on seven markers indicative of nicotine usage found in European populations. The researchers observed that while the seven markers were present in the sample, they were not as predictive of nicotine usage – with variance from the modelled European Programme Reporting Standards increasing the less European ancestry a person had. The researchers concluded that while the same genetic markers may play a role in Native American phenotype-based nicotine usage patterns, the linkage disequilibrium – measures between them were likely different, and other markers may need to be accounted for. As such, further dedicated Native American population research was required.

Diurnal preference and bipolar disorder

There is wide variance in peoples' 'biological clocks', including their sleeping and waking cycles. Such are regulated by endogenous circadian rhythms (circulating glucose and insulin levels) and other metabolic processes (contributing to 'energy levels') interacting with environmental influences. Such are classified as diurnal preference chronotypes – in lay terms, being a morning person or evening person. Of interest, the evening chronotype has been authoritatively associated with bipolar disorder, major depressive disorder and substance use disorders (Potter et al. 2016).

There is increasing interest in the contribution of genetics to biological clocks, with the contribution of hereditary to environmental and other factors being estimated at between 21–54 per cent. Several GWAS on sleep duration, sleep latency, sleep depth, sleep quality, insomnia, daytime sleepiness and so on have occurred, but many of the specific phenotypes identified and associated with these are yet to be associated with chronotypes. Further, until Melroy-Greif et al. (2017), most of these studies had occurred in European populations. Yet epidemiological (and not genetic) studies among non-European groups have reported poorer sleep quality when compared with Europeans, particularly among those from lower socioeconomic groups.

The researchers looked at Mexican American (about 600 individuals) and Indian American population groups (about 3000 individuals). By psychometric testing, they asked participants about their usual bedtime, wakeup time, actual hours slept, number of minutes to fall asleep and night-time awakenings. They identified 'evening preference' people (those who went to bed usually after 11.00 pm). They then conducted a GWAS on diurnal preference and polygenic risk score profiling to determine whether variance in diurnal preference might also be associated with genetic association with bipolar disorder and depression. Four variants in KIAA1549, a gene previously associated with attempted suicide in bipolar patients, were suggestively associated with an evening diurnal preference. The research provided further evidence of genetic risk factors for bipolar disorder, including in Native Americans.

Type 2 diabetes

Multiple SNPs across over 70 regions have been associated with T2D in various, but mostly European, population groups, and with significant variance between European and other population groups reported. Variants on the gene TCF7L2 have been associated with diabetes. While the precise association is unclear, the gene contributes to the metabolic functioning of the pancreas, liver and adipose tissue or fat. It has been associated with colorectal cancer and even schizophrenia in certain populations (Stone, McPherson & Gail Darlington 2018).

As among all the Indigenous populations discussed in this review, higher rates of T2D are reported among Indigenous Americans when compared with their non-Indigenous counterparts, and this is particularly so among the Pima Nation of Arizona. Indeed, among the Pima, some of the highest rates of T2D in the world are reported and they have become a focus population for T2D research, including an ongoing longitudinal study involving thousands of their members.

Genomic researchers have long drawn on this foundation (and the members of the longitudinal study) to identify whether alleles associated with T2D in other populations were also associated with high Pima T2D rates. In sum:

- in 2003, because an SNP had also been associated with obesity and T2D in other populations, the gene responsible for the PPARgamma-2 hormone – with a role in maintaining body energy levels, fat production and insulin sensitivity – was investigated in Pima populations; the researchers found several novel gene SNPs in the Pima that were associated with T2D rates (Muller et al. 2003)
- in 2007 researchers ruled out six variants in the TCF7L2 gene found in Icelandic, Danish and some United States populations as being significantly associated with Pima T2D (Guo et al. 2007)
- in 2009 researchers investigated six SNPs associated with T2D in Caucasian-European populations. They reported only one of the six appeared to play a role in BMI, but not directly to T2D, risk (Fawcett & Barroso 2010).

Hanson et al. (2013) tested a further six T2D-associated SNPs in Icelandic populations and whose impact was dependent on maternal or paternal inheritance among the Pima. Along with two other SNPs, four variants of gene KCNQ1 were assessed. In fact, all six SNPs were associated with Pima T2D with bias towards maternal inheritance in all, but with particularly strong effects noted in KCNQ1 variants. Indeed, one variant in particular – rs22299620 – was associated with a 28 per cent decrease in insulin secretion. Overall, maternally acquired KCNQ1 variants were estimated to account for about 4 per cent difference in whether a Pima individual had diabetes or not.

A large 2014 international study identified seven new T2D-associated SNPs. Drawing on the longitudinal study participants, Nair et al. (2014) assessed these associations among the Pima using previously obtained GWAS data. Two of the seven new SNPs were – to varying degrees – associated with Pima T2D. However, a novel SNP in the Lipoma Preferred Partner (LLP) gene was identified with T2D association in the Pima. LPP is a protein associated with cell movement (motility) and adhesion.

Hanson et al. (2015) also drew upon the longitudinal study participants to investigate associations with the 63 to date otherwise un-investigated T2D-associated SNPs, with an overall sample of around 3500 Pima individuals who were members of sibships (i.e. shared the same parents), to also consider parent of origin effects. These were assessed for TD2 and BMI, with a subset of 405 assessed for insulin sensitivity and insulin secretion. The research suggested that most of these SNPs (but not all) had varying effects on Pima T2D, with the cumulative impact being on insulin secretion, as was the case in other populations. Having said that, the correlations accounted for little, if any, of the high T2D prevalence among the Pima compared with populations of European ancestry. The researchers concluded that the prevalence of T2D in the Pima was likely the result of environmental factors or genetic factors that remain largely unidentified.

The shared ancestry of East Asian and Indigenous American genomes has been a major archaeogenetic discovery (Der Sarkissian et al. 2015, discussed above). A 2011 meta-analysis of GWAS had identified eight new loci for T2D (related to T2D onset age, BMI, insulin sensitivity and insulin secretion) in East Asians populations, but whether these were relevant to Indigenous American T2D rates was unknown (Cho et al. 2011). To investigate further, Muller et al. (2016) drew on longitudinal study participants. The researchers reported that only three of the eight East Asian markers were significantly associated with Pima T2D. Further, that novel variations on two of the markers associated with T2D were found in the Pima and associated with female inheritance. One at GLIS-3 was found to be associated with pancreatic cell production, with previous associations to neonatal diabetes reported. The researchers concluded that further research was required to fully understand the implications of these findings, but that in broad terms the need for population-specific studies to understand the genetic, environmental and other contribution to conditions like T2D was evident.

In relation to the immune system

The human leukocyte antigen (HLA) system is a group of six cell-surface antigens (see above) responsible for the regulation of the immune system. HLA genes have many different alleles, allowing the immune system to rapidly adapt to new challenges. Different HLA have different functions within the overall HLA system. In particular, 'HLA class II histocompatibility antigen, DM beta chain' (HLA DMB) is a protein that in humans is encoded by the HLA-DMB gene. It has been shown to be protective against cancer in European but not African populations, but is also associated with immunological diseases in some populations. Until research by Arnaiz-Villena et al. (2016), little research had been undertaken in Indigenous American populations. The researchers genotyped 168 volunteer American Indians for alleles to establish a database for further research activity.

C-reactive protein (CRP) is a protein made by the liver and secreted into the blood. It is often the first evidence of inflammation or an infection in the body. Its concentration increases in the blood within a few hours after the start of infection or other inflammatory injury. Increased levels of C-reactive protein in the blood in combination with environmental factors are also associated with CVD, which disproportionately affects American Indians, as it affects many Indigenous populations.

Research in this area, however, has wider significance because it is increasingly clear that inflammatory responses also influence the pathogenesis and complications of metabolic conditions, cancer and other chronic diseases.

The Strong Heart Family Study investigated whether variations on the gene that expresses as CRP were associated with elevated CVD risk. Best et al. (2019) had access to serum CRP measurements for almost 2500 tribal members, recruited as large families from three regions of the United States. The study looked for associations with elevated CRP and STR and SNPs within a GWAS. The researchers identified genes in which variance showed suggestive linkage to CRP levels. An additional 46 SNPs located at seven novel loci were also identified for further investigation.

Other Australian and/or international literature by subject

Trauma

The origins of all trauma are experiences of, or exposures to, distressing, often violent, potentially traumatic events (PTEs). Although there are many ways to understand trauma, the presence of four symptoms is required for a DSM-5 (APA 2013) defined diagnosis of post-traumatic stress disorder (PTSD):

- re-experiencing the trauma
- avoiding reminders of the PTE
- negative changes in thoughts and mood
- feeling 'on edge' and overly aroused (including hypervigilance against repeating the PTE) (Black Dog Institute n.d.).

Understanding trauma, including preconception trauma, could be expected to make a significant contribution to de-colonisation (and, potentially, molecular decolonisation) practice among Indigenous peoples in Australia – particularly in relation to the practice of forcible removals of Indigenous children from their families for placement in 'white' families or institutions for the purpose of assimilation (HREOC 1997). Most Indigenous families in Australia were touched by this practice before it petered out in the early 1970s. Between one in three and one in ten Indigenous children were removed over that time (HREOC 1997). In 2014–15 it is estimated that about 21,000 Indigenous people who were removed were still alive and that this cohort had about 115,000 descendants, including grandchildren and great grandchildren (AIHW 2018:vii–viii).

The biological basis of trauma centres on the hypothalamic-pituitary-adrenal (HPA)-axis. When an individual is exposed to a PTE, glucocorticoids are released by the HPA-axis. These connect to glucocorticoid receptors throughout the body and result in the 'fight or flight' response. Once a PTE has passed, the HPA releases other enzymes to 'disconnect' the glucocorticoids from the glucocorticoid receptors and the person can start to return to a pre-PTE state (Stephens & Wand 2012). In this context, the 'genetics of trauma' is about the functioning of genes related to HPA-axis functioning – in particular, the influence of epigenetic processes whereby genes are 'switched on or off', but without modifying the genes or DNA itself.

Researchers have associated PTSD with epigenetic changes to genes in the HPA-axis that regulate the fight or flight state. In particular, gene NR3C1 works closely with another – KPBP5 – to produce enzymes that activate, and then neutralise, the fight or flight response during and after PTE. A growing body of research suggests that when NR3C1 or KPBP5 are epigenetically suppressed, a person can remain in a chronic fight or flight response longer than it is useful for (Liu & Nusslock

2018); in other words, the person remains in trauma (Center for Substance Abuse Treatment (US) 2014).

Miller et al. (2020) explored this in a small-scale, but nonetheless important, study among a sample of 47 Queensland university students. These were, first, assessed and graded for both PTSD using validated trauma assessment tools; second, epigenetically analysed around their NR3C1 and KPBP5 genes; and, third, the results were correlated. The research demonstrated for the first time an association between increasing levels of gene methylation across NR3C1 and KPBP5, and increasing degrees of PTSD.

Although biological mechanisms and intergenerational and even transgenerational transmission mechanisms of trauma are important discussions to address (see below), they should not be mistaken for the totality of a response to trauma as an Indigenous population health issue, and should otherwise be located in a broader multidisciplinary context that ultimately includes political, social and economic addresses to the position of Indigenous peoples in Australia – that is, particularly to the degree that trauma as an Indigenous population health issue is exacerbated by poverty, social exclusion, racism, overcrowded housing and so on.

Miller et al. (2020) caution that addressing non-biological traumatisation pathways will likely always remain a critical program element in any Indigenous population-wide approach to halting the transmission of trauma. Such program elements include, for example, parenting programs that address the needs of children who live with traumatised parents. The results of traumatisation are that the child becomes 'a container for the unwanted, troubling experiences of the parent' (Yehuda & Lehrner 2018:244, with reference to Barocas & Barocas 1980 and Kestenberg 1980).

Challenges in diagnosing PTSD is that the person often spends considerable energy and resources warding off the traumatic memories with behaviours that are mistaken as independent problems in themselves: numbing anxiety with alcohol or drugs (sometimes leading to addiction); anger and rage at the PTE displaced onto family and others (sometimes leading to violence); becoming 'emotionally numb' and dissociating from the present (sometimes leading to neglect); and maintaining 'chaos' so the life emphasis is on survival (it tends to be the quiet moments when memories re-surface) (Khoury et al. 2010). These symptoms, in turn, are mediators for secondary traumatisation, particularly of children. But even when correctly placed with a PTSD diagnosis, they will continue to require an address on their own terms (i.e. alcohol and drug programs), in addition to any epigenetic approach.

Epigenetic healing

Psychotherapy is one avenue to healing trauma by the integration of the PTEs such that healthy HPA axis functionality can resume. This includes 'exposure therapy' whereby patients are exposed to stimuli, which provokes the fear and anxiety associated with the trauma, but in a safe, controlled environment (Stephens & Wand 2012). Over time, with the therapy promotion, the re-learning of responses, a decreased connection between the stimuli anxiety, and the other symptoms of trauma are observed (Sherin & Nemeroff 2011).

Further, in relation to exposure therapy, two enzymes – referred to in shorthand as BDNF and NMDA – are associated with brain plasticity, enabling the brain to 're-learn' faster different reactions to the trauma, apart from anxiety. In turn, the two enzymes are associated with the two genes that express or transcribe them. And in order to increase brain plasticity, the epigenetic activation/stimulation of these genes by histone acetylation has been the focus of research into the

treatment of anxiety disorders and could help within a wider program to heal trauma and other stress-related conditions (Whittle & Singewald 2014).

Indeed, brain plasticity-boosting epigenetic drugs tested in humans have been demonstrated to increase the clinical effectiveness of exposure therapy (Whittle and Singewald et al. 2014). It should be noted, however, that the administration of such drugs without accompanying exposure therapy is also reported to have the potential of making trauma worse, with brain plasticity also leaving the patient vulnerable to anxiety increasing associations in the absence of therapeutic direction (Watkins, Sprang & Rothbaum 2018). Overall, the potential of epigenetic therapies is only just beginning to be explored.

Understanding and halting the transmission of trauma and stress effects experienced in utero

There are biological in utero pathways of trauma-effect transmission by foetal exposure to maternal stress 'fight or flight' chemicals. Again, the HPA axis is implicated. It is known that its development can be impacted particularly in the first 22 weeks of pregnancy. In fact, throughout a pregnancy, maternal genes active in the placenta work to effectively neutralise maternal 'fight or flight' chemicals and their impact on the foetus (Reynolds 2013). But extreme maternal stress can be such that these genes are epigenetically 'switched off' by methylation, leaving the growing HPA axis-development exposed to the 'fight or flight' chemicals with its development potentially compromised (Reynolds 2013).

Such impacts were observed by researchers in adults who were exposed in utero to the Dutch famine of 1944–45 (Heijmans et al. 2008) or to intimate partner violence during pregnancy (Radtke et al. 2011), among the children of women caught in warzones (Mulligan et al. 2012) and genocides (Perroud et al. 2014), and even in relation to pregnancy-related anxiety itself (Hompes et al. 2013). These include higher rates of lower birthweight babies (also reported at high rates among Indigenous births in Australia), impacts on cognitive development and increased later life risk of anxiety, depression, attention deficit and hyperactivity disorder, and schizophrenia (van den Bergh et al. 2017).

Research by Serpeloni et al. (2017) also suggests the possibilities of transgenerational transmission (i.e. from grandmother to mother to grandchild and beyond) of in utero stress and trauma effects, and that these may include vulnerabilities to CVD in addition to potential HPA axis impacts (discussed above).

The researchers, first, undertook a genome-wide DNA methylation profile (i.e. for potential epigenetic changes) among a cohort of 121 children from São Gonçalo, Rio de Janeiro, Brazil, where a high proportion of low-income families and high levels of community and domestic violence (CDV) are reported. Second, they assessed the cohort children's grandmothers for CDV before, during and after their pregnancy with the children's parents, and for present-day PTSD and depression. By corelating and analysing the results, the researchers noted (1) five epigenetically 'switched off' genes involved in circulatory system processes and (2) that these five epigenetic changes were statistically significantly associated with the grandmother's increasing reports of exposure to CDV while pregnant.

Serpeloni et al. (2017) deem these changes as a potential biomarker for health problems in the grandchildren as they grew older. But the researchers themselves also noted the limitations in their study, including the small cohort and the potential for confounding factors, particularly in the socio-economic context of the research cohort (Serpeloni et al. 2017).

Understanding and halting the transmission of trauma and stress effects

Research into the transgenerational transmission of trauma effects has its root in late 1980s animal experiments whereby newborn rat infants (pups) were separated from their mothers for several minutes each day: a PTE. In adulthood, these pups had altered basal HPA-axis 'fight or flight'-state chemical balances and displayed associated behavioural characteristics. But, critically, the same effects were also detected in the offspring of the pups. And by elimination of confounding factors (i.e. in utero effects and parenting), the researchers proposed that the trauma effects had not only been epigenetically transmitted from mother to pup (i.e. intergenerational transmission) but then on to the pups of the pups (transgenerational transmission) (Yehuda & Lehrner 2018). Taking this and other studies into account, Yehuda & Lehrner's (2018) review summarises the evidence for the transgenerational maternal-line transmission of trauma effects as follows:

> In summary, the limited data suggesting an association of an epigenetic alteration with maternal age at trauma exposure imply potential contributions of both in utero effects and possibly preconception epigenetic changes to [early foetal development]. However, while it is tempting to assume that findings of preconception trauma and epigenetic changes in the mother are passed on in the ovary through sexual reproduction, maintained throughout foetal development and manifest post-conception, there are no studies to date examining this possibility in either animal or human samples mainly due to the enormous methodological challenges of such research, and the number of variables to be accounted for, requiring innovative methods of investigation.

But this is the maternal line. In contrast, preconception trauma-related epigenetic changes in sperm cells (i.e. in the paternal line) that contribute to trauma effects in children have been demonstrated. This is in part because they are easier to study, with the potentially confounding effects of in utero impacts and parenting not as apparent (Bohacek & Mansuy 2015; Rando 2012). Among the epigenetic mechanisms that have been implicated in paternal transmission of stress effects via sperm are DNA methylation, oxidative damage to sperm DNA and histone modifications (Schagdarsurengin & Steger 2016).

As with the transmission of preconception trauma down the maternal line, compelling data demonstrating heritable epigenetic alterations to sperm come from animal experiments (Reik, Dean & Walter 2001). According to Yehuda & Lehrner (2018), however, there are no known studies that have directly examined transgenerational effects mediated through sperm in humans. What there are, though, are observational studies strongly suggesting that preconception exposure of fathers to famine, obesity, smoking, alcohol consumption, toxins and stress are associated with biological effects and behaviours in their offspring, with the Y chromosome implicated as the mediator, and with potential implications for the high rates of depression and suicide reported among Indigenous males (Fullston et al. 2013).

Yehuda and Lehrner (2018:251) describe the situation in 2018 as follows:

> In the absence of studies examining the effects of trauma through the male germ line in humans, the above findings demonstrate that a wide range of environmental exposures, not only exposure to extreme trauma, can have biological and behavioral effects that persist in one or more generations. Future studies examining behavioral and epigenetic effects in sperm in relation to pre- and post-pubertal trauma exposure in males and their offspring will greatly shed light on this topic.

It is also noteworthy that epigenetic healing, including to HPA axis functioning, may only require environmental–experiential changes to occur. For example, a 2002 study demonstrated that the persistence of the epigenetic changes associated with a PTE (in this case, separation of newborn rat 'pups' from their mothers for several minutes) corelated to the effects of maternal licking and grooming when the pup and mothers were re-associated – in other words, 'flight or fight' being epigenetically 'switched off' epigenetically at the rat equivalent to gene NR3C1 (see above). In other words, the experience of 'love and affection' could reverse offspring equivalent NR3C1 DNA methylation (Yehuda & Lehrner 2018).

Tuberculosis control across the Torres Strait Protected Zone

Tuberculosis (TB) is caused by the mycobacterium tuberculosis bacterium that most often affect the lungs. TB is spread from person to person through the air. About one-quarter of the world's population is estimated to have latent TB, which means people have been infected by TB bacteria but are not symptomatic and cannot transmit the disease. But people so infected have a 5%–15% per cent lifetime risk of falling ill with TB. And people with compromised immune systems, such as people living with HIV, malnutrition or diabetes, or people who use tobacco, have a higher risk of falling ill and dying. In 2018, an estimated 10 million people fell ill with TB worldwide, and 1.5 million people died from TB in 2018 (including 251,000 people with HIV). Worldwide, TB is one of the top 10 causes of death and the leading cause from a single infectious agent. But most strains of tuberculosis are curable and preventable (WHO 2020), barring some drug-resistant strains.

Australia, along with many other countries, has committed to a program of TB elimination. A particular challenge in doing so is cross-border spread from Papua New Guinea through and across the Torres Strait Islands. In that regard, it is telling that Queensland currently reports around 4.0 cases/100,000 population compared to rates approaching 3000 cases/100,000 population in some areas of Papua New Guinea (Bainomugisa et al. 2019). The Torres Strait Protected Zone (TSPZ) is an area where cross-border movement without passports or visas is permitted for purposes of traditional customs and economic activities. This area contains a number of Papua New Guinea villages and 14 Torres Strait Island communities that are part of Queensland.

The TSPZ provides a potential route of TB entry into the Torres Strait, northern Queensland and Australia. Bainomugisa et al. (2019) used whole-genome sequencing to identify risk factors of transmission among and from Papua New Guinea residents of the TSPZ, and who had tuberculosis diagnoses during 2010–2015. Of 117 samples from those infected, 100 were genotyped. Of these, 79 were of the so-called Beijing sublineage 2.2.1.1, including four multidrug-resistant TB versions. Given the risk involved in transmission of the drug resistant strain in particular, the researchers recommended including whole genome sequencing in TB surveillance within the TSPZ (Bainomugisa et al. 2019).

Managing diseases with dog vectors

Cryptosporidiosis is a diarrhoeal disease caused by the Cryptosporidium parasite, which infects the intestine. Cryptosporidium infections have been reported in humans and in a variety of farm, pet and native animals. The majority of human disease is caused by two varieties of the parasite (IbA10G2 and IdA15G1) that are distinguishable by genomic testing.

In Australia, parasite outbreaks occur every few years and there is a national surveillance programme. Ng-Hublin et al. (2018) reviewed epidemiological and genomic data from 2003, 2007 and 2011 outbreaks in Western Australia. All three outbreaks were predominantly in the Perth

metropolitan area and, overall, children aged zero to four years and non-Aboriginal people comprised the majority of cases. However, when Aboriginal people were considered in isolation, in the 2003 and 2007 outbreaks, a higher proportion of cases was from remote areas by the IdA15G1 subtype, potentially requiring different responses in relation to stopping potential spread by animals, something that may be particularly important in relation to 'camp dogs'. The researchers recommended that genotyping data should routinely be incorporated into the cryptosporidiosis national surveillance programme (Ng-Hublin et al. 2018).

Trachoma

Chlamydia trachomatis causes both sexually transmitted urino-genital (UGT) infections and the blinding disease trachoma, which is now reported in Australia almost exclusively among Aboriginal peoples (Andersson et al. 2016) and which is a major focus of research efforts and strategic responses such as the Vision 2020 initiative.

In relation to this, Andersson et al. (2016) sequenced the genome of chlamydia trachomatis from Aboriginal people with trachoma and compared it to genomes from other strains. Unique to Australian strains, the researchers modelled that two distinct lineages of chlamydia trachomatis had arisen from an ancestral strain: (1) a trachoma strain with alleles that made it particularly 'ocular' adapted and (2) a uro-genital strain. These two strains had since admixtured in various ways but in such a way that when environmental/social conditions favour the emergence of trachoma, the strains that have acquired the most 'ocular' alleles were at a selective advantage.

The study has public health implications. It supports reducing the burden of chlamydia trachomatis infections – ocular and UGT – in disadvantaged communities where trachoma re-emergence is possible, as well as continuing to address the social conditions that maintain trachoma endemically in these areas (Andersson et al. 2016).

Glossary

Research

Genomics studies a person's genes (the genome), the genetic interactions in that person and with the person's environment. This branch of biotechnology applies techniques of genetics and molecular biology to the genetic mapping and sequencing of genes, the results of which are organised in databases and applied to biology and medicine.

Metagenomics is the study of genetic material recovered directly from environmental samples, especially community of microorganisms impacting human health.

An **Indigenous kincentric ecological research agenda** is a program of research based on an Indigenous worldview and the connectiveness of Indigenous peoples' culture, health and wellbeing with their ecosystems, ancestry and origins.

A **cardiometabolic healing research agenda** seeks to improve the heart health of Indigenous community members by minimising heart diseases such as cardiovascular disease and diabetes.

Genetic material

DNA (deoxyribonucleic acid) is a molecule that encodes the genetic blueprint of an organism, necessary for building and maintaining the organism.

A **chromosome** is a DNA molecule found in a cell nucleus and containing genetic material.

A **genome** is the sum of the genetic material in all the chromosomes in each cell of a multicellular organism.

A part of DNA or **loci** associated with a specific trait (i.e. red hair) is referred to as a **gene.**

A **genotype** is expressed when the information encoded in the genes' DNA is used, including by RNA, to make protein and other molecules by a process called **transcription**. The expression of the genotype contributes to an individual's observable traits, called the **phenotype**.

Variants and genetic markers

The vast bulk of material in the human genome is all but identical in all human populations, as would be expected within one species – *homo sapiens*. However, variance (also called a mutation or morphism) at specific sites or **loci** along the strands of DNA is common enough and is used in genomics as **genetic markers**.

Single nucleotide polymorphisms (SNPs) are the simplest and most commonly used genetic markers in research.

SNPs are common – scientists have found hundreds of millions of SNPs among individuals – and most appear to have no effect on **genotype** or **phenotype**. But when SNPs occur within a gene or in a regulatory region near a gene, they may affect the gene's function.

In general, the closer together two SNPs on a DNA strand are, the more likely they are to be inherited together. This enables **fixation indexes** to be calculated combining data on SNP variations shared by populations and the likelihood that this variation is by genetic descent. Further, by statistically associating SNPs with health conditions, their role as a health determinant can be assessed.

Short tandem repeats (STRs) are a different kind of variant to SNPs and are also used as genetic markers. They occur at thousands of **loci** within any organism's genome. STRs also have a higher mutation rate than other areas of DNA. Because of their propensity to mutate, STRs mark points at which to compare genomes for any difference. By statistically associating STRs with health conditions, their role as a genetic determinant of health can be assessed. STRs are also used to compile genetic fingerprints of individuals and are used in forensics.

Reference datasets

A **reference genome** is a database proposed as a representative example of the set of genes in one notional individual – even though they are actually a combined sequence from a number of individuals. The main purpose of reference genomes is to be a location guide for genetic features broadly shared by humanity. But at finer levels, the differences between populations groups can mean they are inherently unrepresentative. Work is currently underway to establish an Indigenous reference genome.

Reference datasets are collections of genome sequences that researchers are able to access, making comparing sequences considerably easier and cheaper. Most datasets focus on European populations but a number of attempts to provide more balance are noteworthy. The **1000 Genomes Project** is, to date, the largest whole-genome sequencing survey undertaken to analyse multiple individuals from 26 populations of European, East Asian, South Asian, American and sub-Saharan African ancestry. However, it has focused on demographically large populations, with a relatively low degree of coverage in parts. Information about this project is available from: https://www.sciencedirect.com/topics/neuroscience/1000-genomes-project.

The **Simons Genome Diversity Project** reference database is a set of 300 genomes from 142 diverse populations (Simons Foundation 2017). The project data set is important for a number of reasons, not least because it provides a complementary reference set for genomes generated from United States (broadly European) populations, which tend to overlook Indigenous populations. For the Australasian population group, the project includes three Aboriginal, 16 Papuan and two Bougainvillean genomes.

The **International HapMap Project** developed a haplotype map to describe the common patterns of human genetic variation within population groups. (An **allele** is a version of one of at least two known mutations (include SNPs and STRs) at the same place or **loci** on a chromosome – a set of alleles that tends to be conserved and inherited intact from one parent to child is referred to as a **haplotype**.) HapMap is used to find genetic variants affecting health, disease and responses to drugs and environmental factors. The information produced by the project is freely available for research. It comprises two phases: the complete data obtained in Phase I were published in October 2005. The analysis of the Phase II dataset was published in October 2007. The Phase III dataset was released in spring 2009, and is available from: https://www.genome.gov/11511175/about-the-international-hapmap-project-fact-sheet.

Sequencing technologies

Genome-wide association studies (GWAS) represent a great advance in genomics – rather than focusing on particular areas of DNA, a GWAS involves sequencing the entire genome, identifying cohort-wide or other genetic variants and then, by statistical analysis, associating them (or not) with **genotypes** and **phenotypes**. GWASs generally focus on identifying SNPs.

In GWAS, **genome-wide significance** is a statistical threshold that indicates a reported association between a SNP and a genotype or phenotype is significant.

Coverage refers to the number of times a sequencing machine sequences a genome. Sequencing only once carries risks because misreads can and do occur. With about six billion 'letters' to read per genome, even a small error factor can have significant consequences – e.g. a notional 1 per cent error estimate means that 60 million misreads may have occurred per genome sequenced. So, in short, the higher the coverage, the more sequences have been undertaken, and the better the data quality.

GWAS rely on vast computer power and particular applications and as such remain relatively expensive. A less expensive alternative is **exome sequencing**, a technique for sequencing **exons** – the protein-coding regions of a genome (known as the exome).

Epigenetics

There is a 'missing heritability' challenge in genetics because genetic variations in isolation do not account for a wide range of phenotype heritability. In fact, it has long been surmised that processes other than genes in isolation play a significant, if not determinative, role in whether otherwise inherited genes express themselves as phenotype. Candidates include:

- significant 'background' contributions made by the whole genome apart from specific genes (and hence the importance of GWAS in understanding heritability)
- epigenetics
- gene-environment interaction (Douglas, Bielawski & Langille 2020).

The best understood epigenetic process is DNA methylation, which turns genes 'off' and blocks the gene's capability to make enzymes or proteins. What is blocked by methylation can also be unblocked by other chemicals – thereby creating the ability to turn a gene 'on or off' by these mechanisms.

Gene-by-environment interaction

Sometimes, sensitivity to environmental risk factors for a disease are inherited rather than the disease itself being inherited. A phenotype then relies on gene–environment interaction (or genotype–environment interaction) to be expressed. Environmental variation can be physical, chemical, biological, behavioural patterns or life events. As an example, identical amounts of sunlight exposure can have a stronger influence on skin cancer risk in fair-skinned humans than in individuals with darker skin. The consensus opinion is that neither genetic differences nor environmental differences are solely responsible for producing phenotypic variation, and that virtually all traits are influenced by both genetic and environmental differences.

Abbreviations (selected)

ARF	acute rheumatic fever
ACCHS	Aboriginal Community Controlled Health Service
CSEWB	cultural, social and emotional wellbeing
DNA	deoxyribonucleic acid
GWAS	genome-wide association studies
HPA	hypothalamic-pituitary-adrenal
HRG	human reference genome
MRFF	Medical Research Futures Fund
NCIG	National Centre for Indigenous Genomics
NHMRC	National Health and Medical Research Council
PAR	participatory action research
PTE	potentially traumatic event
PTSD	post-traumatic stress disorder
RHD	rheumatic heart disease

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