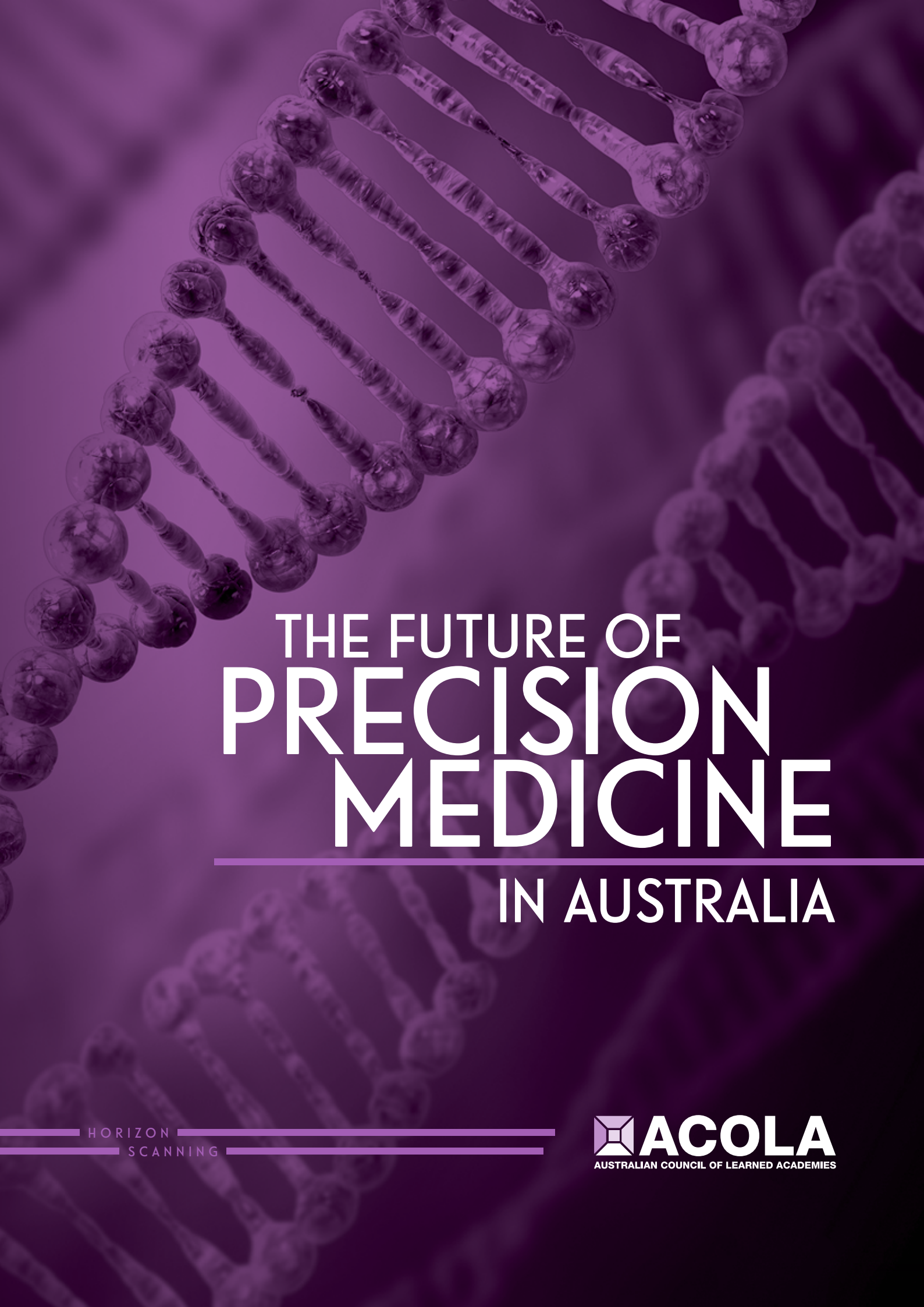

THE FUTURE OF PRECISION MEDICINE IN AUSTRALIA

HORIZON SCANNING

ACOLA
AUSTRALIAN COUNCIL OF LEARNED ACADEMIES

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CONTENTS

FIGURES

TABLES

BOXES

PROJECT AIMS

Aims of the project:

- To examine the transformative role that precision medicine may play in the Australian health care system;
- To examine the future opportunities and challenges precision medicine may face;
- To consider the development and application of precision medicine and the use of 'omics' technologies in the context of their social, cultural, economic, legal and regulatory implications; and
- To examine the role of 'big data' within precision medicine, as it relates to data integrity and standards, and to explore issues surrounding security and privacy.

EXECUTIVE SUMMARY

Recent technological advances allow the determination of a wide range of data about an individual's genetic and biochemical make-up, as formed by their genes, environment and lifestyle. These advances can and do affect the clinical management of a person's health and disease. The ability to analyse disease in terms of an individual's make-up, when compared with and studied alongside aggregated clinical and laboratory data from healthy and diseased populations, is termed 'precision' or 'personalised' medicine. Although medicine has always had personal and predictive aspects, precision medicine allows health and disease to be viewed at an increasingly fine-grained resolution, attuned to the complexities of both the biology of each individual and variation within the population.

Precision medicine has a broad remit, encompassing genomics and other omics (metabolomics, microbiomics, proteomics and transcriptomics), epigenetics (associated with gene-environment interaction), gene editing technologies (such as CRISPR) and the development of targeted therapies specific to an individual's disease profile. Advances in precision medicine, and the technologies that support it, are poised to reshape health care, invigorate biotechnology and ripple out to fields such as agriculture, environmental science, defence and beyond.

Three developments have catalysed advances in precision medicine:

- The first is the completion of the sequence of the human genome and accompanying developments in biotechnology that have made a whole genome sequence of a person, animal, plant or microorganism attainable at low cost in a matter of days.
- The second is the availability of new strategies and medicines that allow diseases to be treated, predicted or prevented more effectively. Treatment

may in the future target specific disease-causing genetic mutations or be selected according to the patient's genetic make-up or, for infections, the specific virus or bacterium affecting an individual. Such strategies are important not only in human medicine but also in veterinary practice and agriculture, and even trauma prevention in contexts such as defence and sport. The approaches are shared with many new initiatives in biotechnology and underpin the wealth creation of new and innovative small and medium-sized enterprises.

- The third is the increasing ability to collect and codify clinical and laboratory data in aggregate through the use of big data tools – including supercomputing capacity, cloud storage and automated biometric, diagnostic and therapeutic data collection – allowing association of genomic and related information with biomarkers, diagnosis and clinical outcome.

This report sets out the status of precision medicine, where it is likely to go over the next five to ten years, opportunities on which to capitalise, challenges for which to prepare and the considerable potential of precision medicine to enhance medical practice and transform other industries, both in Australia and internationally. It broadly discusses the potential economic implications of new precision medicine technologies for the health care system and explores potential future implications for biotechnology and agriculture. It also highlights ethical considerations relating to precision medicine, the importance of community engagement and the health economics of implementation.

Advances in genomics and related laboratory tests have already brought great opportunities for improving health for individuals. The most obvious focus has been in well-supported clinical areas, including cancer, and 'rare' single-gene disorders which are a significant cause of intellectual and physical disability in children. However, in the long term, the opportunities to improve health outcomes for complex disorders, such as diabetes and cardiovascular disease, are equally exciting and will optimise individual patient management through aggregation of data across populations. Precision medicine will transform health care from its focus on diagnosis and optimising treatment to optimising disease prevention and early intervention. Aspects of our health system will move from crisis management to health management.

Australia has a strong tradition of medical research in fields such as immunology, vaccine development, bionics and imaging. The country also has an excellent health system, which is regarded as one of the world's best, and has already embraced some of the technologies that underlie precision medicine. Australia is using these technologies to inform national clinical and research programs on the implementation of genomic medicine in cancer therapy and rare genetic diseases, growing capacity in genomic sequencing and analysis, and research excellence in the study of disease mechanism (functional genomics) and therapeutic development. These attributes will allow rapid assimilation of efforts to use genomics (and other omics) to develop personalised medicine for all Australians. The implementation of a national program of precision medicine will also provide a necessary incentive to expand and improve tertiary education and training opportunities in human genomics and related fields, for which Australia could become an international education centre in our region and more widely.

Science and medicine are advancing at a rate that demands agile regulatory conditions that do not inhibit implementation, and an adaptable, widely skilled workforce capable of working across disciplines. Worldwide advances in the application of omics to health care, and more broadly to agriculture and other sectors, are occurring rapidly. It will be important to put mechanisms in place to ensure that Australia can participate in international cooperative efforts and lead in defined areas of research and clinical practice.

All parties will need to be mindful of the social and ethical nuances of research in this area. Ethical questions range from wide-ranging social justice issues regarding access and equity to specific complexities in terms of consent, safety and the support

structures and clinical resources available to patients. Although discussions about ethics and genomics have a long history, focusing first on eugenics and more recently on the Human Genome Project, the issues are not easily resolved, as they involve judgements on the balance between health gains and possible loss of privacy and increase in cost, warranting sensitive, ongoing attention. It is worth noting that investment in the Human Genome Project included a commitment of the project's annual research budget (initially three per cent, increasing to five per cent in later years) to study the ethical, legal and social implications of human genome research. It stands that any Australian precision medicine initiative should allocate specific resources to studies on ethics, law, education and community issues.

A recent survey in the United States (Scheufele et al. 2017) showed overwhelming support for clinical use of precision medicine and gene editing, but only in the context of full community consultation and involvement. It will only be possible to implement the benefits of precision medicine if the community understands and supports applications of the new genomics and has a voice in the progression of precision medicine, especially the use of DNA editing of human genes. Studies on ethics, and a commitment to social dialogue, are of the greatest importance, as is proper cost-benefit analysis in both the short and long term. All these areas represent opportunities for return on investment: the more effort and resources put into them, the more educated our society, sophisticated our research and robust our health care system.

Precision medicine research requires more diverse disciplinary approaches than traditional medical research. Clinicians will have to work with research scientists, engineers and data experts, and the ability to scale up will be crucial. Australia has historically maintained a separation between biomedical and agricultural research, medical and farming practice, ethics and education, mathematics and biology, and investment in new technology and innovation. These silos must not inhibit Australia's ability to take full advantage of this technological shift; to build our scientific workforce; to encourage science, technology, engineering, mathematics and medicine (STEMM) education; to holistically address the ethical, regulatory and legal issues presented by new technologies; and to participate internationally in cooperative projects. There is an appetite within the research and medical community for collaboration, translation and clarity of purpose regarding precision medicine. Precision medicine will provide new opportunities for experts in traditionally non-medical fields, such as mathematics, computer science, ethics and law, to participate in determining both priorities and outcomes, and it will help to provide a holistic approach that encourages people to respond to health information, turning it into health action.

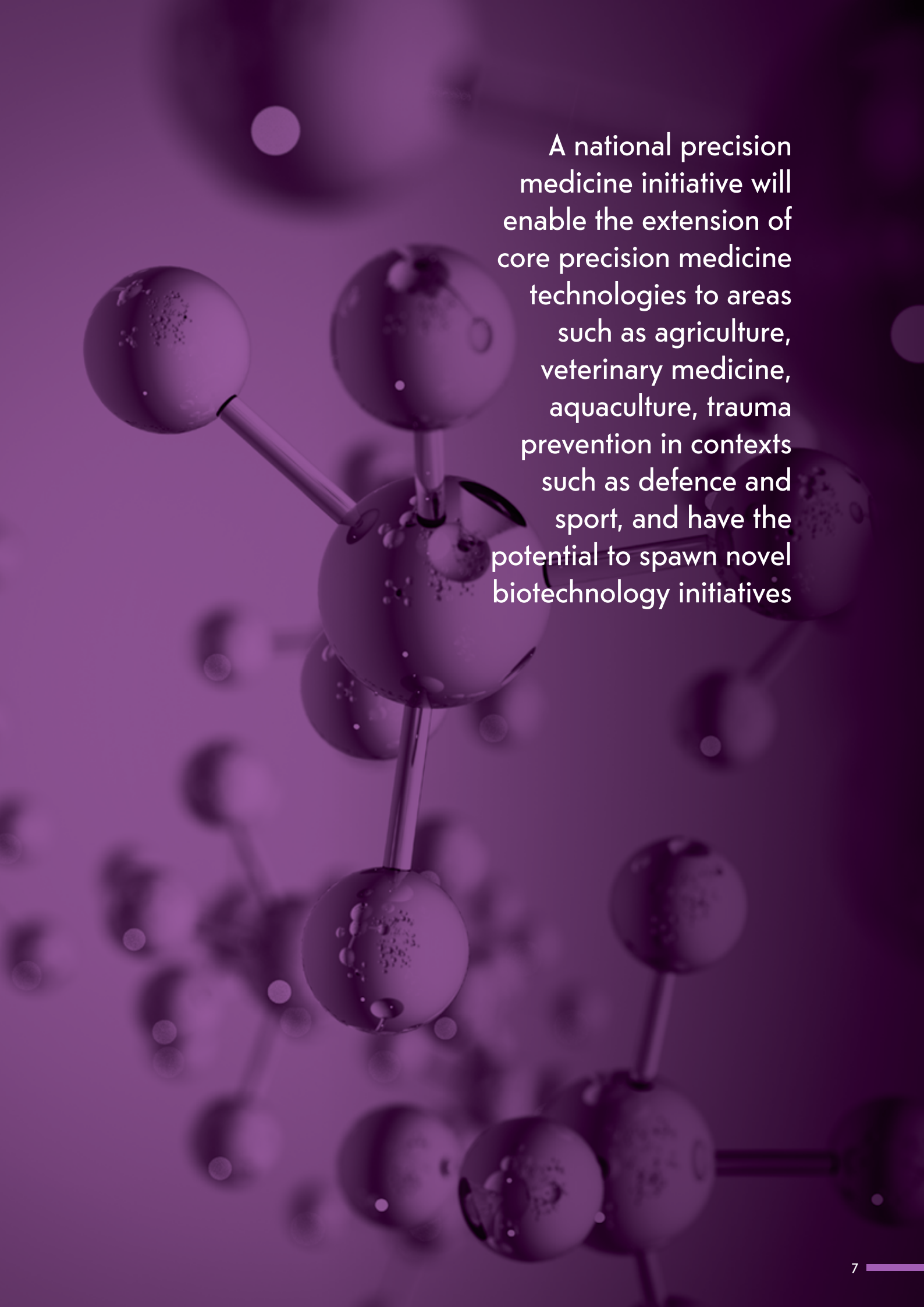
Building a broad capacity is essential: wide-scale omics information aggregated into big data can inform basic research, which, in turn, will lead to improved understanding of fundamental disease mechanisms and interventions that could lead to improvements in prevention through public health. Storage and analysis of big data

raise both logistical and ethical questions. The community will only have confidence in the use of these data (which, in the end, are personal data relating to individuals) if privacy can be guaranteed. New techniques developed to handle big data show promise to achieve this outcome.

Experience internationally suggests that improved health outcomes are modest in the short term, with medical advances gradually emerging from new insights into basic biology. While there will be costs in establishing the infrastructure required for genomics and related omics, these may eventually be offset by improved health in the community, new employment opportunities and growth in the innovation sector. Discussion of precision medicine is not only for doctors and geneticists, but requires a broad approach to STEMM and Humanities, Arts and Social Sciences (HASS) education to ensure a health-literate community.

Questions about how well equipped Australia is to implement precision medicine warrant further attention. Will Australia be able to use precision medicine to bring targeted health solutions to disadvantaged groups, such as Indigenous Australians, and those living in rural and regional locations? Do we have the infrastructure, including data capabilities? Can our existing health system use precision medicine to diagnose and treat ill people in an equitable and timely fashion? Can we foster good health and disease prevention in the areas that particularly burden the Australian population, such as type 2 diabetes and mental health? It is important that the gap between hospital medicine and primary care, which is also a gap between federal and state responsibilities, does not hinder the implementation of omic approaches to precision medicine at a community or personal level. The challenge is to ensure Australia's health system can adapt to take advantage of the potential to apply precision medicine as a tool for prevention where it is cost-effective, and to adopt new technologies when the opportunity to benefit from them is greatest.

Appropriate policy will assist in harnessing precision medicine, gene editing and related technologies to benefit patients and the community. The significance of any national precision medicine initiative, however, goes far beyond the health system. The application of precision medicine will be transformative and will benefit many industries and offer new opportunities for skilled graduate employment. A national precision medicine initiative will enable the extension of core precision medicine technologies to areas such as agriculture, veterinary medicine, aquaculture, trauma prevention in contexts such as defence and sport, and have the potential to spawn novel biotechnology initiatives. As our health and agriculture sectors are advanced by international standards, and because we have an excellent education system, Australia is well positioned to take advantage of these opportunities. The long-term implications for us are substantial, and there are important ethical, social and economic considerations. However, with careful planning and evaluation, precision medicine technologies and application could provide exciting technological, scientific and medical opportunities over the coming decade and beyond.



A national precision medicine initiative will enable the extension of core precision medicine technologies to areas such as agriculture, veterinary medicine, aquaculture, trauma prevention in contexts such as defence and sport, and have the potential to spawn novel biotechnology initiatives

KEY FINDINGS

1. **Australia has a world-class health system, with a strong tradition in public health research and clinical research. The country has significant laboratory and research capability in genomics and functional genomics as basic sciences and as components of laboratory medicine, and in the application of genomics data at the clinical level. Our expertise in this field can be leveraged to establish precision medicine not only within our region but more widely.**

- An enhanced understanding and application of genomics is already allowing for better classification and treatment of certain cancers, rare diseases and genetic and multifactorial conditions.
- Australia is well connected internationally and is recognised for the quality of its clinical research and clinical data.
- We have leadership in global genomics consortia and are well placed to promote the coordinated sharing of data, resources and expertise to ensure rapid progress and avoid duplicate investment.
- Australia needs to develop an overall strategic vision on how precision medicine and the necessary underlying laboratory technologies will integrate with the whole health system to give maximum health benefit to the community. By approaching genomics at a national level, we can offer a focal point of contact to leverage significant additional industry and clinical trial investment in Australia. The National Health Genomics Policy Framework provides a starting point for integration of genomics into the health system.

2. **There is a need to address the social, cultural, ethical, legal and economic issues in parallel with investment in and commitment to precision medicine technologies, and before any attempt to scale these up. Australia has existing capacity in these areas, but further investment will be needed across the humanities, arts and social sciences (HASS) to ensure that the challenges precision medicine will bring, can be met appropriately.**

- Insofar as precision medicine has the potential to improve people's health and lives, it also has the potential to facilitate discrimination, exposure to risk and inequities of access. Ensuring it does not will require careful ethical thought and planning. The societal impacts of precision medicine are, in short, also an ethical matter.
- Different ethical issues apply at different stages of the precision medicine development process. There are unique ethical considerations associated with research and development, with clinical application, and with the processes of regulating and funding precision medicine.
- The ethical values that underpin precision medicine are not universal; they should be agreed upon and enacted in accordance with local cultural and social values. This might manifest in, for example, new models of consent.
- Regulations of relevance to precision medicine are currently being reviewed. These will need to be agile, in keeping with the rapid developments in the field, but must also unequivocally safeguard patients' wellbeing and interests.

3. **Genomics data have the potential to underpin precision medicine. Although genomics will initially dominate the field, metabolomics, transcriptomics, proteomics and other omics approaches will also make significant contributions. There is a need for coordination across omic platforms to ensure an integrated impact of precision medicine. This will require harmonisation at national, state and institutional levels.**

- Precision medicine stands to benefit from the integration of omics beyond the genome (e.g. epigenomics, transcriptomics, metabolomics,

proteomics). In combination, these various omic approaches will provide clearer and more timely information on causes and consequences of inherited and multifactorial diseases, as well as improving diagnostic, disease prevention and treatment pathways.

- Development of advanced treatments based on omics data or gene editing techniques is expected to play a role in the understanding, prevention and treatment of many diseases.
- Technical advances for genomic sequencing, study of gene expression and epigenetic analysis will be easier to access and decrease in cost. Advances in data management should aid accurate interpretation; the data will need to be monitored through quality control and quality assurance programs, as for other areas of pathology testing.
- Precision medicine technologies are in a state of rapid change, and early commitment to a single technological approach should be avoided.

4. **Australia has an opportunity to lead in precision medicine – in terms of integration into clinical practice; evaluation of cost-effectiveness; and data sharing, security and storage – particularly in this region; but the opportunity is perishable. The ability to connect, collaborate and share data and information within Australia and internationally will be important in progressing precision medicine. The importance of aggregating genomic and related data with health care outcomes cannot be overstated; this promises to be one of the most significant outcomes for precision medicine.**

- Multidisciplinary collaboration between researchers, clinicians and other professionals from both the STEMM and HASS disciplines to strengthen and produce the knowledge to allow for diagnosis will be important in optimising patient welfare and provide the information required for clinicians to make the most appropriate treatment plan for that individual. This involves greater emphasis on training for a broad range of skills (including bioinformatics, mathematics, computing and engineering) than has been the case.
- Developments in our ability to collect, analyse and safely and responsibly share data between individuals and organisations will support precision medicine by granting health care practitioners and policy makers access to broader, interoperable data sets, provided that attention is given to ensuring individual privacy.
- Implementing accepted shared data integrity standards will speed up data sharing and linkage, which may in turn catalyse the development of new therapies, technologies and predictive systems.

5. **Rapid advances in precision medicine technologies may outstrip societal and regulatory responses. Regulatory agencies will need to understand precision medicine technologies and practices and be agile to ensure that the field can advance rapidly, but with community engagement and support to ensure public trust and confidence.**

- Appropriate regulation that maximises the potential benefits while avoiding potential harms to society and excessive bureaucracy will be key for the implementation of precision medicine.

- Working closely with regulatory agencies to develop expertise and knowledge of precision medicine and to promote greater harmonisation of the regulatory approval processes across states and territories is essential.
- Precision medicine will change the relationship between patients, practitioners and the private market. Direct-to-consumer tests and use of genomics by private providers are becoming commonplace, and regulation of the tests themselves is needed, as well as accreditation of allied health practitioners to ensure quality patient support.

6. **Precision medicine will need to acknowledge the ethnic and cultural diversity of the Australian population. Genomic research in the context of Indigenous health is immature, and investments in precision medicine are unlikely to benefit Indigenous Australians and Australians of diverse ethnic backgrounds unless specific efforts are made to engage these communities.**

- Aboriginal and Torres Strait Islander peoples of Australia are among the most disadvantaged groups in Australian society. While addressing socioeconomic disparities is undoubtedly the most important step towards health equity, there is potential for genomics and precision medicine to make specific contributions to addressing Indigenous health inequalities.
- If Indigenous Australians continue to be excluded from the research that leads to advances in precision medicine, any health benefits that accrue from precision medicine may instead *widen* the gaps of health disadvantage.

7. **There are opportunities for public communication and engagement initiatives relating to precision medicine that will improve collaboration and dialogue across the health ecosystem.**

- Effective engagement with precision medicine will be inclusive, integrated throughout the technology development process and oriented towards 'opening up' big questions about the impact of precision medicine and its place in Australia's future.
- Public engagement must be broad, across all interested communities and groups.
- Engagement with science and technology developments may be *invited* through institutionalised mechanisms, but may also occur *uninvited*, particularly where a technology touches on deep-seated social concerns. Likewise, formal invited engagement can fail if it is tokenistic or overly narrow in focus.
- Inclusionary measures need to be implemented early and integrated with the design and conduct of precision medicine initiatives. Participation by citizens in community engagements concerning precision medicine and related topics would be bolstered by increased population health and science literacy, including that fostered by school science education programs.

8. **The way in which precision medicine technologies will be financed and funded will have a significant bearing on the efficiency, equity and sustainability of the health system.**

- The value proposition for omics depends on both the benefit for the treated individual and the cost borne by the taxpayer. The cost of treatment will be particularly affected by the prices charged

by drug and test manufacturers, who may seek to extract supernormal profits from the new technologies. Policy makers will need to ensure that cost-effectiveness considerations are part of any omics development.

- The rapid development of precision medicine technology will lead to lower upfront testing costs. However, this may result in increased demand for, or use of, high-cost interventions that may not yet have demonstrated benefits.
- In recognition of the opportunity for market growth and profit generation, government policy will need to consider how to regulate the market to ensure appropriate use of these technologies to ensure benefits flow to patients and the community.
- The Pharmaceutical Benefits Advisory Committee (PBAC) and the Medical Services Advisory Committee (MSAC) will need to review evaluation processes for precision medicine to make sure diagnosis and treatment can be considered jointly as part of the cost-effectiveness process.

9. There is a need for continuing professional development and training of the health workforce in precision medicine.

- Successfully implementing precision medicine will require an appropriately skilled, educated and accredited workforce across all levels of the system, from skilled laboratory workers to scientific and engineering researchers, bioinformaticians, medical and allied health professionals and genetic counsellors. Precision medicine will also need to be integrated into health professional education, from undergraduate study through to continuing education for the non-specialist health care workforce.
- Multidisciplinary professional development will support Australia to be at the forefront of rapid advancements in precision medicine research, technologies and applications. This could be provided in part through formal programs or through multidisciplinary (STEMM and HASS) teams. Australia is well positioned to be a leading regional centre for education and training of experts in precision medicine.
- A cohesive national approach to professional development and training, supported by evaluation frameworks to ensure programs are evidence-based and of high quality, is essential.

INTRODUCTION

Developments in genetics, biotechnology and medical science over the past few decades have provided a host of new tools and procedures with which to identify, interpret and act upon various aspects of human health. A prominent trend in these advances is a shift towards medical techniques that operate at increasingly fine scales of analysis. Thus, cancers are recategorised according to genetic mutation profile, and individual genomes are informing care. The task of this report is to analyse this emergent field of precision medicine across its scientific, technical, economic, regulatory, health and social impacts and to envision how it might evolve in the next ten years.

Defining precision medicine

For the purposes of this report, precision medicine is treated as **an umbrella category encompassing medical and scientific techniques that work at a molecular level to identify and address disease-related variations**. Precision medicine can thus be thought of as an approach to acquiring knowledge and organising scientific practice (Hawgood et al. 2015). Definitions of precision medicine in the scientific literature stress the *molecular* or *individual* scale of this work, and the subsequent *targeting* or *tailoring* of medical treatment, with the effect of administering treatment according to information about how a given patient is likely to respond. Because of the breadth of sources that inform this report, this definition alters slightly according to context (e.g. in relation to infectious disease, precision medicine is treated as relating to information on the genetic variability of pathogens, as opposed to patients).

Often the terms 'precision' and 'personalised' medicine are used interchangeably. However, the United States National Academies note that the latter may be misread as implying treatment crafted individually for each patient and therefore choose to employ the language of precision. This, too, is

not without misleading connotations: in colloquial use, precision suggests a degree of certainty that is unlikely to be reflected in the realities of precision medicine (Hunter 2016). These conceptual limitations noted, the report proceeds with an overview of the key issues and the state of play in precision medicine, in Australia and internationally. Although this umbrella category of precision medicine includes such diverse fields as immunotherapies and omics, alongside the more widely recognised genomics disciplines (gene sequencing, editing, epigenetics and so on), it is the latter that comprise the primary focus of this report. Genomics is central to much of precision medicine and often serves as a central platform from which other approaches extend; there is already a developing genomics capacity in Australia; and it is likely that genomic advances will continue to dominate the precision medicine domain in years to come. This is not to say that precision medicine is exclusively genomic in nature, and, as such, other aspects of precision medicine are addressed throughout this report. Epigenetics, biomarkers and other omics will be needed to monitor the effectiveness of interventions and treatments based on genomic analysis.

A measured approach to precision medicine

Advances in medical science, and particularly in genomics, tend to generate considerable hype. This manifests in a rhetoric of imminent and transformative change, which is assumed to follow closely from whatever new finding or project is in the spotlight at the time. The consequences of these 'hype and hope cycles' have been critically analysed and accused of misrepresenting the nature of scientific progress, while unfairly raising the hopes of those who stand to gain the most from medical advances – patients. There is thus an obligation to approach new or emerging fields, such as precision medicine, from a carefully balanced standpoint. The task here is to evaluate realistically, insofar as current expertise allows, what precision medicine can, cannot and may in the future offer.

In some cases, there is clear evidence of precision medicine directly and positively affecting patient health. For example, the US Food and Drug Administration (FDA) recently approved tisagenlecleucel (Kymriah; Novartis Pharmaceuticals), a chimeric antigen receptor (CAR) T cell therapy for young patients with B-cell acute lymphoblastic leukaemia who do not respond to standard treatment; 82 per cent of the patients in whom the therapy was trialled had achieved remission three months after treatment (FDA 2017). However, the value of newly developed interventions is rarely unequivocal or even clear-cut. Another example from precision medicine in cancer is the role of sequencing tumours to elucidate the molecular pathogenesis of multiple cancers. This has led to new standard-of-care therapies such as trastuzumab, a monoclonal antibody that targets breast cancers expressing human epidermal growth factor receptor type 2 (HER2). However, while this drug extends survival and promotes tumour regression, it also comes with serious side effects and, in time, cancer progression resumes (Tannock and Hickman 2016). Even tisagenlecleucel comes with potential serious side effects. Advances in precision medicine must be met with a critical eye, to both proceed in the most sensible way possible and ensure that patients and the wider public are not misled.

It follows from this cautionary note that social and ethical considerations must be at the forefront of any considerations of precision medicine in Australia. Well-established ethical principles, such as respect for autonomy, beneficence, non-maleficence and social justice, can help guide decision making about the field as it evolves. These principles serve to keep the interests of patients and the wider public at the front and centre of the precision medicine enterprise. That enterprise is a thoroughly social one, implicating people with different backgrounds, different forms of expertise and different visions for the future of health in Australia. This, in turn, will require dedicated efforts to engage Australia's diverse public, who are likely to want input into how precision medicine develops, and who will also have valuable insights into aligning this with broader social values and priorities. Coordinating and preparing a skilled and sensitive workforce will be a key task.

The structure of the report

The report begins in Chapter 1 with a brief overview of current precision medicine capacity in Australia, encompassing facilities, initiatives and research groups, as well as the recently devised National Health Genomics Policy Framework. This is followed by a summary of relevant international undertakings, which are detailed more fully in Appendix A and Appendix B.

Chapter 2 examines 12 areas where precision medicine is either already underway or is likely to make an impact in the near future. Some of these areas refer to technologies, such as genome sequencing or immunotherapies, and others refer to potential applications, including infectious diseases research and interventions for age-related conditions.

Chapter 3 considers workforce capacity in Australia and its future needs, alongside the need for public engagement; both areas will be crucial to the long-term success of precision medicine.

Chapter 4 considers many of the important ethical and social dimensions of precision medicine; how we can maximise the benefits of this field and minimise any potential harms.

Chapter 5 examines how the turn to precision medicine might affect Aboriginal and Torres Strait Islander populations, noting past harms in the name of science and contemporary opportunities for collaboration, ownership and closing the 'gap' in Indigenous health outcomes.

Chapter 6 turns to the question of how to store, share and manage data safely.

Chapter 7 details the health economics challenges and opportunities that precision medicine raises, and how these might best be navigated.

Chapter 8 considers applications of precision medicine techniques beyond health care; namely, in the context of environmental management and agriculture.

The final chapter summarises the key messages developed throughout the report, closing with a scenario of what clinical precision medicine might look like in the coming decade.

CHAPTER 1
CURRENT ACTIONS, ALLIANCES AND INITIATIVES

1.1 Australia

This chapter provides an overview of current activity and capacity in the Australian precision medicine sphere. The 2016 inception of the National Health Genomics Policy Framework provides a structured approach to making genomics work in the Australian context and builds on the existing resources and expertise around Australia, which are described in the following sections. Multiple institutions nationwide have built up genomic sequencing capacity, which they provide as a service to patients and consumers. There are also government-supported clinical genetics services operating in several key hubs and an increasing number of clinical trials focused on developing precision medicine therapeutics. The prominence of genomics in this chapter is by and large a reflection of current capacity. However, there are pockets of work in other precision medicine areas, including therapeutics development and omics, as well as research into relevant ethical and social questions. In addition, there is small-scale implementation of specific tests and practices that fall under the banner of precision medicine, such as a range of point-of-care tests, an expanding number of omic biomarkers and the rapid uptake of gene editing technologies in laboratory settings.

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Views expressed in this chapter do not necessarily reflect the views of these contributors.

1.1.1 National Health Genomics Policy Framework

In 2016, the Australian Health Ministers' Advisory Council (AHMAC) agreed that a whole-of-government National Health Genomics Policy Framework was required to "capitalise on emerging genomic knowledge by better integrating genomics into the Australian health system" (Australian Government 2017, p. 7). The framework has been developed to integrate existing support from federal, state and territory governments with leveraged support provided through research institutes and philanthropic foundations, to establish a "consistent, national and strategic view for integrating genomics into the Australian health system" (Australian Health Ministers' Advisory Council 2017, p. 2).

With feedback received through a comprehensive nationwide consultation process, the first Australian National Health Genomics Policy Framework (2018–2021) has been developed to ensure that genomics knowledge is applied in ethically, legally and socially responsible ways and that community trust is actively promoted. The proposed key strategic areas for action are: supporting a person-centred approach; building the workforce; ensuring sustainable and strategic investment; and ensuring safety and quality and responsible collection, storage, use and management of genomic data. In November 2017, the framework was considered and approved by the Council of Australian Governments (COAG) health ministers (COAG Health Council 2017).

Health ministers also agreed to the development of a three-year implementation plan, which will be used to establish priority actions, timeframes and responsibilities (COAG Health Council 2017). The implementation plan will be informed by stakeholder consultations and is expected to be submitted to COAG health ministers for approval by mid 2018.

Box 1: Genomics key terms

Every living organism is made up of two types of cells: **somatic cells** are the body cells of an organism, whereas the **germ cells** or **gametes** are the reproductive (egg or sperm) cells, which are combined during reproduction to form an embryo. Each somatic cell contains a copy of all that organism's DNA, whereas each germ cell contains half of it. The full sum of that DNA is the **genome**. Within the genome are **genes**: stretches of DNA that code for specific proteins. There are about 20,000 of these in the human genome. All of an organism's genes, when taken together, make up the **exome**. There are also stretches of DNA outside of the exome that do not code for genes; the function of these regions is not yet well understood. Genes are turned into proteins through a process called **transcription**. This involves a molecule called **RNA**, which has been copied from unravelled DNA. Amino acids attach to that RNA strand according to which bases are present, and the resulting string of amino acids folds up into a protein. Proteins perform a wide range of functions essential for life. **Mutations** arise when a piece of DNA is deleted, inserted or otherwise changed. If these changes result in the protein being miscoded, a disease might develop. Mutations in the germline (the cell population that arises from the germ cells) are transmissible to an organism's offspring, but those in the somatic cells are not.

1.1.2 Major Australian medical genomics programs and consortia

Several genomics initiatives have been proposed or are currently underway in Australia. Each of these aims to address clinical needs by sequencing DNA sourced from patients' cells as either an entire genome (genome sequencing) or from expressed gene sequences (exome sequencing). The following sections outline the large-scale genome and exome sequencing programs that are in operation.[1]

1.1.2.1 The Australian Genomics Health Alliance

The Australian Genomics Health Alliance ('Australian Genomics') was established in 2014 as a national network of clinicians, diagnostic pathologists and researchers working together to translate genomic approaches into clinical practice. Australian Genomics integrates and leverages the expertise of CSIRO, the Australian Genome Research Facility, the National Computational Infrastructure and the state government-funded genomics programs in Victoria (Melbourne Genomics Health Alliance), New South Wales (Sydney Genomics Collaborative), Australian Capital Territory (Canberra Clinical Genomics) and Queensland (Queensland Genomics Health Alliance), as well as philanthropic and competitive grant funding, to drive its activities. Australian Genomics unites 78 partner organisations, including diagnostic pathology and clinical genetics services from each Australian state and territory and numerous research and academic institutions, encompassing some

1. Note that some of the specialist sequencing services, such as those examining epigenetic tags, are not covered fully here and that only Australian laboratories offering sequencing services are detailed. As it is increasingly common for DNA samples to be sent to services in other countries for partial (e.g. 23andMe in the US) or full genomic analysis (e.g. BGI in China) sequencing, further detail of international initiatives and companies working in the space are provided in Appendix A and Appendix B.

30 clinical sites. Australian Genomics participates as a 'driver project' in the Global Alliance for Genomics and Health, using this network to develop and test data sharing tools, ethical standards and data security approaches.

Australian Genomics has four major work programs oriented around different challenges to integrating genomic medicine into Australian health care. These comprise a national diagnostic and research network; a federated data infrastructure; a focus on regulatory, economic policy and examination of the barriers to implementation; and an education, ethics and workforce focus. Two flagship clinical programs are currently piloting genomic medicine for patients with rare diseases or cancers. Each flagship project is examining the clinical utility of a variety of genomic sequencing technologies (whole genome, whole exome and RNA sequencing, and large single-nucleotide polymorphism [SNP] panels) and using the resulting data to support data sharing and inform the regulatory, ethical, economic, policy and workforce infrastructure required to integrate genomics as a key part of the Australian health system. Australian Genomics has also analysed the legal and regulatory landscape governing genomic data, as well as existing workforce education and training opportunities, and is collaborating with patient groups and the Australian Digital Health Agency to integrate genomic information into the My Health Record.

1.1.2.2 Melbourne Genomics Health Alliance

The Melbourne Genomics Health Alliance (Melbourne Genomics) was formed in 2013 and is a collaboration of ten Victorian health care and research organisations, in partnership with the Victorian government, dedicated to using genomics to benefit the individual care of Victorians. Melbourne Genomics has established a model for using genomic sequencing to support clinical diagnosis and care of patients with 11 diverse conditions, spanning immune system defects, genetic heart conditions, neurodegenerative disease and both solid and blood cancers.

With some 2,000 patients to date receiving genomic information alongside their usual care, Melbourne Genomics is building evidence for how genomics can find application in health care and, at the same time, building genomic knowledge and experience among health care professionals and establishing systems to support genomics in practice. The approach is focused on long-term sustainability and establishing a flexible approach that can adapt to advances in test methodologies.

1.1.2.3 Sydney Genomics Collaborative

The Sydney Genomics Collaborative at the Garvan Institute of Medical Research, in partnership with the NSW government, was established in 2014 with the aim of boosting genomics research into inherited diseases and disorders with a genetic component (including cancers) across New South Wales (Sydney Genomics Collaborative 2017). The Collaborative comprises several programs and initiatives:

- The Medical Genome Reference Bank, which sequences healthy elderly ('wellderly') individuals to establish a broad-spectrum control for analysing disease-based cohorts;
- The NSW Genomics Collaborative Grants program, to undertake genome sequencing of patients with diverse medical conditions, such as melanoma, heart disease and schizophrenia, to improve understanding of the genetic causes of disease; and

- The Genomic Cancer Medicine Program, which undertakes research dedicated to applying genomics to the understanding, early detection, prevention and management of cancer.

Extending a broad research base, the Garvan Institute interlinks its program activities with other institutions and initiatives, including:

- The NSW State Government collaboration with the US National Cancer Institute on the 'Cancer Moonshot' initiative; and
- The Lions Kids Cancer Genome Project collaborative partnership, to unify Australia's national personalised medicine program in childhood cancer.

1.1.2.4 Queensland Genomics Health Alliance

The Queensland Genomics Health Alliance was established in 2016 with funding from the Queensland Government. It unites clinical and scientific skills and experience from across the state to accelerate sharing of genomics knowledge and support its clinical application to benefit the community.

Four Clinical Demonstration Projects have commenced and are comparing the impacts of genomics-based diagnostics and treatment for lung cancer, melanoma, mature onset diabetes in the young and infectious disease. These projects are underpinned by five capability building workstreams in workforce development; evaluation of clinical genomics; genomic testing innovation; genomic information management; and ethical, legal and social implications.

1.1.3 CSIRO initiatives

CSIRO's Australian e-Health Research Centre (AEHRC) runs a health and biomedical informatics program that includes high-throughput genomic data analysis and computational genome engineering, as well as high performance computer systems. The AEHRC health informatics research includes using artificial intelligence and machine learning to support the integration of genomic information into health care systems. Key to this is ensuring interoperability with existing patient management systems. AEHRC is part of CSIRO's Health and Biosecurity business unit, which includes research into epigenetics, nutritional genomics and wellbeing.

CSIRO's Data61 is a major Australian data science research program, with research spanning platforms for open data, privacy preserving analytics, cybersecurity and confidential computing, to machine learning and artificial intelligence.

1.1.4 Existing genome sequencing resources

1.1.4.1 Gene sequencing

The **Australian Genome Research Facility** was established in 1997 by the federal government, together with the University of Queensland and the Walter and Eliza Hall Institute. Its operations are managed across five Australian states, with much of its DNA sequencing infrastructure concentrated in Melbourne. The Melbourne laboratories, located within the Victorian Comprehensive Cancer Centre, contain sequencers capable of completing about 15,000 human genomes or 140,000 clinical-grade exomes annually. These services are accredited by the National Association of Testing Authorities, Australia (NATA) to ISO/IEC 17025:2005 (Biological Testing) standard and are currently being revised to ISO/IEC 15189:2012 (Clinical Testing) standard. Exome and RNA sequencing account for most of the facility's output. The facility also provides bioinformatics support

to its clients. It has a staff complement of 11 FTE, and its funding comes from both fee-for-service arrangements and public funding, primarily the National Collaborative Research Infrastructure Strategy (NCRIS) through Bioplatforms Australia.

The **Kinghorn Centre for Clinical Genomics** was established in 2012 at the Garvan Institute of Medical Research. The primary focus of the sequencing work performed at the centre is whole genome sequencing; at maximum capacity, it is capable of completing the equivalent of 25,800 human genomes annually. Its services include clinical genome sequencing and analysis, with NATA ISO/IEC 15189 accreditation, delivered through Garvan's wholly owned subsidiary Genome.One. Genome.One has a staff complement of 55 FTE involved in sequence production, genome analysis and software development.

A smaller facility, the **Ramaciotti Centre for Genomics** based at the University of New South Wales, was established in 2000 by a consortium of universities. In 2016–17, the Ramaciotti Centre sequenced about 1,500 exomes. It has a current staff complement of 15 FTE. About ten per cent of the bases sequenced over the past year were human, as opposed to other species, and comprised transcriptome or RNA sequencing.

1.1.4.2 State-based Department of Health-funded diagnostic genomic services

State-based (government-funded) diagnostic laboratories are NATA-accredited for genomic panels. Those in Victoria and South Australia also offer accredited clinical whole exome sequencing. In addition, the state-based diagnostic laboratories provide a suite of population screening tests that are gradually incorporating genomic technologies, including reproductive carrier screening for conditions such as cystic fibrosis and thalassaemia, non-invasive prenatal testing, and newborn screening.

Box 2: Sequencing key terms

Gene sequencing is the process of 'reading' the order of base pairs that make up a gene or genome. Whereas sequencing previously focused on the exome (the protein-coding parts of the genome), more recent methods permit **whole genome sequencing**.
It is now also possible to sequence the **transcriptome**, which provides a record of which genes are being expressed in a certain cell type at a certain time; this is important because not all genes are 'on' all the time, and their expression can influence disease. **Gene panels** allow targeted sequencing of specific genes; perhaps those associated with a disease of interest. More information on gene sequencing can be found in Chapter 2.

Box 3: NATA accreditation

NATA accreditation provides a means of determining, formally recognising and promoting the competence of facilities to perform specific types of testing, inspection, calibration and related activities. NATA accreditation formally recognises that a facility has met standards and competences of international standard (ISO/IEC).

ISO/IEC 17025:2005 specifies the general requirements for the competence to carry out tests and calibrations, including sampling.

ISO/IEC 15189:2012 specifies requirements for quality and competence in medical laboratories.

www.nata.com.au
www.iso.org

Victorian Clinical Genetics Services (VCGS) provides clinical, diagnostic and genomics services for Victoria, Tasmania and the Northern Territory, and is the national provider for some services. VCGS is a not-for-profit, wholly owned subsidiary of the Murdoch Children's Research Institute. VCGS currently screens about 190,000 specimens each year, including 140,000 newborn and pregnancy samples. VCGS is NATA-accredited to ISO/IEC 15189 for clinical exome sequencing. VCGS provides a fully integrated 'end-to-end' clinical genomics service, with a focus on the interpretation of genomic testing (panel, exome or whole genome) for patients in a clinical setting. It employs a staff of 135 FTE, including clinical geneticists, genetic counsellors, bioinformaticians and laboratory scientists.

SA Pathology in South Australia has capacity to sequence the equivalent of 3,600 exomes per year. The service screens a variety of samples for research and runs whole exome, RNA and microbial whole genome sequencing. SA Pathology offers NATA-accredited exome and panel screening and in 2016 delivered 660 clinical exomes, with the capacity to perform about 1,000.

In Western Australia, **PathWest** undertakes 2,500 clinically accredited targeted genome panels and 390 clinical exomes per year. The service employs 16 FTE staff.

The Children's Hospital at Westmead, in New South Wales, does not offer a whole genome or exome clinical sequencing service but does provide accredited targeted panel sequencing (661 panels per year), with staffing of 10.4 FTE.

1.1.4.3 Other facilities

BGI (previously known as the Beijing Genomics Institute), a Chinese company based in Shenzhen, has established large-scale DNA sequencing infrastructure at the QIMR Berghofer Medical Research Institute in Queensland, and has signed collaborative agreements with several Australian research institutions.

1.1.5 Existing clinical and professional staff resources

1.1.5.1 Clinical genetics

Clinical genetics is a growing medical specialty in Australia. Data on clinical genetics staffing are derived from the Australian Genomics Health Alliance's Professional Status Survey, conducted in conjunction with the Australasian Society of Genetic Counsellors, Australasian Association of Clinical Geneticists and Human Genetics Society of Australasia. Across Australia, there are about 450 genetic counsellors, most of whom (about 300) are in clinical practice. Genetic counselling is an allied health practice that provides patients and families with non-directive guidance on interpreting and acting on genetic information. There are about 150 clinical geneticists (those who have received specialist training in the field), almost all of whom are employed in clinical practice (Table 1).

	Genetic counsellors	Clinical geneticists
Estimated workforce (those trained in Australia and assumed to be working here)	450	150
Working clinically	67.0% (300)	97.8% (147)
Working in public system (hospital, pathology service)	68.6% (309)	82.7% (124)
Working in a publicly funded job (hospital, state, regional or federal government Department of Health)	67.3% (303)	88.9% (133)

Table 1: Overview of clinical counsellors and clinical geneticists in Australia

1.1.5.2 Pathology

The Royal College of Pathologists of Australasia (RCPA) provides a variety of services relevant to precision medicine. These include developing standards (for clinical databases of genetic variants and for interpreting sequence variation), establishing guidelines (for implementing massive parallel sequencing in laboratories) and developing educational and information-gathering resources (including surveys on genetic testing use; a website detailing the various laboratories, tests and variants included in genetic testing in Australia; and a National Molecular Pathology Curriculum that is under development).

Appendix C provides an overview of the existing resources of NATA- and RCPA-accredited molecular laboratories in Australia that are currently performing molecular testing.

1.1.5.3 Metrics

The National Measurement Institute is home to a Bioanalysis Research Group, which produces and validates standards and infrastructure for DNA measurement, with the aim of improving the accuracy and comparability of biomeasurements (such as those resulting from methylation or PCR quantification). The group is currently undertaking several projects related to precision medicine, including one that aims to develop an internationally comparable measure of DNA methylation for cancer diagnosis, and another aimed at creating a high-sensitivity assay to detect doping genes in athletes' blood. The group also creates genetic reference materials and operates a commercial arm that supplies analytics and contract measurement.

1.1.5.4 Clinical trials

Australia has an established clinical trials infrastructure, with over 1,300 clinical trials beginning each year, and a number of contract research organisations that possess recognised capacity in trial administration. International biotechnology, medical device and pharmaceutical companies stimulate about A$1 billion of economic activity in Australia. This has provided an environment for testing precision medicines in patients over the past decade.

The most prominent area at present is immunotherapy trials, of which 265 are either underway or actively recruiting. These are broadly focused on therapeutic vaccines, immune checkpoints, cellular immunotherapies and immune modulators, and most are sponsored by the pharmaceutical industry. A smaller number are investigator-driven studies supported by public money. Trials of one subset of immunotherapies, CAR-T cells, have progressed well at some local hospitals.

Although other countries are beginning to introduce gene editing technology into clinical trials, there are not yet any registered Australian trials doing so. There has been modest activity in clinical gene therapy over the past 20 years. A small number of trials are examining how gene sequencing and expression testing can inform treatment decisions. Other trials are assessing the impact of genomic knowledge on patients' health behaviour and psychosocial wellbeing. The Australian New Zealand Clinical Trials Registry keeps a record of trial activity and is searchable online. In the future, genomics may be integrated into a wider range of clinical trials, to determine eligibility, to stratify patients according to their likelihood of responding or to provide data on any genomic correlates of poor outcomes.

1.1.5.5 Social and ethical research

Alongside efforts to implement precision medicine in Australia, social science, humanities and medical experts are investigating the social and ethical issues associated with the field. Australia has a robust body of expertise in the **ethics** of emerging technologies and medicine. Research is underway into the psychosocial and ethical aspects of cancer genomics (Butow et al. 2016), including the use of personalised genomic information in skin cancer prevention (Cust et al. 2016), the ethics and legal implications of genetic carrier testing (Karpin 2016) and biobanking (Kerridge et al. 2015) and the ethical, legal and social implications of heritable modification (Mills et al. 2017).

The **regulatory** complexities surrounding precision medicine are also being highlighted by Australian researchers (Nicol et al. 2016a), who have engaged with the protections in place regarding consumer genetics (Castle and Ries 2009), the disclosure of genetic testing results among family members (Otlowski 2015), funding of high cost cancer medications (Lipworth et al. 2015), and regulatory issues relating to stem cell therapies (Stewart et al. 2016; Lysaght et al. 2017). Activity in this area has accelerated with the establishment of HeLEX@Melbourne, a satellite of the Oxford-based Centre for Health, Law and Emerging Technologies (HeLEX) research group (Kaye 2017). The initiative will bring UK-based researchers to Australia to strengthen research capacity on the legal dimensions of emerging medical technologies.

Several strong **social science** projects and consortia are at work across a range of topics and methodologies. Current research strengths include patients' and the public's understanding of genomic information

Box 4: The current regulatory context of precision medicine

The *Therapeutic Goods Act 1989* (Cth) (amended 2017) plays a crucial role in regulating the supply of health-related products in Australia. The Act is administered by the Therapeutic Goods Administration (TGA) and regulates the introduction of therapeutic goods into the Australian market. Drugs must satisfy rigorous pre-market assessment standards before receiving marketing approval, requiring evidence of clinical utility, safety and efficacy through clinical trials approved and monitored by human research ethics committees (HRECs). Fast-track registration may be allowed in limited circumstances where there is unmet clinical need. Precision medicine is creating some challenges for this well-established system of drug approvals. For instance, the requirement for Phase III randomised double-blind clinical trials is problematic for personalised therapies, the effectiveness of which cannot be evidenced statistically across a population. Some of the exemptions from regulatory approval also need to be revisited in the context of precision medicine.

For devices, including diagnostic genetic tests, which are classified as in vitro diagnostic medical devices, the stringency of pre-market assessment depends on risk classification. It is prohibited in Australia to make genetic test kits available to individuals for self-testing for the presence of or susceptibility to disease. In contrast, genetic test kits used in the laboratory, as well as laboratory-developed tests, can be supplied if they comply with essential principles relating to quality, safety and performance. However, foreign providers of genetic tests who make their services

available directly to consumers through the internet are not regulated through this legislation. As argued by Nicol and Hagger (2013), further work is needed to explore regulatory options and to improve consumer understanding of genetic testing. To help address these issues, the National Health and Medical Research Council (NHMRC) has produced an information resource for consumers (NHMRC 2014a), as well as a more general statement cautioning about the use of direct-to-consumer genetic testing (NHMRC 2014b).

Genome editing research using human embryos comes within the ambit of the *Prohibition of Human Cloning for Reproduction Act 2002* (Cth) and the *Research Involving Human Embryos Act 2002* (Cth), administered by the NHMRC Embryo Research Licensing Committee, as well as the *Gene Technology Act 2000* (Cth), administered by the Office of the Gene Technology Regulator. Currently, germline gene editing is indirectly prohibited by the first of these Acts, which makes it illegal to modify human cells for the purpose of causing heritable modification. The *National Statement on Ethical Conduct in Human Research* also applies. The Gene Technology Act, along with the Gene Technology Regulations 2001 and corresponding state and territory legislation, provides Australia with a national gene technology scheme that regulates development and use of gene technology in Australia (Office of the Gene Technology Regulator 2014).

Since 2001, the National Scheme for the Regulation of Gene Technology has undergone two reviews, which have found the scheme to be a sound and effective regulatory framework. The significant advances in technologies since the last review have made gene technology more accessible, which is presenting opportunities in medical and agricultural applications. A third review of the scheme was initiated in 2017, with the aim to strengthen and improve the scheme's effectiveness while ensuring it is appropriately agile and supports innovation (Office of the Gene Technology Regulator 2017a).

Further, in 2017, the Office of the Gene Technology Regulator initiated a technical review of the Gene Technology Regulations to ensure that they reflect current advancements in technology and scientific knowledge. The technical review also aims to ensure that new technologies are regulated in a manner commensurate with the risks they pose and to provide clarity about whether organisms developed using a range of new technologies are subject to regulation as genetically modified organisms (Office of the Gene Technology Regulator 2017b).

In the context of precision medicine, there are definitional issues and overlapping obligations with these regulatory frameworks, and a lack of central coordination. There can be little doubt that it would be beneficial to society to clear the 'regulatory soup' (Nicol *et al.* 2016b) and to ensure that the regulatory requirements for precision medicine are efficient, effective and transparent. Each new technological development poses new legal challenges. At present, Australia is in a phase of considerable uncertainty, and this is unlikely to change any time soon. Australia will need to be constantly vigilant in ensuring that the law achieves the purpose that society expects of it.

(Metcalfe et al. 2015; Smit et al. 2017) and biobanking (McWhirter et al. 2014), public engagement with science in Australia more widely (Marks and Russell 2015), the relationship between Indigenous worlds and genomics (Kowal 2013; Kowal and Radin 2015) and the economies of hope that surround emergent medical technologies (Petersen et al. 2017). Several researchers in this area have been working on precision medicine-related issues internationally (Addison and Taylor-Alexander 2015; Gardner and Webster 2017; Kaye et al. 2015; Savulescu, Gyngell and Douglas 2016; Taylor-Alexander and Schwartz-Marín 2013) and are now bringing their work to bear on the developing Australian context.

1.2 International initiatives

A wide variety of precision medicine activities are underway around the world. Although the US and Western Europe continue to lead advances in this field, owing largely to their willingness to invest in precision medicine research and train and attract relevant expertise, significant initiatives can also be found in all other regions. Full lists of international precision medicine initiatives and companies can be found in Appendix A and Appendix B, respectively. Here, the international precision medicine research scene is discussed according to the broad aims and organisation of the field.

Biorepositories or biobanks are in place in various national and transnational settings, often as part of broader infrastructure-oriented undertakings. In Europe, the Biobanking and Biomolecular Resources Research Infrastructure is established as a continental infrastructure for personalised medicine, with funding from the European Commission. The Human Heredity and Health in Africa (H3Africa) Initiative similarly coordinates the collection and storage of biospecimens from 22 African countries, which are made available for genomics research through their repository locations. The Qatar Biobank, established in 2012, comprises a national facility for storing biological samples from a planned 60,000 people.

Some countries are pursuing **disease-specific** precision medicine programs. These include the Cancer Research UK Genomics Initiative; the Deciphering Developmental Disorders project, also based in the UK; Canada's 'Care for Rare' rare disease research program; and Japan's Initiative on Rare and Undiagnosed Diseases. Cancer and rare diseases are common targets for precision medicine. The former represents a significant disease burden for developed countries and arises in part from increasingly identifiable genetic causes. Rare diseases have been appealing targets because they often originate from single gene mutations and have a clearer pathogenic pathway than more aetiologically complex conditions. In contrast to these frequent targets, Sardinia is pursuing a genome sequencing effort that aims to define the genetic origins of age-related disease.

Several **large-scale population sequencing** projects have been established, with the aim of sequencing the whole genomes of large cohorts of patients and members of the public. The most prominent of these is the UK's 100,000 Genomes Project, which launched in 2012 and focuses on patients with either rare diseases or cancers. Others include GenomeAsia 100K (based in Singapore) and the Saudi Human Genome Program. The All of Us Research Program in the US, which falls under the remit of the Precision Medicine Initiative, aims to collect sequence data from one million people, alongside other biospecimens and health information. The US Department of Veterans

Affairs is also leading a project that entails collecting genomic information from veterans. The genetic variation of human populations around the world means that sequencing operations in different regions can produce valuable genomic information even if other countries are more advanced in this area.

Other **national and international initiatives** are focused on supporting precision medicine more widely. Examples of nationally driven programs include the US Precision Medicine Initiative and National Human Genome Research Institute, Canada's Personalized Medicine Initiative and Genome Canada, Mexico's National Institute of Genomic Medicine, the France Genomic Medicine Plan and the China Precision Medicine Initiative. In Europe, some projects represent collaborative endeavours between research groups in different countries, often centrally funded through the EU. Examples include the EU Horizon 2020-funded Multiscale Complex Genomics project, and the European Alliance for Personalised Medicine. There are, in addition, several international alliances that have been fundamental in accelerating precision medicine research. The Global Alliance for Genomics and Health (of which the Australian Genomics Health Alliance sits alongside the US Precision Medicine Initiative and Genomics England as a key component), the International Consortium for Personalised Medicine and the Global Genomic Medicine Collaborative are all important collaborative endeavours. These national and international projects tend to foster precision medicine research writ large, including technology development, the integration of new genomics research with existing health care systems and, potentially, specific disease priorities. Some national initiatives are specifically focused on innovation, R&D and technology transfer. These include Innovate UK, which until recently operated the Precision Medicine Catapult, and Canada's Genomics Research and Development Initiative. This is also a focus of the Indian Department of Biotechnology Human Genetics and Genome Analysis program.

In some cases, these programs are linked to the work of various **national academies**, which in many places have been commissioned to produce reports on precision medicine and related topics. Significant national academy reports include those from the US National Academies of Science and Medicine (on gene editing and, previously, precision medicine), the UK's Academy of Medical Sciences (on 'stratified' medicine), the French National Alliance for Life Sciences and Health (on genomic medicine), the German National Academy of Sciences (on individualised medicine) and, closer to home, New Zealand's Royal Society Te Apārangi (on gene editing).

In addition to these government-driven programs, **university-, researcher- and industry-led projects** make up a significant proportion of precision medicine work. For example, Orion Health operates in Canada and, as of recently, New Zealand, integrating patients' existing health records with omic data through digital platforms; the Innovative Genomics Institute operates out of the University of California, Berkeley, and University of California, San Francisco, with a focus on CRISPR research; and the Wellcome Trust-funded Transforming Genomic Medicine Initiative promotes the integration of genome sequencing into medical practice. A list of commercial companies involved in precision medicine research can be found in Appendix B.

Box 5: Generation Genome: a UK report examining genomics

The Chief Medical Officer for England, Professor Dame Sally Davies, published her annual report, entitled *Generation Genome*, on 4 July 2017. The report looks at the current use of genomics in various parts of the UK's health care system to make 24 recommendations proposing that system-wide standardisation, coordination and integration can realistically establish a first-class genomic service that delivers value for money and improves care for all people across the UK.

The recommendations are categorised as 'systems and services', 'research', 'data, standards and regulation', and 'engaging staff and patients' and propose reforms that would integrate systems and services to support better interaction between fragmented health services, as well as between researchers and clinicians. Similarly, the reforms would encourage multidisciplinary teams that allow collaboration and learning between clinicians, researchers, laboratory staff, computer scientists, data scientists and bioinformaticians, among other professions.

Together with investment, standard-setting, patient consent processes and appropriate regulation, coordinated efforts across the National Health Service (NHS) are proposed to facilitate the responsible collection, sharing and use of genomic data. Collation of these data at a large scale is fundamental to providing well-informed advice to individuals that accurately describes their genetic state and its variation from the reference norms. It also adds significant value by allowing reciprocal sharing of research data across the globe.

With broad-reaching recommendations addressing infrastructure, governance, research and clinician training, *Generation Genome* draws a comprehensive map of how to make precision medicine a central and productive feature of the UK's health system.

CHAPTER 2
THE FUTURE OF PRECISION MEDICINE IN AUSTRALIA

2.1 Introduction

This chapter outlines 12 areas where precision medicine is likely to show significant impact in the next five to ten years. Genomics represents a 'platform' of sorts, from which many of these other fields emerge. However, the future success of precision medicine will rely on the ability to integrate multiple kinds of information, ethically and efficiently, in a way that is meaningful and effective in the context of patient care. In practice, this will require drawing on a host of new advances in sequencing, imaging, pathology and molecular modification (including gene editing) to determine, as accurately as possible, the disease characteristics of a patient and how best to act on these to bring about clinical benefit. As knowledge in this area develops, it is increasingly clear that the genome, environment and human behaviour all work in concert to produce various states of health and disease, as well as the individual phenotype. This highlights the importance of interpreting genomic and other information in the context of the patient. As is to be expected when dealing with such large volumes of complex health data, a range of expertise will be necessary. Multidisciplinary input from treating physicians, pathologists, scientists and signalling experts will enable accurate interpretation and prediction of the

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Views expressed in this chapter do not necessarily reflect the views of these contributors.

functional consequences of genetic data, which will in turn inform improved treatment pathways. The end user of these advances – the patient – deserves to remain at the centre of the precision medicine agenda.

One example of how integrated precision medicine can feed into clinical decision making is cancer care. Pathological diagnosis and classification of tumours is fundamental to routine clinical oncology. In the future, tumour characterisation will likely entail a multipronged approach, drawing on any combination of morphology, immunohistochemistry (using tissue biopsies to identify protein expression), genomics (to find a tumour's specific mutations), in situ hybridisation (identifying the expression of tumour genes within the tissue biopsy specimen), methylomics (diagnosing methylation of certain genes, a known prognostic indicator for certain cancers) and transcriptomics (to gain a 'readout' of which genes are being expressed in a group of cells). While the first two of these strategies are already part of routine care, the rest are being developed in accredited clinical laboratories, and their full clinical impact is thus yet to be realised.

It follows that the various advances described in this chapter should be seen as synergistic. The chapter begins with three sections covering various aspects of genomics: sequencing, gene editing and epigenetics. These are followed by discussion of the highly complementary areas of omics and microbiomics, both of which provide windows onto the dynamism of the body in health and disease, and the growing role for point-of-care testing (PoCT). The next section examines the role of precision medicine in infectious diseases, followed by sections describing developments in pathology and the rapidly

advancing field of immunotherapies. Some of these areas (e.g. sequencing) are already more advanced than others (e.g. PoCT), while some have the advantage of existing expertise and resources that will provide a base for future work (e.g. infectious disease genomics). Each section details how these technologies are changing, how they articulate with existing and future capacity in Australia and what role they might play in the future of health and medicine here. The final sections examine the role of precision medicine in complex diseases, ageing and mental health.

2.2 Emerging sequencing technologies

The advent, several decades ago, of recombinant DNA technology (gene cloning) and PCR gene amplification allowed for DNA sequencing to shift from the population to the individual scale. More recent advances in sequencing technologies and data analysis have stimulated knowledge of genetic variation and gene function. Older sequencing technologies include gene panels (in which a select few genes are tested), Sanger sequencing (which works by assembling short lengths of DNA) and microarrays (where a person's DNA is placed on a small chip containing synthetic DNA, to which it binds according to its precise sequence). These methods tend to be cheaper, faster and less computationally intensive than newer methods but are constrained by high error rates and short read lengths. Significant insights have arisen, and continue to arise, from SNP testing, which detects variation in single genetic bases of known interest. Recent developments, particularly in high-throughput or next generation sequencing, allow more bases to be sequenced and whole chromosomes to be covered at lower cost. Whereas previous methods, such as SNP testing, usefully detect the 'known knowns' of the genome (e.g. variants known to be disease-causing or risk-affecting), whole genome sequencing is capable of capturing a more comprehensive range of clinically relevant information, including information from non-coding regions of the genome that may nonetheless crucially modulate disease. However, transitioning from research to clinical environments often presents challenges in terms of costs and quality assurance, as well as equity of access.

2.2.1 Short-read sequencing

Next generation sequencing works by fragmenting a target stretch of DNA and reconstructing it by piecing together the fragments according to their overlaps. Short-read sequencing (based on short lengths, or 'reads', of DNA) dominated the past decade of genomics research, providing rapid and economical ways to generate draft genomes and investigate variation at both individual and population levels. Technological improvements have brought the cost of sequencing down to about US$1,000 for a whole human genome (although this excludes the cost of processing and interpreting the data). As a result of this activity, hundreds of thousands of human genomes have now been sequenced, along with more than 100,000 bacterial, viral and fungal genomes, including important pathogens, and thousands of animal and plant genomes. These efforts have improved our understanding of microbial communities within bodies and their environments (through microbiome research) and led to novel diagnostics for infectious diseases, such as HIV (Fisher et al. 2015) and tuberculosis (Pankhurst et al. 2016).

However, short-read sequencing has limitations, as genomes assembled from short reads tend to exclude complex genomic

regions. As a result, genes with complex structures or multiple duplications may be under-represented or misassembled. Transcriptomes produced with short reads can lack information on isoforms of gene transcripts. These problems have seen a major shift towards long-read sequencing.

2.2.2 Long-read sequencing

As it is based on comparatively longer reads of DNA, long-read sequencing can produce more complete coverage and assembly of genomes and transcriptomes while tolerating genomic complexities. There are currently two main types of long-read sequencing. One uses barcodes to assemble short reads from large DNA fragments. The other, rather than amplifying and sequencing fragmented molecules, produces a single continuous read. A recent study using the latter method to genotype the *PKD1* gene in patients with autosomal dominant polycystic kidney disease (ADPKD) successfully dealt with the gene's complexities (high GC content and homology with multiple pseudogenes), showing high sensitivity (94.7 per cent) for identifying patients carrying ADPKD-causing variants (Borràs et al. 2017). This illustrates the potential use of long-read sequencing in diagnostics, especially for diseases involving complex genomic regions. Cost remains a limitation of this technology, exacerbated by current error rates that demand multiple runs, each at a cost. Hybrid genome assembly allows short-read and long-read data to be combined at a reasonable cost, with additional data from genome-wide physical mapping.

2.2.3 Nanopore technology

Nanopore technology can provide real time sequencing of single DNA molecules. Nanopore structures determine DNA sequence by measuring changes in electrical resistance in response to DNA moving through a pore. The benefits of this method are threefold. First, by sequencing ultra-long (1 Mb) DNA regions, bioinformatics costs for data assembly are reduced or eliminated (Jain et al. 2017). Second, by directly detecting native DNA and RNA molecules as they exist in situ, epigenetic signatures can be discriminated, from simple CpG methylation (Euskirchen et al. 2017) to rare or novel modifications in DNA (McIntyre et al. 2017) and RNA (Smith et al. 2017). Finally, direct detection coupled with minimal bioinformatics provides a same-day question-to-answer timeframe (Euskirchen et al. 2017). Some nanopore devices are sufficiently compact to have been used in remote and extreme environments, including Antarctica (Johnson et al. 2017) and the International Space Station (Castro-Wallace et al. 2016). This portability is more relevant in the context of, for example, PoCT (Votintseva et al. 2017) or time-critical medicine (Euskirchen et al. 2017). Uptake of nanopore sequencing is tempered by some barriers to its adoption. Most significant is a high (although lowering) relative error rate (currently about five per cent). Further, the technology has a high 'cost per base' – a metric used to compare economy across sequencing platforms. The broader technical context is also important: upper limits on read length are now set more by DNA handling during extraction and preparation for sequencing than by the technology's limitations. Pipetting long DNA strands, for example, causes fragmentation (Jain et al. 2017).

As nanopore technology advances, systems will likely move away from biological to solid-state nanopores, such as graphene (Garaj et al. 2010). This will enable low-cost, industrial-scale manufacturing and integration with point-of-care diagnostics,

and perhaps also with user electronics, providing mass-produced tools of citizen science. The availability of these portable, efficient tools will likely allow uses beyond medicine; agriculture and veterinary medicine, for example, are both 'genetics-sophisticated' fields that may find value in such techniques.

2.2.4 Sequencing in Australia

Whole genome sequencing is a skill and resource that is presently found more in academic than clinical settings. Clinical sequencing of patients' genomes, tumours and infectious agents will likely be central to precision medicine in the future and, if so, may warrant the uptake of sequencing technologies in hospitals and primary care facilities around Australia. Resources will be needed for training and infrastructure to allow this new technology to run, initially in parallel with existing procedures. As new and innovative technologies emerge, the existing procedures and technologies they will replace will need to be phased out. This will allow Australia to keep up with the pace of change and to compete internationally. Training bioinformaticians to establish, validate and extend precision medicine pipelines is key, as is training clinical staff to ensure they can act appropriately upon the results. Harmonised platforms for data generation, analysis, access and secure storage will facilitate monitoring at the national level.

2.3 Gene editing

Gene editing describes chemical or biological processes that change DNA sequences in the genome of any organism. Current gene editing methods use enzymes called nucleases that are engineered to cut DNA at specific sites, after which the cells' natural repair process is harnessed to insert, delete or replace targeted DNA segments. The aim is to correct or create mutations and ultimately influence gene expression, restoring protein function and thereby alleviating disease. The long-term goals for gene editing are to be able to predict individual patients' responses to therapies and to develop patient-specific treatments. At present, gene editing is being used extensively in research. However, most experts do not think it is yet sufficiently accurate for clinical use, due to 'off-target effects' resulting in genes other than the target gene being changed.

Although several gene editing methods have been tested over the years (including transcription activator-like effector nucleases, or TALENs, and zinc-finger nucleases), the most game-changing technique has been CRISPR (clustered regularly interspaced palindromic repeats). CRISPR uses programmable RNA to guide an enzyme, most often the Cas9 nuclease, to a specific DNA sequence in a cell (Figure 1). Once the Cas9 cuts the DNA, the cell tries to repair the cut, but a scientist can provide chemicals that determine exactly how that repair occurs. The CRISPR-Cas9 system evolved in bacteria as a defence mechanism to ward off viral attack (Barrangou et al. 2007). It is relatively simple to use, taking only one to two weeks to produce edited cell lines. It is also low-cost, precise and can alter transcriptional repression and activation, as well as epigenetic modifications. If several different guide RNA sequences are used, CRISPR-Cas9 can activate and repress multiple disease-causing genes at different sites simultaneously (Dominguez et al. 2016).

This ability to insert or delete DNA segments quickly and accurately allows gene function to be tested at different stages of disease progression in model systems prepared from an individual patient's cells. At its simplest, research correcting a mutation in a patient's cells is invaluable for proving whether a mutation causes disease. Also invaluable are cell lines that

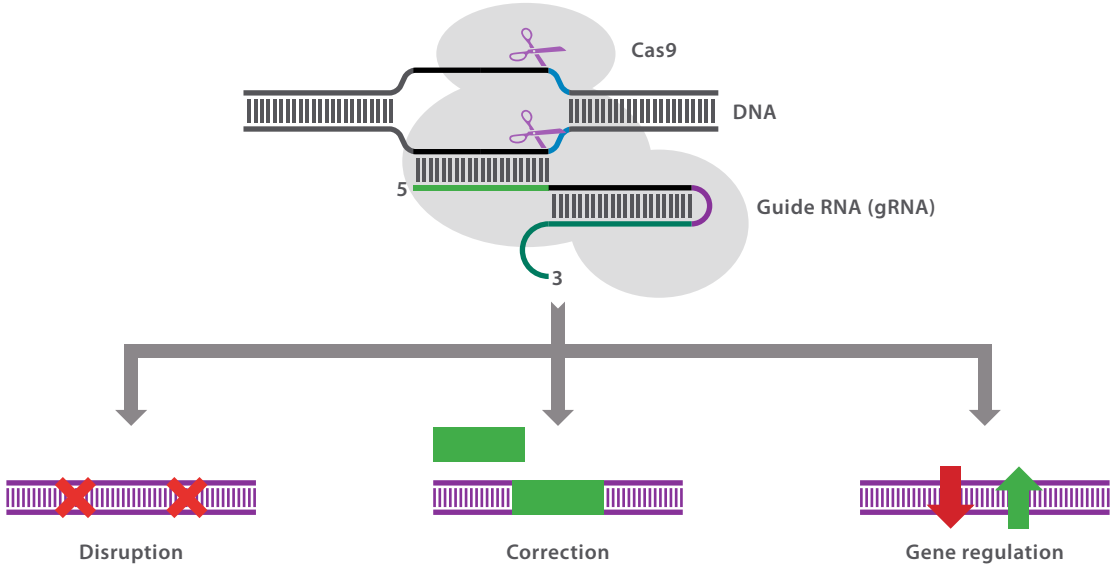

Figure 1: Depiction of the CRISPR-Cas9 System

The Cas9 enzyme, which cleaves the DNA, is represented by scissors. The Cas9 molecular scissors can cut, edit or correct disease-associated DNA in a patient's cells. Attached to the lower part of the construct is a guide RNA, matched to the genomic region being targeted, which guides the molecular scissors. Along the bottom of the figure are three potential applications of the CRISPR-Cas9 system, which can be used to disrupt genomic function, correct a mutation or modify regulation. In each case, the system cleaves the DNA at a specific region and harnesses the cellular repair process to achieve the intended effect.

Adapted from: CRISPR Therapeutics 2017.

can be used to test how pharmaceuticals work for different genetic attributes; this may also reduce the number of animals used for safety tests on new drugs. The ability to edit multiple sites on the genome simultaneously makes it possible to model complex diseases, such as cancers and dementia. This broad spectrum of uses has seen a rapid global uptake of CRISPR-Cas9 in both research laboratories and the commercial sector.

There are, however, challenges with gene editing that currently prevent its widespread translation into human trials. The most important technical challenge is the need to eliminate off-target effects, where an edit occurs somewhere other than the target region (Fu et al. 2013; Cho et al. 2014; Lin et al. 2014). Off-target effects might activate oncogenes (that cause cancer), for example. Mutations that are on-target but unintended may also arise during the repair process. Research is currently focused on developing ways to identify (Frock et al. 2015; Tsai et al. 2015) and reduce (Kleinstiver, Pattanayak, et al. 2016; Kleinstiver, Tsai, et al. 2016) non-specific gene editing, which will be key to making CRISPR-Cas9 technology safe and effective.

Gene editing technology is well suited to contributing to improving disease models, understanding early embryonic development and some clinical applications. Cell lines and small (and occasionally larger) animals are crucial for modelling disease, and gene editing techniques allow mutations to be introduced into or modified in these model organisms. It bears noting that human health cannot be directly extrapolated from model animals, as these do not contain patients' polymorphisms, which will often modify their disease. It is preferable to use patients' own cells, and this is becoming increasingly possible. Making mutation panels for specific genes will allow compound libraries to be screened for clinical use, while editing pathogenic mutations will allow patient-specific treatments to be tested.

Early embryonic development offers crucial insights into gene function, especially in relation to disease. American researchers recently edited human embryonic genomes (Ma et al. 2017), and a licence has been granted in the UK to use CRISPR-Cas9 to identify genomic markers associated with healthy embryos and placental disease. There are conflicting views within the Australian research community about how desirable such research would actually be (Alexander 2017). In Australia, it is illegal to allow research embryos to develop beyond 14 days. Despite this, media and public attention is drawn to the topic of implanting modified embryos; it is essential to communicate that this is not the goal of gene editing, and ensure that the true aims and complexities of this technique are adequately acknowledged. A recent survey of public opinion in the US shows that a majority of people support gene editing for medical but not cosmetic uses and strongly support community engagement in the field's development (Scheufele et al. 2017).

Although gene editing is currently limited to research settings in Australia, the technology shows potential for treating viral infections, such as HIV/AIDS (White et al. 2015), where gene editing methods could prevent viruses integrating into the genome; cancers (using gene editing tools to modify patients' immune cells); and rare diseases (where gene editing might follow earlier gene therapy in targeting particular disease-causing mutations).

Australia's skilled workforce, depth of clinical and scientific expertise and current innovation focus (Innovation and Science Australia 2017) align well with gene editing opportunities. However, although these tools are widespread in basic research, there are as yet no Australian gene editing companies operating. Current regulation permits basic research in cell lines and animal models but not in embryos beyond the 14th day of development. A key task for Australia is to begin national discussions to define clear and sustainable goals for gene editing that will both benefit our health care system and reflect public opinion on acceptable applications. These goals must be consistent with ethical principles and achieved in conjunction with communication with the wider public about actual and envisioned uses of this technology.

2.4 Epigenetics

Not every difference between individuals can be explained by DNA sequence alone – environment is also crucial. It is now clear that the environment and the genome interact in more complex ways than originally thought. The mantra that 'DNA makes RNA makes protein', which implies that the DNA sequence alone controls heredity and phenotype, is now outmoded; environment makes its marks on the DNA, and these epigenetic modifications can be passed from one generation to the next.

Epigenetics describes the suite of chemical modifications of DNA that regulate gene *expression* without altering the DNA *sequence*. While much research defines the genetic architecture of disease at the DNA level, it is increasingly clear that epigenetic factors, resulting from gene-environment interactions, cause or modify disease by altering gene expression. Although all of a given organism's cells contain the same DNA sequence (and thus genes), those genes are expressed differently in different cell types, and at different times. This variability allows the same genome to provide appropriate gene expression as needed: although a liver cell and a neuron contain the same DNA sequence, they differ in expression due to epigenetics.

Box 6: Epigenetics key terms

An individual's **genotype** is what is commonly referred to as their 'genetic make-up'. **Phenotype** is an individual's observable characteristics. Historically, it was assumed that there was a direct relationship between genotype and phenotype – that genes coded directly for traits. Now we know that this process is heavily mediated and that the genome interacts closely with external influences, such as cues from the environment. Genes are not static; they are multipurpose and can be expressed at different ways at different times. **Gene expression** refers to whether a gene is 'on' or 'off'. Changes in gene expression are essential to normal health and development, but can also be **dysregulated**, causing disease. Expression is altered by chemical modification, such as the attachment of a molecule to the DNA. These expression-affected attachments are known as **epigenetic markers**.

A large body of evidence shows that epigenetic processes are sensitive to environmental influence. Epigenetics as a field of research thus defines the gene-environment interactions that underlie a range of diseases. DNA methylation is one well-studied epigenetic mechanism. Methylation usually locks genes into an 'off' position; during embryonic development or cell differentiation, they may be switched on by removing the methyl group. Methylation errors are associated with many serious diseases, including those affecting young children and various cancers, such as acute myeloid leukaemia (Schoofs et al. 2014). Several key advances in epigenetics research have occurred in Australia, including work on the transgenerational heritability of epigenetic profiles (Youngson and Whitelaw 2008) and the role of epigenetics in cancer development (Melki et al. 1999; Clark and Melki 2002).

Typically, genetic mutations and epigenetic errors both contribute to disease by disrupting the patterns of gene expression necessary for health, and they are part of the analysis central to precision medicine. The epigenome often changes in dramatic and specific ways with human diseases. Cancers may show gross changes in epigenetic profile compared with healthy tissue, which may play a role in the transition to malignancy, tumour progression and metastasis. In some cases, altering epigenetic change can restore gene expression.

A range of imprinting disorders have been associated with epigenetic variations, and emerging evidence suggests links between early life epigenetic variations and the adult onset of non-communicable diseases, including type 2 diabetes (Toperoff et al. 2012; Dayeh et al. 2014), obesity (reviewed in van Dijk et al. 2015), cardiovascular risk factors such as elevated blood pressure (reviewed in Udali et al. 2013) and insulin and cholesterol levels (Hidalgo et al. 2014; Ma et al. 2015). The emerging picture suggests that some epigenetic variants act as predictors of disease, offering the possibility of identifying those people most at risk and providing targeted intervention or prevention accordingly.

Specific epigenetic variants, modifiable by dietary, pharmacological or epigenome editing, represent a largely unexplored therapeutic avenue. Determining how epigenetic markers track disease stages will provide patient-specific insight into disease progression and treatment response. This

is already routine in some adult cancers (e.g. glioblastoma multiforme (Paz et al. 2004)), where methylation signatures inform treatment, prognosis and disease progression. This is a particularly active area for epigenetics clinical trials, several of which are seeking to inhibit specific protein complexes that cause pathological epigenetic profiles in cancers (Dawson et al. 2012), while others are inhibiting DNA methylation to reverse gene expression associated with tumourigenesis.

A comprehensive understanding of epigenetic markers may also provide an opportunity to improve risk prediction for other high-burden non-communicable diseases. At present, childhood obesity measures can predict population, but not individual, cardiometabolic disease risk. Risk scores based on genetics, clinical parameters and epigenetic profile may accurately evaluate individual risk. Small-molecule inhibitors are showing promise; a recent study of Prader-Willi syndrome identified two small molecules that selectively inhibit one epigenetic mechanism that activated silenced genes associated with the disease (Kim et al. 2017). The role of nutrition, exercise and environment in establishing and maintaining a 'healthy' epigenome is also under study (Ferguson 2008; Corella 2009; Li et al. 2010; Hardy and Tollefsbol 2011).

Micronutrients (folate and vitamins B_6 and B_{12}) play a key role in regulating epigenetic functions. Deficiencies have been linked to disease predisposition, and supplementation in animal models suggests a capacity to reverse epigenetic variation associated with aberrant genetic behaviour. Many foods contain chemicals with direct epigenome modifying properties, including chilli (capsaicin), turmeric (curcumin), carrots (retinoic acid), broccoli sprouts (sulforaphane), grapes (resveratrol), green tea (polyphenols) and soy (isoflavones), each of which inhibit or potentiate specific epigenetic processes. These compounds have chemoprotective (cancer-preventing) or cardioprotective properties, leading to speculation that a tailored 'epigenetic diet' (not unlike the Mediterranean diet) could be appropriate for individuals at high risk. Undernutrition and overnutrition are both linked to epigenetic disruption, in some cases across generations (Heijmans et al. 2008), while obesity risk is known to be influenced by a host of common and rare genetic variants that operate through mediating metabolic and neurological processes to affect energy balance (Locke et al. 2015). The field of nutrigenomics examines how gene expression, diet and lifestyle interact. Several Australian companies use these epigenetic modifiers extensively, supplying kits and information that allow health practitioners to prescribe medical and behavioural changes based on genetic variants associated with inflammation, metabolism and other physiological processes.

Australia has been a key player in epigenetics research and has the workforce, innovation emphasis and patient and population cohorts to support further work in this area. However, epigenetics research is still largely carried out in disparate laboratories that are actively competing for resources and research outcomes. A firm strategic overview is essential if we are to employ epigenetics as part of precision medicine, with the aim of risk prediction and health improvement.

2.5 Omics

While genomics is central to precision medicine approaches, other omics present alternative ways of viewing and analysing individual differences, therefore better accounting for the multifactorial nature of most common diseases. Proteomics,

metabolomics, microbiomics and epigenetics can together produce multidimensional understandings of disease, capturing change over space and time and reflecting the links between genotype and phenotype (Figure 2). They are thus highly complementary to genomics research and make a major contribution to precision medicine.

Metabolomics is the study of small molecules (metabolites) in cells, biofluids, tissues or organisms. Cells constantly metabolise nutrients and biosynthesise products to maintain homeostasis and support growth. As the products of the genome most proximal to phenotype, metabolites are a powerful source of novel markers, effectors and predictors of health and disease. Australia has an established metabolomics infrastructure, with clinical cohort research underway at several locations. Metabolomics has yielded many clinically relevant findings, including markers of longevity (Cheng et al. 2015), myocardial infarction (Ngo et al. 2016; O'Donoghue et al. 2016) and liver disease (Kimberly et al. 2017); and signatures of stroke (Kimberly et al. 2013), insulin resistance (Rhee et al. 2011) and exercise (Lewis et al. 2010). The proximity of metabolites to phenotype means their effect size is often greater than that of genetic variants. For example, metabolites have

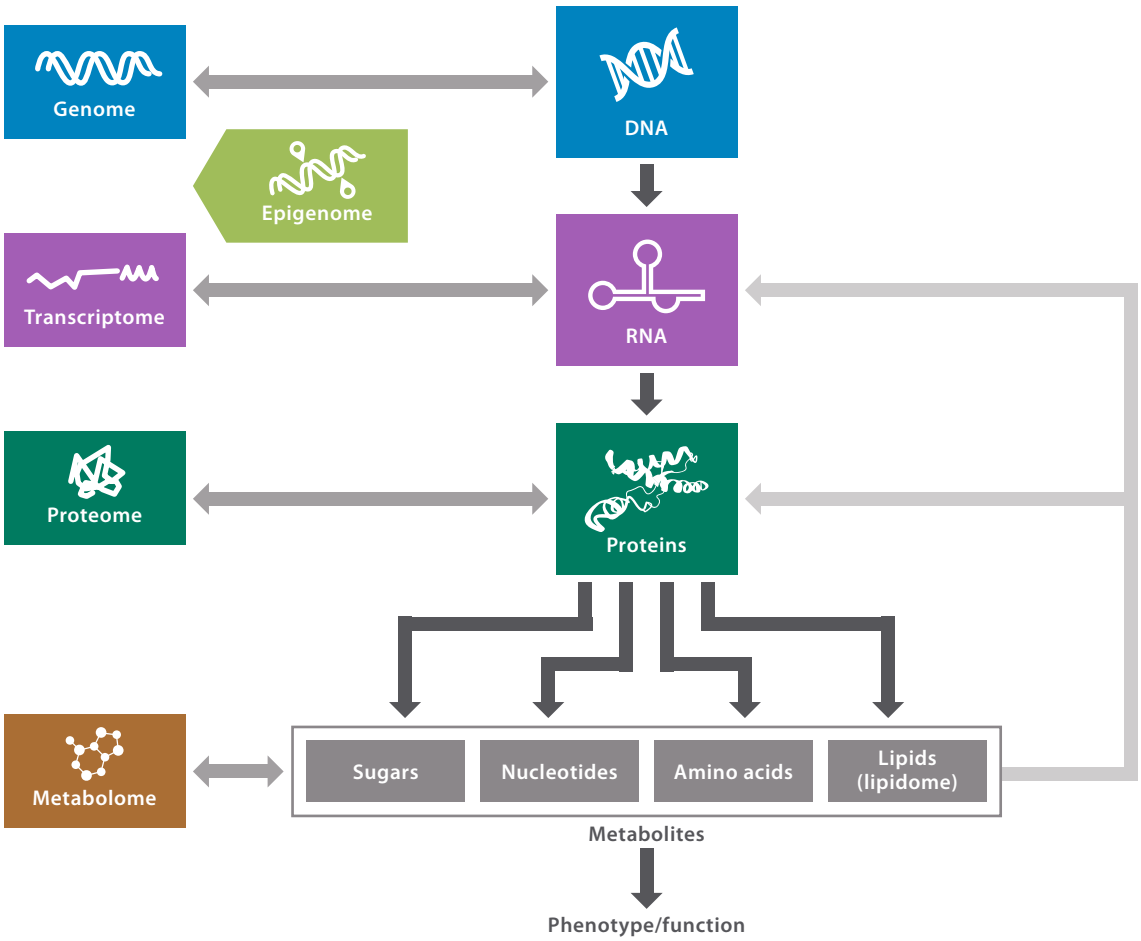

Figure 2: Relationship between the different levels of omics information

Omics technologies harness different molecular entities to gain insight into the workings of the genome and its expression. Combining these levels of analysis can produce a more complete picture of how disease originates and how the body responds to therapies.

Adapted from: Koriem 2017.

proven to be more predictive of diabetes risk than SNPs, and this predictive power increases when three metabolites are considered together (McClellan and King 2010; Wang et al. 2011).

Proteomics refers to the measurement of proteins or their modification in biological specimens. The reliance of this field on mass spectrometry means it has advanced rapidly in recent years, to the extent that it is necessary for any major centre to regularly upgrade its mass spectrometry systems. The recently published human proteome will enable the identification of proteome changes associated with a particular disease (Kim et al. 2014). The proteome is highly dynamic – tissues express different proteins before, during and after a disease, and these patterns may differ between individuals and between healthy people and those with disease. An individual's proteome can be mapped serially over time, enabling a comparison of proteomic changes with an individual's own archived proteome, rather than with a biobanked library 'average'. Alignments of proteomic analysis with genome-wide associations are also revealing genetic variants that are directly related to protein alterations, allowing for a more defined pathway from genome to disease (Sanders and Oberst 2017).

As technology (including bioinformatics) advances, personalised proteomics will become a clinical norm. Proteomic analysis of easily obtained body fluids has, for example, identified novel biomarkers of oral squamous cell carcinoma from saliva (Krapfenbauer et al. 2014) and inflammatory bowel disease from blood (Chan et al. 2016). The use of mass spectrometry for such purposes has the advantage of being able to identify multiple biomarkers simultaneously from a single sample, potentially reducing costs as well as time to diagnosis and treatment. This approach could potentially replace more invasive diagnostic tests, such as endoscopy and angiography. It could also determine antibiotic resistance and bacterial strain in a single test, in cases where the resistance mechanism relies on alterations in protein expression (DeMarco and Ford 2013; March et al. 2015; Heng et al. 2016). There is potential for proteomics to distinguish bacterial from viral infections in patients, thereby limiting misuse of antibiotics (Oved et al. 2015). Serial monitoring of patient proteomes could also detect *response* to therapeutic strategies, outcome measures that are not generally reflected in DNA sequence data.

While availability of equipment such as mass spectrometers is important, so too is the expertise required for robust study design and sample handling. The best omics studies are based on carefully annotated and phenotyped human cohorts, with attention paid to confounding variables (e.g. comparable storage and handling procedures, and samples taken from fasting individuals at the same time of day). This attention to detail is essential. Much of the clinical metabolomics expertise in Australia has been acquired in international centres where high standards are entrenched. Australian precision medicine can harness this expertise, ensure relevant protocols are in place and learn from the mistakes of older institutions.

Precision medicine stands to benefit considerably from the integration of omics beyond the genome. Together, omics approaches can provide clearer and more time-sensitive pictures of multifactorial diseases, leading to improved diagnostics and treatment pathways. The challenge will be to combine strong genetic and epigenetic data with proteomics and metabolomics to provide comprehensive data sets that are also capable of projection into the future.

2.6 Microbiomics

The microbiome is the population of microbes that live in and around and continuously interact with an individual animal or plant. Microbiomics is the study of interactions and processes of a microbial community (such as all the microorganisms in a person's gut) and the individual who is colonised. The human microbiome is a measurable, functional and dynamic interface between our genes, environment and behaviour. Although microbiomics has generated much excitement and attention, key knowledge gaps regarding the actual role of microbiota in health and disease remain: many microbes are hard to culture; their genetic profiles may be known but remain functionally cryptic; some may be seen as beneficial (e.g. probiotics) but evidence is scarce; and their action is often inseparable from the context of their microbial community.

The microbiome is likely to be a key contributor to precision medicine because it differs from person to person (or organism to organism), as well as between communities or populations. It can be predictive and personalised. Host-microbe interactions have long been recognised as a contributing factor to the onset, progression and resistance of many diseases. Recent studies in animal models show that diseases once thought of as 'non-communicable' (i.e. incapable of passing from individual to another) can be transmitted by transplanting microbiota (Morrison 2013; Walter et al. 2017). While microbiomics programs initially focused on the lower gut through stool sample analysis, more recently attention has expanded to encompass other body sites (e.g. skin, oral cavity, urogenital tract), with an increasing emphasis on cohort and translational ('bench to bedside') research.

It is likely that microbiome research internationally will translate into the clinic in the next decade. For example, a microbiome profiling tool has been used to monitor 'dysbiosis score' (a measure of microbial imbalance) for patients with irritable bowel syndrome, and faecal microbial transplants have been used as a first-line intervention to displace antibiotic-resistant *Clostridium difficile* infections (Khoruts and Sadowsky 2016; O'Toole and Flemer 2017). Although results in other areas have been modest, a future in which an individual patient's microbiome status is incorporated into primary care is foreseeable.

Australia has a strong history in microbiology research, contributing to antibiotic discovery, identifying the role of *Helicobacter pylori* in gastric diseases and developing novel vaccines for preventing human papillomavirus (HPV)-mediated cancers. These outcomes have resulted from integrative approaches that gel nicely with microbiome research, suggesting a favourable scientific culture for future work in this area. However, the uptake of technologies that now underpin microbiome research has been gradual and typically supported by small investigator-initiated grants, which do not encourage large-scale strategic collaboration. A working example of how human microbiome research can help deliver outcomes relevant to human health and wellbeing, using the current and emerging networks of researchers centred in Queensland, is outlined in Figure 3.

Much of the microbiome remains poorly understood in terms of evolution, function and effects on health and wellbeing (Anton et al. 2013; Hugenholtz et al. 2016). However, cross-sectional comparisons show that the microbiome varies across human populations due to a combination

of biological variation, culture (e.g. antibiotic use, traditional medicines) and environment (e.g. urban vs rural). This provides a rationale for ecoregional research, which Australia is well placed to supply because of its population diversity, growing burden of chronic 'Western' immune-mediated and metabolic diseases and cancers (suggesting a non-genetic basis), clinical system (which is well provisioned for biospecimen collection and analysis) and geography encompassing both temperate and tropical environments. Australian expertise in agricultural and veterinary research also positions us to bring about advances in knowledge using large-animal models (Morrison 2013) – research that will benefit veterinary improvements in animal health, as well as improvements in the nutritional and commercial value of Australian produce.

Much of Australia's microbiomics research is investigator-led 'discovery' research, as opposed to large consortium-type initiatives. There is a lack of infrastructure, such as facilities to keep germ-free or gnotobiotic (colonised with specific microbes) animal models. Developing the same kind of economies of scale in research infrastructure that supports work in Europe and North America is a challenge, but this should not be a deterrent. Australia also lacks support for the kinds of longitudinal research (cohort studies or placebo-controlled randomised clinical trials) that translational microbiomics will depend on. Translating microbiome data into better medical care will necessitate data linkage with health records from primary through to tertiary systems; this in itself warrants attention to the ethical, legal and social issues associated with large-scale

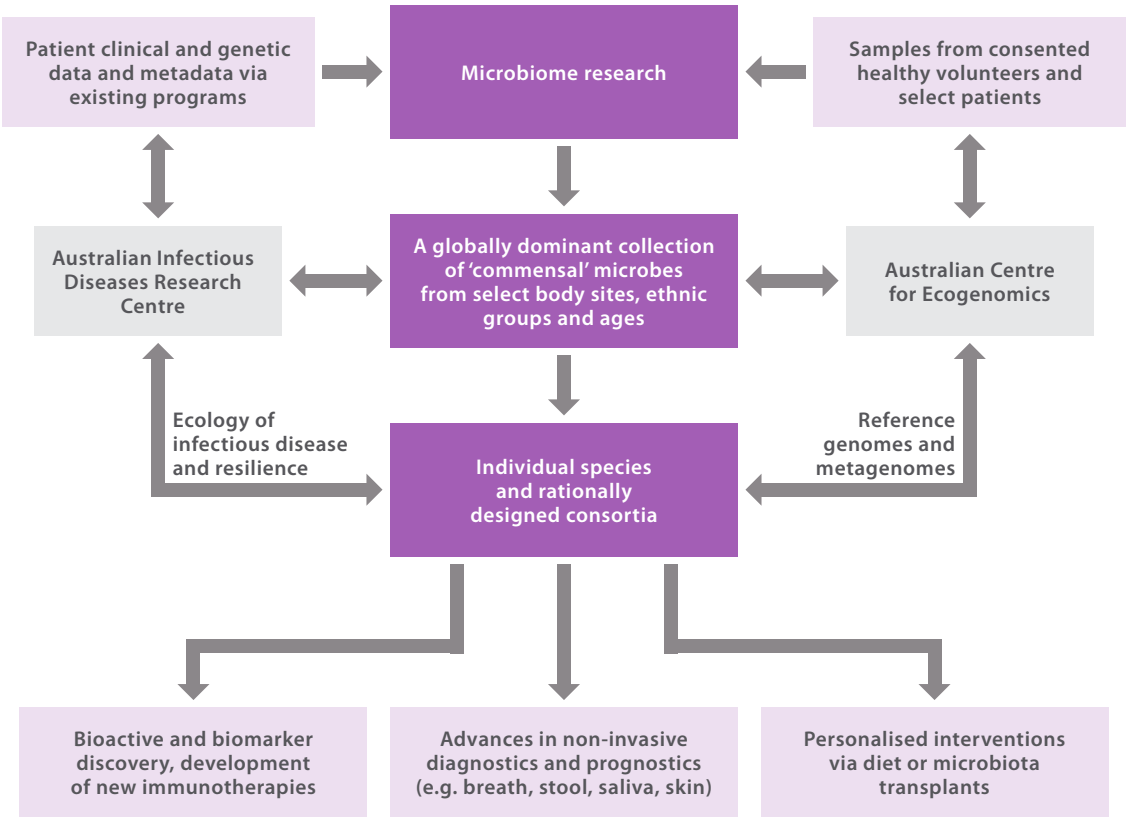

Figure 3: Working example of an Australian microbiomics research ecosystem delivering outcomes to human health and wellbeing

Adapted from image provided by Professor Mark Morrison.

health data usage and management, where confidentiality must be assured. There is a strong argument against adopting a 'fast follower' approach to research in this area: the country's unique ethno-regional needs and health research opportunities would be a good target of Australia-led microbiome initiatives and consortia.

Human microbiome research can support precision medicine throughout the various arms of the health sector but requires a sustained effort to support it as a distinct field of research, separate from infectious diseases and clinical microbiology, that can deliver new diagnostic and therapeutic options for chronic diseases. Australia can play a globally meaningful role in translating microbiomics into medicine, but this will require a focused and integrative effort that uses local and individual variation in the Australian population and environment to do so.

2.7 Point-of-care testing

PoCT refers to diagnostic testing performed at or near the site of patient care. Because patient proximity is central to PoCT, it is theoretically able to generate rapid results, allowing faster decision making about patient care, treatment options and the need for referral. The ability to perform diagnostics 'on the spot' may be especially valuable in rural and remote contexts. The potential efficiency of PoCT means there are both clinical and economic rationales for its uptake. Some advantages and disadvantages of PoCT are outlined in Table 2.

General practice continues to be a cornerstone of Australian health services, with 85 per cent of the population visiting a general practitioner (GP) at least once a year. GPs are most patients' first point of contact with the health system and therefore play a key role in primary intervention, prevention, diagnosis and management. Seventy five per cent of GP visits concern chronic disease management, which is a major challenge to the health system. Pathology tests constitute a core part of diagnostic investigations and patient monitoring. However, a shortage of pathologists and senior scientists could affect service quality, timeliness and effective treatment, leading to delayed discharge, longer hospital stays and increased health care costs. PoCT has been identified as one part of a broader strategy for improving pathology productivity. The ability of PoCT to provide faster pathology results positions this technology to assist with frontline management of chronic disease, while also relieving strain on general practice and expanding the reach of pathology services.

To ensure that PoCT complements, rather than compromises, clinical care, a quality

Advantages	Disadvantages
Simpler sample collection	Increased workload
Reduced pre-analytical errors	Potential errors due to poor analytical performance
Faster availability of test results leading to more timely treatment	Potential incompatibility with local laboratory method
Removal of barriers to pathology access in rural and remote areas	Increased costs
Increased patient satisfaction	Inadequate storage of results
Improved medical outcomes	Inadequate quality control, quality assurance and documentation

Table 2: Advantages and disadvantages of point-of-care testing

Box 7: Trialling point-of-care testing in Australia

In 2005, a multicentre randomised controlled trial of PoCT in general practice began, with the aim of determining the safety, clinical effectiveness, cost-effectiveness and satisfaction with PoCT in a primary care setting. Of 58 practices involved, 32 integrated PoCT into the care of patients with diabetes or hyperlipidaemia and those taking long-term anticoagulant therapy, in accordance with an accreditation program set up for the trial. The trial's results indicated that there was a role for PoCT in enabling GPs to make more timely clinical decisions, while facilitating patient self-management. The trial worked in the then regulatory context and was found to be broadly acceptable to stakeholders. One cause for concern was that the costs of the trialled point-of-care tests were significantly higher than those for tests performed in laboratories, due in part to the comprehensive training undertaken, close monitoring of patients, stand-alone accreditation and proportionally high costs of quality control and quality assurance for small practices running few tests. The trial provides a framework for a broader rollout of PoCT and will serve as a valuable reference for regulators.

framework is essential. All point-of-care tests must be approved for supply in Australia by the TGA. However, as these tests are often performed outside of laboratory settings, the usual laboratory accreditation schemes may not apply. The US, for example, has specific PoCT regulation under the Clinical Laboratory Improvement Amendments. There are currently no mandatory standards or guidelines specific to PoCT in Australia beyond TGA approval. The National Pathology Accreditation Advisory Council has published guidelines on many aspects of PoCT, but their uptake is at the discretion of individual institutions. Sites wishing to receive Medicare rebates for PoCT analyses must also go through an accreditation process, which may be more burdensome than is necessary for many practices (see Table 3: Point-of-care testing accreditation steps). Making such regulatory requirements logical in relation to current expectations and resources would go some way to supporting PoCT.

Other areas that need attention to ensure high-quality and precise PoCT include: equipment suitability; appropriate education, training and certification pathways; ongoing technical support; access to control samples for quality testing; regulations that ensure PoCT is performed within quality frameworks; and regulation to rebate PoCT equipment that meets precision requirements (thereby ensuring that equipment that does not meet

Accreditation steps	Cost
Application to become an Approved Pathology Practitioner	A$500 per practitioner
Registration as an Accredited Pathology Laboratory	A$750
Application to become an Approved Pathology Authority (Proprietor)	A$1,500
Adherence to ISO 15189 dictating that tests be enrolled in an external quality assurance program	

Table 3: Point-of-care testing accreditation steps

analytical requirements is not used). Some point-of-care tests will also require specific certification. For example, a test for glycated haemoglobin in patients with diabetes will need NGSP (National Glycohemoglobin Standardization Program) certification. The relative quality and reliability of PoCT results will be important in terms of integrating these capabilities with precision medicine more widely and for facilitating high-quality patient care.

The Australian Point of Care Practitioners Network (APPN) was established to address challenges of cost and quality relating to PoCT. It is important that the APPN is involved in determining the application of PoCT to precision medicine, as it is responsible for providing information on identifying clinical needs, selecting and installing instruments, training, quality control and quality assurance procedures and certification, as well as test-specific clinical information. The APPN could be used as a cost-effective way of establishing a PoCT quality framework for precision medicine, in partnership with GP accreditation bodies.

2.8 Infectious disease

Although precision medicine typically refers to medicine that acts on an individual (patient) level, in the context of infectious disease it is better viewed as knowledge of precise genetic or phenotypic variability among infecting pathogens, which enables a precision approach for treating or preventing disease in an individual patient. These techniques enable rapid identification of antibiotic-resistant pathogens and outbreak agents, informing epidemiology and public health, while helping to identify new therapeutics and vaccines (Walker and Beatson 2012; Beatson and Walker 2014; Gwinn and MacCannell 2015).

2.8.1 Outbreak monitoring and pathogen emergence

Phylogenetic and comparative analyses, facilitated by the small size of many viral genomes, can be used to monitor viral outbreaks. Viral genome databases allow researchers to identify new infectious agents, monitor changes in virulence, determine new outbreak isolates and transfer known viral strains into new geographical settings. The power of this approach was recently exemplified in the outbreak of Ebola virus disease in West Africa, where genomic sequencing was employed in the field to assess the point-to-point spread of the epidemic and guide appropriate health care interventions. This informed World Health Organization (WHO) strategy, which now has a more active approach to epidemic preparedness, and gave rise to the Coalition for Epidemic Preparedness Innovations. One of the first tangible local outcomes arising from Australian involvement in this coalition is the inception of the Australian vaccine pipeline consortium, which aims to assemble an infrastructure to rapidly develop, test and deploy novel outbreak-targeted vaccines. As bacterial, fungal and parasitic agents have larger genomes, these have only more recently been the target of phylogenetic and comparative analyses. Nonetheless, genomics has improved the ability to monitor outbreaks and the spread of infectious clones. Precise knowledge of outbreak strains has guided responses at the local level (e.g. an outbreak of *Legionella pneumophila* infection at Wesley Hospital in Brisbane (Bartley et al. 2016)), national level (e.g. vancomycin-resistant enterococci and vancomycin-resistant *Staphylococcus aureus* (Australian Commission on Safety and Quality in Health Care, 2017)) and global level (e.g. scarlet fever outbreaks in China (Davies et al. 2015) and the UK).

Box 8: Identifying vaccine and therapeutic drug targets: a sepsis case study

The sepsis initiative of Bioplatforms Australia and Research Data Services demonstrates how a well-orchestrated synthesis of genomics and other omics (transcriptomics, proteomics and metabolomics) can benefit counter-infectious disease efforts. A better understanding of sepsis is crucial for developing new approaches to clinical management; these might include virulence-attenuating approaches that do not necessarily select for more antimicrobial resistance. This strategy requires the coordinated action of multidisciplinary teams to identify common pathogenic pathways that may be exploited for the early diagnosis, treatment and prevention of life-threatening bacterial infections. This national research data infrastructure will support the storage, integration, analysis, annotation, visualisation, sharing and publication of data generated from multi-omic research and facilitate the identification of new vaccine and therapeutic targets against important sepsis pathogens in the Australian context.

2.8.2 Genomic epidemiology and investigating antimicrobial resistance

Genomic epidemiology, the application of high-throughput genome sequencing to microbial infectious disease isolates in the hospital, allows monitoring of infection transmission in clinical settings. This provides unequivocal data on transmission pathways of infectious disease and antimicrobial resistance profiles, which are then deployed to break transmission pathways, develop novel diagnostics and inform precise antibiotic dosing in critical care environments. Routine genomic interrogation of infectious disease agents from the clinical setting will also allow monitoring of the spread of individual resistance genes at a previously unattainable resolution. This can be used to combat antimicrobial resistance and tailor more individualised therapies for infected patients. Given the frequency of, and high costs and morbidity associated with, hospital-acquired infection, the potential for pathogen sequencing is great.

2.8.3 Metagenomic discovery of new human pathogens

A growing number of chronic diseases are being found to have an underlying infectious basis. For example, an Australian researcher found that *Helicobacter pylori* causes stomach ulcers and gastric cancer, and HPV has been identified as causing cervical cancer. Genomic technologies may facilitate the identification of new pathogens that lead to diseases not previously known to have an underlying infectious trigger. In particular, metagenomics allows researchers to collect genomic data directly from a given environment and thus work with the true genetic context (as opposed to a generic or average referent).

2.8.4 The Australian context for precision infectious disease strategies

Genomic technologies are starting to be transferred into public health and pathology as pilot studies in Australia. In hospitals, they will enable the detection of transmission events and targeted patient management in response to data on antimicrobial resistance. For patients with sepsis and others requiring intensive care, genomics will allow real-time identification of resistance gene profiles and resistance development, facilitating improved antibiotic use. In the community, rapid genomic screening of urinary samples could identify resistance and feed into sexual health

network tracking of common organisms, such as *Neisseria gonorrhoeæ*. The availability of personalised microbiomes also opens up the possibility of targeted treatments for urinary tract or diarrhoeal infections, using antibiotics that account for an individual patient's resistance genes. Coordinating and harmonising this work will ensure it is fully in the national interest. Indeed, the introduction of these technologies into laboratory pathology and public health is also an opportunity to harmonise platforms for data generation, analysis, access and secure storage. National sharing of data sets, in particular, will be essential to using genomics in the best interests of the Australian population.

Outbreak response in Australia is currently organised in state-based health systems. This diverges from the centralised models of countries such as China and the US, which each have a national centre for disease control. Such a model has been advocated by some but not adopted here; however, there is strong national coordination through bodies such as the Communicable Diseases Network Australia and OzFoodNet (for foodborne outbreaks). Whichever system is used will need to be resourced in a way that facilitates seamless coordination across state boundaries, given the potentially rapid spread of emergent epidemics. Resourcing will also need to be directed into coordinated training and infrastructure, allowing new technologies to run in parallel with existing ones, then for existing procedures to be phased out when genomic analysis is superior. Training is required both for bioinformaticians, to establish, validate and extend the pipelines for precision medicine, and for clinical staff, to ensure that they are fully informed to act appropriately on the results.

Precision medicine can make a major impact on the monitoring, control and prevention of infectious diseases in Australia, although some modifications are needed to realise this goal.

2.9 Pathology

Recent advances in pathology and imaging highlight how increased phenotypic data can improve patient care on a day-to-day basis. Particularly relevant here are recent advances in anatomical pathology of tumours, detection of circulating tumour DNA (ctDNA) and in vivo patient imaging using nuclear medicine.

2.9.1 Anatomical pathology

Over 500,000 molecular tests are performed in Australia each year, in more than 50 accredited pathology laboratories (see Appendix C). Available tests range from SNP and single gene analysis through to multigene panels, cytogenetics, microarrays and whole genome sequencing. While some of this work occurs outside of traditional pathology laboratories to avoid contamination, anatomical pathologists are key players when it comes to both selecting the type of tissue to be sequenced and subsequently interpreting the results in light of the previous tumour diagnosis, other pathological features and the literature.

The increased activity in this sphere arises, in part, from the growing number of proteins, genetic variants and other biomarkers that are now routinely tested. Much of this testing has focused on identifying targets for more precise treatment options (e.g. cancer treatments specific to certain cellular markers). Tumour typing tests (e.g. to test for HER2 status in breast cancer) are being developed, and pathology is also fundamental to analyses of programmed cell death and immune checkpoint inhibitors (see Section 2.10, Immunotherapy). Recent applications of immunohistochemistry to accurately predict mutations suggest that, in some cases, this could be a faster and cheaper alternative to genetic testing. Many of these kinds of molecular data are now included in the WHO Classification of Tumours.

The evolving nature of this field means that continued validation of both tests and outcomes is essential. Further, while diagnostic criteria continue to shift over the next five to ten years, there will be a need to continually re-evaluate the evidence provided by specific treatments (clinical trials) and updated tumour classifications. Continuing to develop new tests of high (accredited) standards will be made easier by providing Medicare Benefits Schedule (MBS) listing for new tests, continued education on implementing cutting-edge technologies, validated instruments and protocols and a more effective process for driving the joint development of diagnostic tests and targetable drugs.

2.9.2 Circulating tumour DNA

Small amounts of tumour DNA circulate in patients' bloodstreams (Wan et al. 2017), and these can now be accurately measured and used as a biomarker in various aspects of cancer management. This method has the advantage of being easily performed, safe and minimally invasive, and it can also be repeated frequently during patient follow-up. This 'liquid biopsy' thus has several advantages over standard tissue biopsies when it comes to following tumour-specific genomic changes over time. The most immediate clinical application is to use circulating tumour DNA (ctDNA) to identify genomic changes, then use this information to guide selection of targeted therapies. This utility will improve in step with increasing numbers of targeted therapies.

A second clinical application is in monitoring treatment resistance, which is a major problem for patients with cancer. Doctors can use ctDNA analysis to non-invasively detect the emergence of resistance-associated mutations and use this information to change the course of treatment as needed. This approach is likely to be used across a range of cancer types.

Finally, ctDNA analysis can be used after treatment, to identify residual disease and individuals at risk of relapse. Recent studies across several cancer types have shown that monitoring ctDNA levels after surgical resection can identify patients with residual or recurrent disease. Diagnosing relapse early may allow further treatment to be introduced while the disease burden is still minimal and treatment thus likely to be most effective. There are currently only three Australian hospital facilities, all based in Victoria, with the capacity and expertise to perform and interpret ctDNA analysis.

2.9.3 Imaging

Nuclear medicine is a powerful imaging modality that plays a vital role in the diagnosis and management of a wide range of medical conditions, particularly cancers. Major technical developments in the past 15 years, including the combination of position emission tomography with computed tomography (PET–CT), have led to improved diagnostic accuracy over conventional techniques. These advances have translated into improved patient outcomes across cancer types (Hillner et al. 2008). Nuclear medicine also has an established role in the treatment of multiple types of cancer through the targeted delivery of radiation directly to cancer cells.

More recent advances in nuclear medicine are redefining diagnostic and management pathways for patients with cancer, dementia and other medical conditions. These advances include new molecular imaging techniques for prostate cancer, neuroendocrine tumours and neurodegenerative disorders (Alby et al. 2014; Afshar-Oromieh et al. 2015; Sabri et al. 2015; Deppen et al. 2016). Alongside these diagnostic uses, nuclear medicine therapies (e.g. targeted radioligand therapies, radionuclide therapies) are also proving to

be effective, offering hope to many patients with advanced cancer (Kulkarni et al. 2016; Strosberg et al. 2017). In a context of rapidly developing targeted and personalised treatments, precise characterisation of disease processes using nuclear medicine techniques is becoming increasingly central to individualised patient care.

2.10 Immunotherapy

Precision medicine stands to benefit patients not only by improving overall clinical responses but also by reducing adverse effects of existing treatments. Immunotherapies for cancers are a classic example: while chemotherapy and radiotherapy are mainstays of cancer treatment, their often severe side effects can significantly impair patients' quality of life and even cause new malignancies. The development of immunotherapies represents a step change from treatments that work by triggering mass destruction of malignant (and other) cells to more targeted immune-based therapies. Combinations of cancer genomics and immunotherapies have emerged as powerful tools in cancer treatment, showing success with melanoma and lung cancer to date (Pardoll 2012).

Immune dysregulation plays a crucial role in many diseases, including cancers, autoimmune disorders and infectious complications after transplantation. Immune-mediated inflammation has also been linked to cardiovascular disease, Alzheimer's disease, obesity and type 2 diabetes. The immune system has evolved to block pathogens, but it also maintains homoeostatic regulations that support tissue repair and limit organ damage from inflammation; it thus works to prevent collateral damage by sustaining counter-regulatory pathways. Immunotherapies are designed to exploit these immunological pathways, modulating the blood and tissue microenvironment to restore control over homoeostatic processes (Akdis and Akdis 2015; June et al. 2015; Lesokhin et al. 2015; McDonald-Hyman et al. 2015; Suurmond et al. 2015).

There are several promising avenues currently being explored for immunotherapies.

- **Immune checkpoint inhibitors** wield certain molecules against mechanisms that inhibit immune activation or malignancy recognition, effectively reactivating the immune system against certain cells, such as cancer cells. One, ipilimumab, is a monoclonal antibody directed against CTLA-4, a receptor that effectively downregulates the immune response; it has been approved for use in treating several cancers, including melanoma (Drake et al. 2014). Although only a subset of patients respond to checkpoint therapies, those who do often remain disease-free for a long time (Fuerst 2017). For example, risk of death or disease progression among patients with advanced melanoma in one trial was reduced by 42 per cent with the administration of pembrolizumab, another checkpoint inhibitor (Robert et al. 2015).
- **Adoptive cellular therapies** generate a cancer-specific immune response by selecting and modifying specific immune subsets through cell enrichment and gene editing (Fischbach et al. 2013). CAR-T cells, for example, feature an inserted receptor specific to the antigens expressed by a specific tumour. This modification enables the cells to target and eliminate malignant or infected cells. In one case, CAR-T cells targeting the antigen CD19 led to 90 per cent of patients with refractory B-cell acute leukaemia achieving complete remission (Tees and Sokol 2016). Adoptive cellular immunotherapies are extending to a wider range of cell types and applications (e.g. autoimmune diseases, stem cell transplants).

- **Immunomodulation** uses the common base of immunological inflammation that underlies diseases with various clinical manifestations. Identifying the precise immune cell subsets within inflamed tissue can elucidate the molecular pathway that leads to disease and inform the development of targeted drugs that address the relevant molecular actions without affecting the entire immune system. This approach has been used with success in paediatric patients with refractory systemic-onset juvenile idiopathic arthritis.

A major challenge to this type of cellular immunotherapy is safety; newer technologies employ 'safety switch' strategies that enable the modified T cells to be destroyed with the administration of a non-toxic drug. There is also the question of how viable and practical autologous T-cell immunotherapy is in the long term. Autologous T cells entail a one- to two-month delay in activation and expansion of cells in vitro, which is both expensive and, in patients with rapidly progressive disease, clinically unacceptable. One solution to this problem would be to centrally bank HLA-typed T cells established from healthy individuals and activated to viral and cancer-associated antigens for distribution to patients as needed (Figure 4). This is currently being done in Brisbane and Sydney but will perhaps be most valuable for patients in regional areas.

Further attention also needs to be paid to why some patients respond to immunotherapies, while others fail to show any clinical benefit; identifying biomarkers that predict responsiveness will be key. The high cost of many immunotherapies means that they should be applied prudently. More importantly, identification of response- or non-response-specific biomarkers may also lead to new combination treatments that work for additional patients (Patel et al. 2017).

There are currently 265 active cancer immunotherapy clinical trials in Australia,

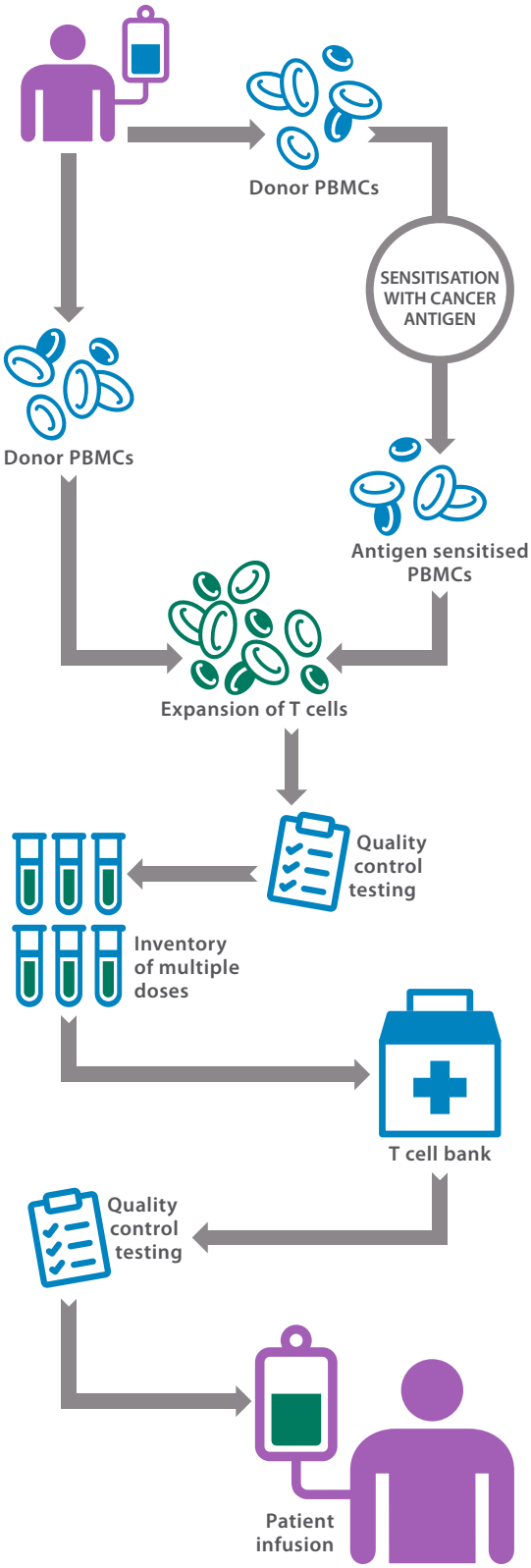

Figure 4: Convenient 'off-the-shelf' manufacturing and distribution

Peripheral blood mononuclear cells (PBMCs) are extracted from healthy donors, expanded and treated according to the desired effect, passed through a quality control (QC) process, and 'banked', for off-the-shelf use as needed.

Adapted from: Atara Biotherapeutics.

broadly focused on the above areas as well as therapeutic vaccines. Most of these trials are pharmaceutical industry-sponsored, with a smaller number being publicly funded and investigator-driven. Several local groups are also developing new platform technologies to improve adoptive T-cell therapies. A concentrated focus on a few key areas could strengthen Australia's existing capabilities in the immunotherapy field. **Manufacturing facilities** able to provide rapid access to clinical-grade material for clinical trials will need to be developed. While autologous cell therapies (those made from a patient's own cells) have been used successfully, they are laborious and time-consuming to produce, making them unsuitable for patients in urgent need. Developing allogenic 'off-the-shelf' T-cell therapies from healthy volunteers would avoid some of these issues. A schema of how this might work is shown in Figure 4. **Regulatory expertise** (e.g. in the TGA) in relation to immune-based therapies should be supported, and **harmonising** regulatory processes across local and international sites would facilitate the translation of novel immunotherapies. A **funding structure** appropriate to translational immunotherapies is desirable and, finally, **workforce training** in good manufacturing practice, clinical trial design and regulatory processes would equip Australian researchers to advance their work.

The significant progress made in immunotherapies in recent years, internationally but also in Australia, indicates that this is a developing area with noteworthy potential for treating cancers and other immune-mediated diseases.

2.11 Precision medicine in primary care

Many common medical problems, including heart disease, diabetes, mental illness and cancer, are complex diseases. Most people will be affected by, and ultimately die from, one of these conditions. An understanding of the role that various omics play in complex diseases can help to reduce the burden of disease through prevention, early detection and optimised management and monitoring. One of the key objectives of the health system in Australia must be to ensure that most people are able to transition into their last years in a good state of health. Complex diseases are both personally challenging and a serious economic burden on the nation. The value of precision medicine is that it provides the individualised knowledge needed to maximise the chance of retaining good health and postpone the advent of complex disease. Over the past decade, advances in genetic technologies have led to the identification of more than 2,000 DNA variants that affect the risk of complex genetic diseases, such as cancers, heart disease and diabetes (Welter et al. 2013). These variants are usually anonymous SNPs, and most have a low individual impact on disease risk (Visscher et al. 2017).

The structure of the health system will influence the extent to which primary care providers are involved in precision medicine, as well as the timing of their involvement. The US National Academies report on genome editing assumes that this and other precision medicine technologies will be introduced primarily through specialists (in fields such as oncology and paediatrics), while England's Chief Medical Officer's report sees a central role for GPs, with equity of access across the system a key objective. The Australian health system accommodates a range of health-seeking behaviour: while many people consult one GP (or a group practice), many others only see a doctor for a short bulk billing consultation when ill. It may be harder to deliver the benefits of precision medicine in the context of complex diseases to those who do not have a relationship with a GP or general practice. If full benefits are to accrue from precision medicine, both for individuals and (through the use of

health records and data) the community, it may be necessary to encourage individuals to identify with and access health care through a general practice. It will be necessary to ensure that results and interpretations are available to primary care physicians and patients in a way that makes both the power and shortfalls of precision medicine clear. Education for professionals and the wider community will be essential in the Australian context. General practice in Australia is almost always adequate and often excellent, but a concerted 'education upgrade' in the values and indeterminacies of precision medicine will smooth the delivery of precision medicine information, technologies and treatments.

The value of precision medicine is already well illustrated for cancer, where the knowledge that underpins the genomics of heritable predisposition, tumourigenesis, disease progression and response to therapy provides the basis for implementing precision management. An individual's pre-existing genomic variation is a major determinant of cancer risk (along with environmental factors, such as diet, smoking and obesity). This information allows for risk stratification and optimisation of cancer prevention through rational screening. Molecular interrogation of tumours (somatic genomics) will guide medical oncologists and immunotherapists in their treatment. Combining knowledge of the patient genome with that of the tumour genome allows clinical experts to determine the best therapy for a particular patient and tumour type.

The role of precision medicine in disease prevention is broad. It is of value to individuals and their families to identify mutations in predisposition genes for multiple adult-onset diseases, such as cardiomyopathy, dementia or renal failure, where early intervention may offer markedly improved outcomes. It is important to note that, while analyses may be genetic or genomic, interventions may be environmental, behavioural or medical. There are data to suggest that supplementing clinical or lifestyle advice with 'precision omic' data can enhance compliance more effectively than advice that is non-specific to patients, in relation to, for example, statin use (Voora 2017) and weight management (Arkadianos et al. 2007). Further research is needed to understand these effects (e.g. is this a result of how patients perceive genomic data, of more contact with health professionals, or of more personalised care delivery?).

2.11.1 Complex diseases

2.11.1.1 Pharmacogenomics

In 2010, more than 14,000 adverse responses to pharmaceuticals were recorded in Australia (Health Centre for Genetics Education 2013). Unexpected responses to routinely prescribed drugs can be caused by genetic and epigenetic variations, as well as external factors, such as drug-drug interactions. Some drugs known to interact with genetic variants (e.g. statins) are widely prescribed for complex diseases such as coronary artery disease and hypertension. Combining personalised medicine approaches to dosage with data collated from large numbers of patients will allow drug-by-drug clinical trials and cost-effectiveness studies.

Pharmacogenomics predicts how an individual's genome will affect their response to certain drugs, allowing for medications to be used in ways that avoid potential adverse events or toxicity, increase clinical efficacy and reduce ineffective medical care (Figure 5). Pharmacogenomic testing is increasingly used to customise treatment with a range of medications, in both primary and specialist care contexts. Although the list of drugs for which a pharmacogenomic test can guide prescription is increasing, the implementation of pharmacogenomics in clinical practice lags behind the technology. Simple

pharmacogenomic tests are available over the counter in Australian pharmacies, although commentators have made cautionary statements about efficacy; some regulation or control may be warranted for customers who may be buying these tests without the advice of their GP.

Cholesterol-lowering and anticoagulation drugs, often used to prevent cardiovascular disease, can benefit from pharmacogenomic information. Statins are used to lower cholesterol by reducing its production in the liver. However, the *SLCO1B1* gene affects the liver's uptake of statins. A mutation in this gene has been found to change the pharmacokinetics of one statin, increasing the risk of drug-induced myopathy. Genotyping for *SLCO1B1* can be used before prescribing high doses of statins to assist with determining a safe and effective dose (Cavallari and Mason 2016). Warfarin, a widely used anticoagulant, can have different effects for patients according to two genes, *CYP2C9* and *VKORC1*, which determine the rate at which warfarin is removed from the blood (Johnson et al. 2011). Similarly, for a patient with renal failure who requires a β-blocker, *CYP2D6* gene testing may help predict their response and reduce side effects of the medication (Cavallari and Mason 2016). Combining genotype with standard patient information, such as body mass index, age, comorbidities and other medications, can make prescription practices more tailored to the individual recipient, potentially reducing side effects and wasted medical resources, while allowing suitable strategies to be determined more swiftly.

A key discovery in pharmacogenomics was made by Australian researchers, who showed that the HLA-B*5701 allele was strongly associated with hypersensitivity to abacavir, a drug that is widely prescribed to patients with HIV (Mallal et al. 2002, 2008). The FDA has since taken the position, articulated in warnings within the abacavir prescribing

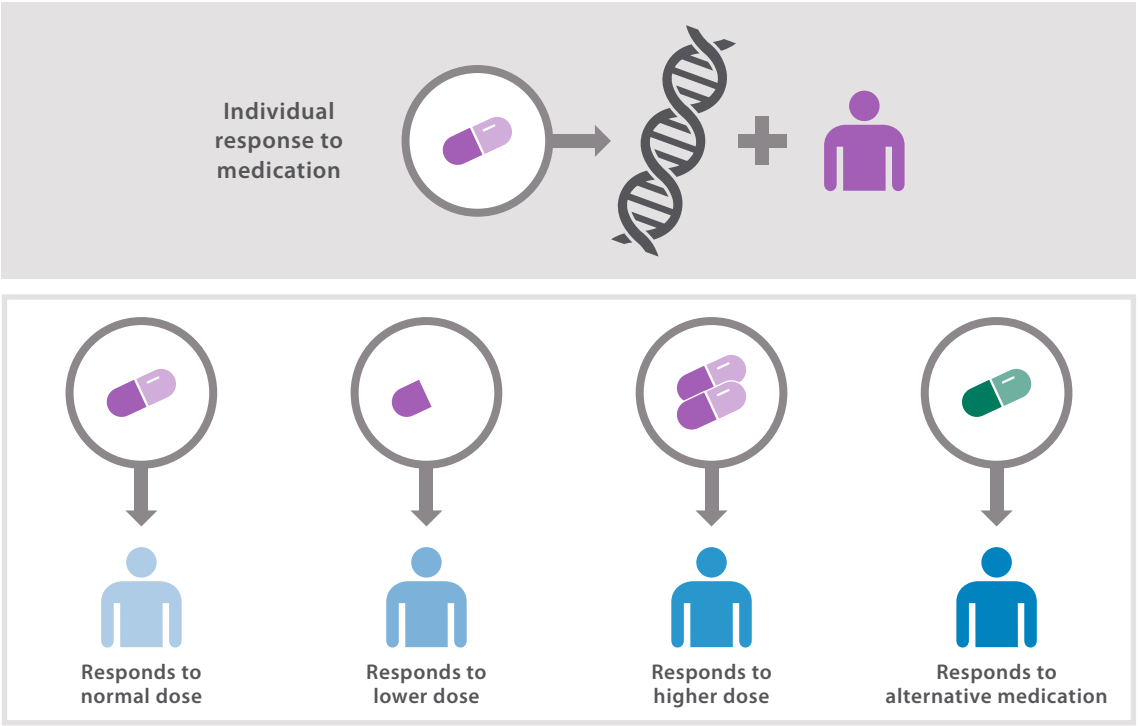

Figure 5: Pharmacogenomics provides insight into how an individual will respond to medication based on their genetic make-up

Adapted from: Alpha Genomix Laboratory 2017.

Box 9: A case study of complex disease

A 59-year-old woman with metastatic hormone receptor-positive (HER+) breast cancer was treated with capecitabine. Within a few days, she developed symptoms of toxicity, resulting in a 50-day stay in intensive care. Life-threatening toxicity may be predicted by knowledge of genetic susceptibility based on deficiency of the enzyme dihydropyrimidine dehydrogenase. Genomic sequencing showed a mutation in the DPYD gene, which explained her clinical course. Cascade testing to her extended family will facilitate a precision approach to any relatives who develop cancer, before triggering a toxic and avoidable drug reaction.

information, that screening should be undertaken before the drug is prescribed (Ziagen Prescribing Information 2008).

There are also target populations who may benefit from pharmacogenomic testing. For example, another HLA hypersensitivity is found in Han Chinese people. For this group, HLA-B genotyping is recommended before use of the anti-epileptic drug carbamazepine, as carriers of the HLA-B*1502 allele are predisposed to an adverse response known as Stevens–Johnson syndrome, which has high morbidity and mortality. It will be of particular value to ensure that vulnerable populations, such as those with Aboriginal and Torres Strait Islander heritage, are not being deprived of the full value of clinical care due to pharmacogenetic differences.

2.11.1.2 Preventing cardiovascular disease

A genetic test has been developed that is able to define a group of people who are at high risk of heart attack or stroke. Existing preventive treatments for heart disease are not completely effective, reducing risk by only 30 to 60 per cent. Large groups of people not needing interventions are treated at great cost, and a significant proportion of people at high risk go unidentified. The current gold standard for predicting heart disease risk is the Framingham Risk Score (FRS). As shown in Figure 6, the new genetic test outperforms the FRS. The data presented are based on samples collected by two large studies, FINRISK 1997 and FINRISK 2002. Researchers ran a novel algorithm over their genome-wide scan data from the studies to identify the specific genes that affect risk, together with following up on the clinical outcomes for these patients. The results for the entire FINRISK 1997 cohort were evaluated.

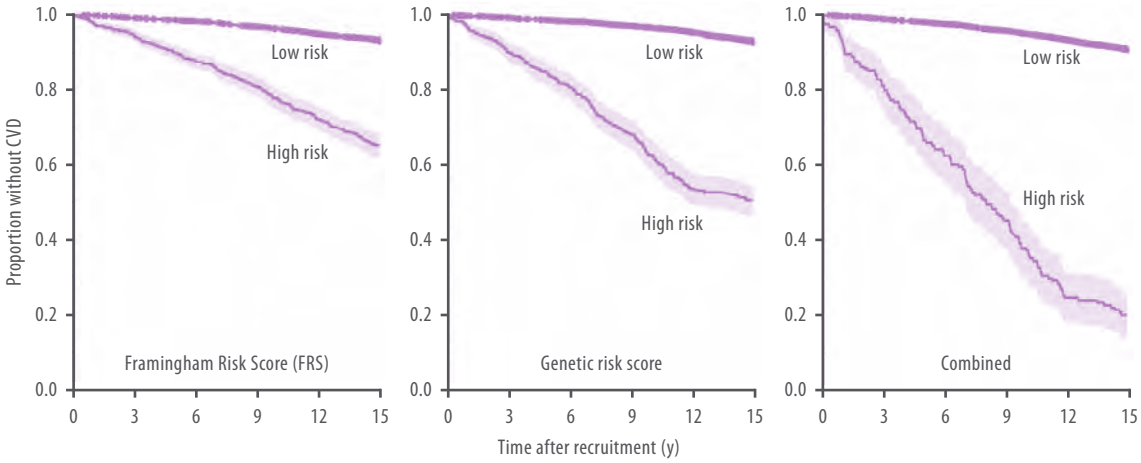

Figure 6: Framingham Risk Score versus genetic test for identifying cardiovascular disease (CVD)

Pers. Comms. Professor Grant Morahan 2017.

Other notable efforts are underway to identify novel omics biomarkers associated with heart failure (ML-Com 2014, 2017), which can be used to provide early diagnosis or to track response to medications.

2.11.1.3 Diabetes

Type 1 diabetes is a complex disease involving both genetic predisposition and environmental factors and is positioned to benefit from precision medicine insights. One study analysed genetic data from 3,348 patients with type 1 diabetes, leading to the definition of six distinct subpopulations at a 99 per cent confidence level. More than 50 SNPs that confer some risk of developing type 1 diabetes have been identified (Morahan 2012). A number of epigenetic methylation markers are likely also associated with type 2 diabetes in some populations; information which may inform risk stratification and preventive efforts (Chambers et al. 2015). The microbiome, too, may play a role in the development of both type 1 and type 2 diabetes, although 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, of course, makes diabetes an excellent example of both the potential pay-off and probable difficulties of bringing precision medicine 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 will no doubt require intensive interdisciplinary efforts.

2.11.2 Primary care considerations

Most medical treatments are currently provided to people after the onset of disease symptoms, regardless of their genetic background. As a result, people may receive treatments too late to be effective, and in some cases unsuitable treatments are administered. Genetic testing can be carried out years before disease symptoms develop, increasing the probability of finding preventive solutions and minimising harm to patients.

Precision medicine for complex diseases will be enabled by a strong health ecosystem: genomics combined with existing multidisciplinary expertise and skills, and cognisance of a patient's comorbidities and lifestyle factors. For common cancers and complex diseases, the line between 'clinical practice' and 'research' is crucial. There is likely to be a 'virtuous cycle' between **research** (discovering the genes involved in disease, understanding their function and using that information to develop effective interventions) and **clinical care** (working off an evidence base that a test or therapy is safe and effective) across complex diseases. Progress will be incremental, and it is important that the framework, expertise and infrastructure are in place to enable implementation of precision medicine in clinical practice.

2.12 Age-related disease

With an ageing population susceptible to chronic disease, Australia's health sector could do well to harness the power of precision medicine to target age-related illnesses. Dementia affects more than 400,000 Australians, and this figure is expected to pass 500,000 by 2025. The disease is the second leading cause of death and the primary cause of disability in Australians aged 65 years or older (healthdirect 2017). The most common form of dementia is Alzheimer's disease, which accounts for 70 per cent of all cases (Alzheimer's Australia 2017).

The genetic basis of Alzheimer's disease makes it a good candidate for precision

medicine interventions, and initiatives are underway around the world to apply genomic knowledge to this condition. The ApoE4 allele, found in about 14 per cent of the population worldwide, is associated with a heightened risk of developing Alzheimer's disease: about 40 per cent of patients with the disease carry this allele (Liu et al. 2013). A homozygous carrier can expect the onset of Alzheimer's disease to occur at an age about eight years younger than average, although the underlying pathways by which this variant causes disease is unclear (Mahoney-Sanchez et al. 2016). Alternative isoforms of this allele, ApoE3 and ApoE2, are only associated with a risk of one or two per cent. PET scanning for brain amyloid plaques would add further predictive power to these tests. However, these types of precision diagnostics are not routinely offered to the population, and the prospect of doing so highlights the complexities that can accompany precision medicine initiatives.

If a person is offered a test for ApoE and is found to carry the high-risk allele, ApoE4, there are not yet any medical interventions available to reduce their risk of developing the disease. Even if they test negative for ApoE, they are still at risk of other forms of dementia. Such a diagnosis should lead to thorough genetic counselling, which is a complex undertaking given that risk is known to be high but ultimately remains uncertain. The diagnosis also implicates family members through genetic heritability, potentially inducing anxiety beyond the individual patient. The results from genetic testing in these situations may make some at-risk people adjust their behaviour according to the test outcome. A further consideration is that testing widely for ApoE could produce several cohorts of people who would be eligible to participate in clinical trials for potential therapeutics. These people may be motivated to enter trials aimed at delaying onset and could be stratified into subgroups according to their genetic profiles.

As this example shows, there is not necessarily a straightforward relationship between the existence of tests for disease-causing genetic variants and the appropriate use of those tests. The decision to offer genetic information to healthy people brings with it ethical and social, as well as practical, considerations. This example also highlights the necessity of translating diagnostic advances into clinically meaningful options for patients and their care providers. At present, the Human Genetics Society of Australasia (2016) advises against ApoE testing because of these complicating factors.

2.13 Mental health

The signal advances in many medical disciplines, including oncology and cardiology, and their application in Australia over several decades have led to our health care system being regarded as one of the best in the world, alongside the UK, Scandinavia and New Zealand (Schneider and Squires 2017). Despite this overall progress – based on a combination of early intervention through population health measures, early detection of problems using imaging and other high-technology approaches, and better precision-based therapeutics – the field of mental health has remained relatively untouched. An outside observer could be forgiven for noting how little has changed in diagnosis or therapy for mental illness during the past 50 years, apart from a more sympathetic approach to patient management in the community.

Mental health disorders are a huge burden on the individuals and families affected, as well as on global health systems. Alongside substance misuse, mental health has been described as a leading source of years lost to disability (Insel and Cuthbert 2015). The WHO statistics state that, globally, close to 800,000

people die from suicide every year. Insel and Cuthbert (2015) suggest that wide-reaching improvements in health could follow from improvements in the diagnosis and treatment of mental health disorders. Is there scope for precision medicine to contribute to this?

A group of 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. Given this slow uptake, they argue that psychiatry still stands to gain considerably from the translation and uptake of promising new precision approaches (Fernandes et al. 2017). One of the reasons that psychiatry has not benefited as much as other clinical disciplines is that, in many cases, mental health disorders are not easily defined using metabolic or genetic biomarkers, imaging or other new technologies. As Insel (2014, p. 395) argues, mental health "diagnostic categories were never designed for biological validity". The relationship between disorder and gene, neuroimaging finding or metabolomic profile tends to speak to population or group changes rather than to individual cases.

However, the neurological turn in mental health signals that the discipline is open to developing new approaches. This is where the key benefits of precision medicine can be brought to bear on the problems of mental health. It will be possible to use big data approaches to integrate data from across Australia and internationally to study particular disease presentations, such as for schizophrenia or depression. These analyses must consider not only genes and how they are associated with symptoms, but also environmental factors, omics (in this case, metabolomics) and epigenetics.

Another valuable area of research is investigating the relationship between patients' genomes and drug response. Genetic differences can cause people to react differently to medication: some may respond well to a medication, while others may experience difficult side effects. If doctors were able to determine which medications were more likely to work for individuals, they could avoid the difficult and often lengthy process of trial and error that is typically necessary today. Perhaps more importantly, the data might begin to indicate important differences that suggest diagnostic subcategories. Researchers are, accordingly, exploring the potential of using genetic testing and electronic health records to individualise treatment of depression with medications. Mayo Clinic researchers in the US are using precision medicine approaches to improve medication treatment of depression, and similar studies are underway in Brisbane.

In the US, the National Institute of Mental Health already hosts genomic, physiological, imaging and clinical data (including treatment response) on nearly 70,000 people who meet the criteria for autism – a syndrome that may represent a single disorder or multiple different disorders arrayed in a spectrum-like fashion (Insel 2014). Data mining is beginning to identify links across levels, including factors that will yield categories predicting prognosis or treatment response for individual patients. This approach requires standardisation, integration and sharing of data by the scientific community, which may be uniquely sensitive in the context of mental health. In other areas of medicine, data collection has not been limited to clinicians and scientists.

Implementing precision medicine strategies in mental health will require a suite of tools that can provide more accurate diagnostic, prognostic and treatment-informing data. These, in turn, are likely to reshape disease categories and best-practice standards.

CHAPTER 3
PROFESSIONAL DEVELOPMENT AND PUBLIC ENGAGEMENT

3.1 Professional development

Successfully implementing precision medicine will require a workforce able to deliver both genomic medicine and precision medicine. These health care professionals will need knowledge and skills relating to genomics and other omics to implement precision medicine. This, in turn, will require education and training, including accreditation, for both new and established medical practitioners. This can be viewed as an opportunity for Australia to develop a leading, highly competent precision medicine workforce.

3.1.1 Literacy and the need for professional development

The need for non-genetic specialists to gain training in genomics has been discussed for more than 20 years (Collins 1997) and, despite the considerable resources that have been devoted to this area, concerns remain (Bennett et al. 2017; Talwar et al. 2017). The ability of the health care profession to keep up with the pace of precision medicine developments is a particular concern, compounded by the fact that, both in Australia and internationally, existing expertise and resources in this area struggle to meet demand for services (Australian Government 2017). Recent international literature suggests that professional development is still required to address gaps in genomic literacy and confidence or competence in requesting tests and interpreting

This chapter is based on input papers prepared by Professor Sylvia Metcalfe, Dr Amy Nisselle, Dr Belinda McClaren and Associate Professor Clara Gaff (professional development); Associate Professor Matthew Kearnes, Dr Declan Kuch, Dr Nicola Marks, Georgia Miller, Dr Wendy Russell and Dr Niamh Stephenson (public engagement); and Dr Avnesh Ratnanesan, with Daniel Damiano, Matthew Tice, Matt Riemann, Yang Jiao and Kiran Nair (consumer engagement).

Views expressed in this section do not necessarily reflect the views of these contributors.

results (Feero and Green 2011; McInerney et al. 2012; McCarthy et al. 2013; Haspel and Saffitz 2014; Alyass et al. 2015).

GPs are central to health care delivery in Australia and will require training and professional development to keep pace with advances in clinical genomics. For example, the market for direct-to-consumer genetic tests has direct implications for GPs, who may be asked by patients to interpret, or give advice based on, their results (Blashki et al. 2014). Interpretation of genetic information requires a specific set of skills and knowledge, which will necessarily need to evolve in hand with the field. It will be essential for GPs to understand the limitations of genetic information (e.g. the probability of returning false positive results) and to be able to correct common misperceptions about genetics (e.g. how genes translate into health and behaviour). GPs will also be in a position to refer patients for genetic testing and may then be responsible for managing patients' health once they are diagnosed, likely in consultation with specialists (Donoghue et al. 2017). The NSW Centre for Genetics Education operates a list of genetic referral services (NSW Government – Health 2013).

A forthcoming report from the Royal Australian College of General Practitioners is expected to explore the genomics-related needs of general practice in greater depth. Additionally, as genomics and precision medicine progress further into general practice, there is the potential for the patient-GP relationship to change; it is envisaged that there will be a need for empirical research to examine if and how this is the case.

There are also calls for clinical decision support tools (e.g. point-of-care guidelines) to be developed and made available for precision medicine (Feero and Green 2011; Mirnezami et al. 2012; McCarthy et al. 2013; Mikat-Stevens et al. 2015). It is important that health professionals see themselves as having a role to play in implementing genomics and precision medicine, and their perspectives need to be taken into account by training providers (Feero and Green 2011b). Accreditation will also assist health practitioners in delivering genomics safely and effectively. There is already a need for this, as evidenced by the uptake of SNP testing among allied health practitioners, who currently operate without robust accreditation frameworks. Establishing quality measures

also provides a path for implementing rebates, if this is justified at a later stage.

International education initiatives stem from governments, professional societies and prominent research funders (e.g. the UK's Wellcome Trust) and take the form of outreach exercises, online training courses and modules, reference resources and workshops. More formalised training mechanisms include massive open online courses (MOOCs) and traditional certificate programs (e.g. the Certificate Course in Clinical Genetics and Genomics offered by the University of Malaya and Chinese University of Hong Kong in conjunction with Baylor College of Medicine). The value of educational and professional development initiatives is highlighted in many countries' national genomics frameworks, including Australia's (at the draft stage). There is also growing expertise internationally and in Australia in the social and ethical aspects of precision medicine, which is another area that will benefit from further future investment.

3.1.2 Genomics training and education in Australia

The specialist genomics workforce in Australia includes clinical geneticists, genetic counsellors, genetic pathologists, medical diagnostic scientists and clinical bioinformaticians. A variety of pathways and resources exist to support education in these areas in Australia. A workforce survey conducted by the Australian Genomics Health Alliance found that 677 people have graduated with an Australian genetic counselling degree (Graduate Diploma or Masters), and about 150 have completed advanced training in clinical genetics through the RCPA. Most of each group are currently employed in clinical roles (67 and 97 per cent, respectively). Many of the former group (genetic counsellors) are currently not contributing to the Australian genetic counselling workforce, either because they are now based overseas (including but not limited to international students) or because they did not pursue the subsequent clinical training and certification that would permit them to practise clinically.

Clinical geneticists and genetic pathologists must have completed a medical degree, internship and residency before training through the Royal Australasian College of Physicians or the RCPA to gain a Fellowship in Clinical Genetics or Genetic Pathology. Fellows must then comply with continuing medical education requirements. **Genetic counsellors** complete a Masters of Genetic Counselling, then gain clinical employment during which they submit cases, log books, supervision reports, publications, reflective essays and evidence of continuing education to a Board of Censors, leading to certification through the Human Genetics Society of Australasia. **Medical scientists working in diagnostic laboratories** typically undertake a science or biomedical science degree, followed by a Masters or PhD. In genomic diagnostics, scientists have traditionally specialised in cytogenetics, molecular genetics or biochemical genetics, then sat Human Genetics Society of Australasia examinations in the specific discipline, followed by on-the-job training to be eligible for Fellowship examinations. From 2018, the entry point into the RCPA Faculty of Science Fellowships will be undertaking a new Master of Diagnostic Genomics while working in a genetic pathology laboratory. **Clinical bioinformaticians** typically gain an undergraduate degree in computer science or software engineering, and a Masters or PhD of Bioinformatics. This would be followed by several years' experience, with exposure to clinical work. This role and job title is not formally certified through a college or professional organisation at present.

In 2016, there were 49 genomics-specific education programs available or imminently available in Australia, ranging from formal degree programs to online courses. These are presented in Table 4 (Prichard et al. 2017). In addition to these formalised programs, many substantive programs are embedded in professional activities such as annual conferences, in the form of workshops and seminars.

In tertiary care settings, another avenue for continuing professional development is multidisciplinary team meetings, which bring together genetic and non-genetic health professionals, scientists and bioinformaticians to discuss the suitability of genomics approaches for specific patients. For example, at molecular tumour board meetings, oncology patients are triaged for appropriateness of sequencing somatic driver variants and, subsequently, prognosis and treatment options (Harada et al. 2017). The peer-to-peer, cross-disciplinary knowledge integration that occurs at these meetings is a valuable source of learning. The Royal Australian College of General Practitioners also manages a resource for GPs wishing to implement genomics, which is being modified to serve as a point-of-care tool.

It will be important to develop a cohesive national approach to education and professional development, as well as an evaluation framework to ensure the quality and evidence base of such programs. The Australian Genomics Health Alliance is currently developing the latter. There are four key challenges for this project:

- Core competencies for precision medicine must be integrated into medical schools' curricula so that the incoming workforce has the necessary skills to engage with this field.
- The genomics specialist workforce needs to enlarge to meet demand; one of the obstacles to this is a lack of resources for clinical placements.
- The role of genetic counsellors should be clarified, with respect to professional identity and recognition, actual responsibilities (e.g. ordering genetic tests) and position in the precision medicine ecosystem (e.g. employment in primary care, private practice).
- The scope for conflicts of interest to arise must be addressed, most pressingly in relation to genetic counsellors working for private genetic testing companies, and the ability of such companies to provide education to health professionals.

Category	Description	No.
Postgraduate course	Masters (two existing, three new to start in 2018–19)	5
	Graduate Diploma/Certificate or individual subjects (may be third-year undergraduate)	15
Substantive program	Substantive ongoing program (workshops, podcasts, resources, case studies) suitable for continuing professional development	27
MOOC	Massive open online course	2
TOTAL		**49**

Table 4: Genomics-specific education that are currently or soon-to-be available in Australia in 2016

3.2 Public engagement

Discussions of precision medicine, especially in the US, have stressed the need for wide-ranging engagement and participation (Blasimme and Vayena 2016). Given its potential impacts on health care, policy and expenditure, prioritising precision medicine in Australia will require a strong participatory ethos. However, there is a danger that this may become embedded in a normative precision medicine 'project' that remains unscrutinised in its broader aims. Participatory processes should be structured in ways that invite consideration of the broad implications and opportunity costs that may arise from commitments to this field. A historical perspective suggests that the formation of public health infrastructures – in Australia and globally – may be viewed as a public and political accomplishment as much as a technological one. From this standpoint, precision medicine policy could be treated as a matter of, and for, democratic appraisal.

There are three dimensions of public engagement in relation to precision medicine:

- Engaging **people as individuals** in relation to health treatments and issues (including applications, consent and privacy);
- Engaging **people as citizens** to consider the futures that precision medicine may create; and
- Engaging **people as health policy makers** to consider the place of precision medicine in broader health futures and with respect to contemporary health spending priorities.

Engagement is a generative process, with the potential to reinforce certain representations of the future, change social and professional relations and produce new identities and hierarchies. This is particularly so with 'disruptive' technologies, such as precision medicine (McLoughlin et al. 2017). Public engagement therefore needs to be done well. This will entail training experts and facilitators of engagement efforts, likely building off existing expertise from HASS disciplines. Evidence suggests that when the public is genuinely included in policy making, they are more likely to feel positive about health and health policy. However, public support should neither be taken for granted nor treated as a binary ('yes or no') condition. Ill-conceived and narrowly defined public consultations can themselves become the focal point of controversy and concern, as much as, or more than, sensitive scientific topics (Eliasoph 1998; Wynne 2006).

3.2.1 Framing precision medicine as an object of public engagement

As 'a family of approaches' to medicine and health (Blasimme and Vayena 2016, p. 173), precision medicine could affect anything from diagnosis and treatment pathways to public participation in science (e.g. crowd-sourced trials) (Hood and Friend 2011) and new forms of data creation and linkage. Aspects of precision medicine that the public may be compelled to engage with include:

- **Health infrastructure creation.** In Australia, the then National E-Health Transition Authority (now the Australian Digital Health Agency) oversaw the shift towards digital health records. Slow public uptake of the digital My Health Record (11 per cent of the population by March 2016) led to an opt-out approach. Yet, a recent Australian Digital Health Agency report shows that this limits opportunities for community engagement (National E-Health Transition Authority Ltd. 2016). Soliciting engagement

with similar infrastructural elements of precision medicine could make these more acceptable, functional and widely used. A more successful example of local engagement with precision medicine infrastructure occurred in Western Australia. Two four-day deliberative forums were held on the topic of biobanking: one for genetic support group members and another for a randomly stratified sample of the Western Australian public. 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).

- **Transformations in workforce training and job specifications,** which may in the future entail handling and interpreting data so complex that artificial intelligence plays a role (National E-Health Transition Authority Ltd. 2016). Meaningful engagement with the future of the workforce will be crucial to creating health futures that promote trust and serve all Australians.
- **The public health system,** its role in developing precision medicine expertise and the extent to which private parties are involved in systems use and design. When the UK's NHS provided 1.6 million patient records to Google DeepMind to assist with app development, the Information Commissioner's Office deemed this a breach of UK privacy law. This is another example of how neglecting the interests of citizens can undermine the functioning of the health system.
- **Decisions about how to allocate benefits of data sharing,** particularly from national records. In the UK, health data have been treated as a public asset, the value of which should be acknowledged and valued (Bell 2017). Members of the public are likely to have strong and valuable opinions on matters of data sharing and management.
- **Regulation development** more widely.

In short, precision medicine is driving a shift not only in immediate medical care but also in the collaborative research, development, design and delivery of health care systems. This change calls for a 'new philosophy of collaboration and trust: underpinning relationships between government and industry' (Bell 2017, p. 5). This new philosophy needs to emerge from social deliberation and engagement, if it is to contribute to building a social licence for precision medicine.

Box 10: Key Australian precision medicine engagement initiatives

The Australian Genomics Health Alliance operates a 'Genomics in the Community' project, centred on patient education and information and professional ethics consultation.

The Australian Law Reform Commission's *Essentially Yours* report followed multiple public forums, targeted stakeholder meetings, international meetings, written submissions and various forms of media dissemination.

The Australian Digital Health Agency runs a 'Conversation' portal that solicits public opinion on topics related to digital health services.

3.2.2 Engagement issues with precision medicine

Public engagement initiatives range from rethinking medical expertise from the 'bottom up' through to 'top down' public deliberation and outreach (Woolley et al. 2016). A lack of clarity regarding the aims of public involvement – who is engaged and to what ends – is discernible in some precision medicine and health data initiatives. For example, 'care.data' was an NHS effort that involved overriding the Data Protection Act to make NHS patients' data accessible without their permission for non-medical care-related uses, such as research (Woolley et al. 2016). The project met with public backlash, particularly regarding concerns that re-identifiable data may end up in the private sector (Carter et al. 2015; Woolley et al. 2016). The US Precision Medicine Initiative is also instructive, highlighting the danger in assuming that public engagement will lead to unquestioning public acceptance. This initiative embeds a participatory approach that has been key to ensuring its political support (Blasimme and Vayena 2016), but this has received a great deal of scrutiny with regard to its inclusiveness and broad public mandate (Bonham et al. 2016; Juengst et al. 2016; Newkirk II 2016; Woolley et al. 2016; Reardon 2017).

Beyond formalised 'invited engagement' (e.g. through surveys and consultative forums), patient and citizen engagement and new social relations may emerge in five areas:

- **Patient 'responsibilisation'.** Precision medicine and the associated empowerment rhetoric highlights personal responsibility as increasingly central to health (Blasimme and Vayena 2016). This responsibilisation is part of a broad devolution of power from government to citizens (Shamir 2008) and can give patients more say in their health, but it must not come at the expense of good care (Trnka and Trundle 2014).
- **Consumer devices and sensors** are often imagined as vehicles for this shift in power relations. Researchers at the University of California San Diego foresee a transformation in health care based on technologies such as the Apple Watch (Topol 2016), while also warning of potential market power issues (Wilbanks and Topol 2016). How these devices will fit with precision medicine, including whether they should be considered medical grade, is yet to be seen.
- **Data sharing and commons.** New data repositories with novel forms of access and governance will be central to precision medicine. The creation of a data commons is a central theme of the US National Research Council's report (2011) that prefigured the US Precision Medicine Initiative. These initiatives are important to public engagement insofar as they promise that patients' shared data will benefit society more widely. A related concern is the privatisation of such data by parties who can then 'trade people's disease profiles … or aggressively market health-related services to people regardless of whether those services actually benefit their health' (Wilbanks and Topol 2016). The potential impacts and importance of large-scale health data suggest this is likely grounds for engagement.
- **Justice.** There are concerns that precision medicine will inflame rather than reduce racial health injustices, perpetuating mistrust between minorities and state health agencies (Bonham et al. 2016). The regular canvassing of these issues by the media, academics and advocates is a form of civic engagement that may be described as 'uninvited engagement'.

3.2.3 Lessons from public engagement with emerging and health technologies

Past public engagement efforts have succeeded in engaging diverse groups in shaping policy and regulation, while others have alienated citizens and resemble mere lip service. Precision medicine must not be rushed into use, not least because it has the potential to cause controversy. Resistance to genetically modified organisms (GMOs), particularly in Europe but also in parts of Australia, shows that the public do not automatically adapt to or adopt new technologies upon introduction (Einsiedel and Goldenberg 2004; Kearnes et al. 2006). A similar lesson arose in Australia and the UK from e-health records, towards which patients and professionals were unexpectedly ambivalent (Baines et al. 2014; Aitken et al. 2016; McLoughlin et al. 2017). These unsuccessful efforts are often thought to result from misunderstanding, the inference being that support would follow from increased or better education. This 'deficit model' of public understanding (Wynne 2006) has been strongly critiqued; there have been calls instead for better *engaging* with a range of groups (Hagendijk and Irwin 2006; Felt and Wynne 2007; Delgado et al. 2011; Stilgoe et al. 2014; Marks 2016).

The timing and sentiment of engagement is crucial. This work must be genuine and not tokenistic if it is to avoid alienating people (Wynne 2005; Kearnes et al. 2006). It should occur upstream during development rather than right before a technology is ready to launch (Einsiedel and Goldenberg 2004; Joly and Kaufmann 2008; Felt et al. 2009). It should also 'open up' (Stirling 2008) questions about the desirability of a technology, how it might fit with existing practice, how it might disrupt ethical and professional norms, how it should be regulated and by whom, how it might affect existing inequalities and what work would be sacrificed if a given technology went forward (Garrety et al. 2014; Wynne 2014; Fan 2015; Soulier et al. 2016).

Evidence suggests that people want to influence the research, implementation and governance of technologies; a recent survey indicates similar sentiment about precision medicine (Scheufele et al. 2017). Indeed, there are companies in the US selling or crowd-sourcing access to research tools with the promise of updates and continued information. The outcomes of engagement (e.g. passive public support) should thus not be pre-empted (Epstein 1996; Sandler and Kay 2006; Callon and Rabeharisoa 2008; Corrigan and Tutton 2009; O'Doherty et al. 2011; Nicol and Critchley 2012). Trust-building is central, and trust is not an automatic outcome of engagement (Stranger et al. 2005; Wynne 2006; Bates et al. 2010; Marks 2011; Carter et al. 2015; Aitken et al. 2016; Salter and Salter 2017). Rather, engagement is a process: a commitment to openness and listening, rather than a one-off event.

3.2.4 Opportunities for public engagement

Meaningful democratic involvement of the community in decisions about precision medicine requires engaging with people across all three of the dimensions noted above (as individual patients, as citizens and as health policy makers). Deliberative methods – citizens' juries, deliberative and multicriteria mapping, planning cells, deliberative polling and consensus conferences (Stirling and Mayer 2001; Burgess et al. 2007; Dryzek 2010; Mansbridge et al. 2012) – enable engagement with questions about the societal dimensions of new technologies. They accommodate diverse views, shift participants from a role as consumers to that of citizens, and bring a public interest lens to bear on the benefits,

risks and opportunities of a given issue (Hagendijk and Irwin 2006; MacLean and Burgess 2010).

Citizens' juries have been used in Australia (Russell 2013), but the method's focus on reaching a verdict can limit how nuanced and wide-ranging the preceding debate can be. **Consensus conferences** are better suited to complex issues such as precision medicine. These have been used in many countries, particularly to explore GMO foods, and, in some cases, have directly informed regulation and innovation (Joss and Durant 1995; Joss 1999; Sclove 2000; Dryzek and Tucker 2008; Laurent 2009). A similar form of deliberative democracy was trialled in Tasmania, in which a group of citizens were engaged in deliberation over biobanking; the exercise resulted in concrete suggestions for the design and management of the biobank and a high degree of acceptability for those involved (McWhirter et al. 2014). Though not yet tried in Australia, **technology assessments** offer an integrative approach to considering more fully and democratically the societal aspects of emerging technologies (Felt et al. 2009; Hennen and Nierling 2014). This approach resonates with 'Responsible Research and Innovation' approaches, which interweave public engagement with scientists' and decision makers' analysis, anticipation and reflexivity (Stilgoe et al. 2013; Guston 2014; Chilvers and Kearnes 2017). A further deliberative strategy tested in Australia was a citizens' parliament, which brought together 150 citizens from across the country to debate how democracy in Australia could be improved (Chaney and O'Donoghue 2009). Although not related to science or medicine, the exercise provides another potential model for future engagement processes. Challenges to future public engagement efforts include the obfuscating and trust-eroding effects of hype and a lack of understanding (within but also beyond the scientific community) of the societal implications of precision medicine.

Citizens give reasonable and useful answers, even about highly technical topics, when asked sensible questions (Fischer 1999; Burgess 2014). Thought needs to be given to where democratic and technological imperatives meet values and technologies (Felt et al. 2009; Korthals 2011; Laurent 2017). This means beginning with a sophisticated understanding of the social, moral and political dimensions of innovation so as to have a nuanced conversation about what precision medicine might and should look like (Kerr et al. 2017). This kind of engagement goes beyond success stories to consider what success looks like for society as a whole. These conversations must address equity, not as an ethical side effect or risk of precision medicine, but as a precondition of its use and a determinant of how much public funding and policy support the field should attract (Bayer and Galea 2015).

The promises made for precision medicine imply a significant reordering of relations in health care: the way patient citizens, medical experts and private sector suppliers relate to each other is shifting. This requires a participatory ethos that can consider questions of purpose, responsibility and the opportunity costs of investing in precision medicine. A comprehensive participatory approach would also involve the wider public in discussions about the objectives of health policy and the envisaged place of precision medicine in addressing the nation's health: who cares for whom, and how?

Box 11: A model of consumer engagement

The 6E engagement model (Figure 7) derives from the notion that value is increasingly something co-created between system actors and consumers (here, patients) who desire a more active role in their health. In such a context, consumers exercise more choice and control over how health services are delivered, and public trust in traditional institutions may erode. There is an affinity between this shift and the offerings of precision medicine. The 6E framework encompasses key methods of consumer engagement and patient experience, and it can be used to think through public engagement in the health sector (Ratnanesan 2017).

E1. Experience describes the need to define current health sector experiences against a precision medicine backdrop. Key considerations will be the costs of accessing health care, the social value placed on the Australian health system as this relates to the quality of care, and opportunities for participation in clinical research as new medical developments unfold.

E2. Emotions highlights the person-centred frustrations and delights in individual and population health care. There is an appetite for precise medical techniques to be matched by more personalised care and relations between patients and health care providers (Budin-Ljøsne and Harris 2016).

E3. Engagement entails taking seriously the participation of consumers in planning around precision medicine foci and conduct. Engagement can include varying distributions of power, ranging from consultative to participatory to partnership models. All should involve two-way dialogue.

E4. Execution turns a focus to policy development considerations and technology implementation. Uptake of precision medicine technology may differ among practitioners and between the medical community and patients. Policies must be designed to accommodate technological change.

E5. Excellence emphasises the need for clarity on target outcomes, including patient health outcomes, standards of care and the safety and efficacy of specific precision medicine techniques.

E6. Evolution prompts for reflection on how proactively precision medicine should be taken up in Australia. Online platforms are already engaging consumers (e.g. direct-to-consumer genetic testing).

The 6E framework can be used to ensure that patients' needs are being met by precision medicine as effectively as possible and to emphasise the interconnectedness of different groups and practices in the broader landscape of precision medicine.

(Energesse 2017)

Figure 7: The 6E Framework for consumer engagement outlines six steps for engaging consumers in health science advances

Adapted from: Energesse 2017.

CHAPTER 4
SOCIAL AND ETHICAL IMPLICATIONS

4.1 Thinking 'ethically' about precision medicine

Precision medicine has significant potential to improve the lives of individuals and populations, but 'targeted therapies' can be expensive, have serious adverse effects and are not always as effective as hoped. It is crucial, therefore, that the right targeted therapies are developed, and that these are tested, regulated, funded and used in practice in the right ways. However, it is not always easy to determine what is right because precision medicine affects, and is shaped by, many different stakeholder groups – including patients, clinicians, government and industry – each of which has its own, often strongly held and competing, concerns and commitments. Managing these interests, and identifying and acting on the challenges of precision medicine, will require the focus of ethicists, social scientists, and humanities scholars, who can engage the complexities of a changing medical field.

In each case, these perspectives are underpinned by values such as autonomy (which, in this context, usually refers to self-determination), beneficence (doing good), non-maleficence (not causing harm), justice, solidarity and integrity. People also value the pursuit of knowledge and the social benefits that derive from scientific inquiry. In this chapter, the ethical issues raised by precision medicine are summarised, with reference to such values and ideas. The aim is not to fully articulate stakeholders' perspectives or to provide answers to ethical dilemmas, but to map the moral territory of precision medicine. This chapter focuses on the ethics of the development, regulation, funding and clinical use of targeted therapies developed using genomic technologies.

This chapter is based on input papers prepared by Dr Wendy Lipworth and Professor Ian Kerridge. The chapter also includes material on regulation drawn from an input paper prepared by Professor Dianne Nicol and Professor Margaret Otlowski.

Views expressed in this section do not necessarily reflect the views of these contributors.

4.2 Ethics of developing and testing precision medicine

4.2.1 Identification of therapeutic targets

There are numerous ways in which potential targets for precision medicines can be identified, and each raises its own set of ethical issues. When cell, animal or embryonic models are used to identify genes and proteins that contribute to disease, the ethical issues that arise are similar to those raised by any kind of laboratory research (including animal welfare, the moral status of embryonic material and research integrity). More often, however, potential targets for precision medicine are identified by finding patterns in the DNA, RNA or proteins of diseased and normal human cells that may provide information about the cause, expression, prevention and treatment of disease.

This kind of 'molecular epidemiology' requires many hundreds or thousands of tissue samples. The collections of such samples are usually referred to as biobanks. Although these samples can theoretically be completely anonymised, analysis is most productive if samples are linked to data about the donors' exposure to risk factors, disease progression and treatment responsiveness. For the purposes of this chapter, collections of tissue and linked data are referred to as 'databanks', and the research that they facilitate will be referred to as 'databank research'.

4.2.1.1 Ethics of databank research

The collection, storage and use of human tissue and data for research purposes raises numerous ethical issues. Key among these are how to obtain consent for the storage of samples and their use in unspecified future research; maintenance of donors' confidentiality; interpretation and management of incidental findings;

ownership and control of tissues; acknowledgement and management of cultural sensitivities; reporting of results; community participation; benefit sharing; return of materials to communities; and disposal of unused material (Lipworth 2004; Lipworth, Ankeny and Kerridge 2006; Lipworth, Forsyth and Kerridge 2011; Morrell et al. 2011). The need to link tissue and data from different sources creates further ethical and regulatory challenges, particularly related to consent, privacy, custodianship and data sharing (see also Chapter 6).

Box 12: Relevant laws and guidelines on databanks

At present, no legislation in Australia explicitly deals with databanks; therefore, most databanks have their own policies and procedures. These databanks must, however, comply with Australian laws regarding, for example, consent, privacy and human tissue, or they risk prosecution. In addition, the NHMRC's *National Statement on Ethical Conduct in Human Research* (henceforth National Statement) and the *Australian Code for the Responsible Conduct of Research* provide important ethical and legal guidance for HRECs overseeing databank research.

4.2.1.1.1 Confidentiality and privacy

Although participants in databank research are subjected to only minor physical risks (e.g. those associated with blood collection), they do face the risk of their data, including that derived from tissue samples, being accessed by unauthorised parties. In this regard, it is worth noting that insurance companies can demand that applicants disclose genetic results derived from research, notwithstanding that such results are typically not generated in accredited testing laboratories (see Section 4.4.1.1, Confidentiality and discrimination).

As databanks become larger and more extensively linked, there is a greater need to protect confidentiality and greater challenges associated with doing so. This is partly for practical reasons and partly because of a blurring of distinctions, such as those between health-related data and non-health-related data, personal and non-personal data, identifiable and anonymous data, individual and group-level privacy, and 'primary' and 'secondary' uses of data. These distinctions often form the basis of policies and regulation regarding confidentiality (Lipworth et al. 2017).

It is important to bear in mind that informational norms are shifting, and many people now freely share highly personal data that can be used for research – for example, through social media platforms. At the same time, privacy advocates are fighting for more stringent data protections. It thus remains to be seen what the norms for data sharing and secondary uses of personal data will be in years to come (Lipworth et al. 2017; Schadt 2012).

Box 13: Relevant laws and guidelines on confidentiality and privacy

As a form of 'sensitive information', health information is given enhanced protection under the *Privacy Act 1988* (Cth) (Australian Commonwealth 1988), as is genetic information about an individual that is not otherwise health information. This translates into specific requirements for research, which the NHMRC National Statement outlines. According to the National Statement, it is up to individual databanks to justify whether to make samples or data identifiable, re-identifiable (coded) or non-identifiable. The National Statement is, however, explicit that 'with advances in genetic knowledge and data linkage, and the proliferation of tissue banks of identified material, human tissue samples should always be regarded as, in principle, re-identifiable' (2007, p. 27).

4.2.1.1.2 Consent

Obtaining consent from research participants is one of the key ways in which biomedical researchers demonstrate respect for the participants' autonomy. It is now broadly accepted that for tissue and data to be used in research, participants' consent is required. Models of consent that are generally deemed acceptable include:

- Project-specific consent, in which participants are approached each time their tissue or data is used;
- Categorical consent, in which individuals specify which uses of their specimens and data are acceptable and which are not (e.g. people might consent to only certain types of research, to research in particular settings or to research conducted by particular researchers); and
- Open-ended consent, in which participants allow researchers – under the guidance of ethics committees – to determine how tissues and data might be used.

Many kinds of precision medicine research will work off the same models of consent as existing forms of experimental research. However, obtaining informed consent for databank research is complicated by:

- The challenges of obtaining consent from large numbers of research participants across a large number of institutions;
- The fact that tissue and data are often collected for unspecified future research purposes, making it necessary to consider whether consent can be open-ended or whether participants need to have more control; and

Box 14: Relevant laws and guidelines governing consent

Australian privacy legislation, at both the federal and state levels, requires biobanks to ensure privacy in the collection, storage, use and release of, and access to, personal information. As health data and genetic information are 'sensitive personal information' according to the Privacy Act, it may only be collected with consent, except in specified circumstances. The *Human Tissue Act 1983* (NSW) and associated directive state that tissue can only be collected after donors have given written, revocable consent. This consent does not need to be project-specific.

The NHMRC National Statement asserts that consent to databanking should be in writing, voluntary and given after participants have been provided with explicit information and opportunities for further explanation. In addition to being informed about the research, potential participants need to be told about their right to withdraw (including any limitations on this right), the potential for commercial application and distribution of benefits, and conflicts of interest of anyone engaged in collecting, processing, storing or distributing research materials.

The National Statement requires HRECs to approve the consent procedures to be used before samples can be collected. It also requires participants to be informed if any changes are made to the use of their tissue or data after consent has been obtained. Research participants should be free to withdraw without needing to give any reasons for their decisions.

With respect to the various levels of consent, the National Statement says that consent may be 'specific', 'extended' (to closely related projects or projects in the same general area of research) or 'unspecified' (given for the use of data or tissue in any future research). The National Statement is explicitly supportive of open-ended consent, provided there is clarity about the justification for such consent and about any restrictions that apply.

- The fact that tissue and data used in research are often collected for non-research (clinical or administrative) or even non-medical (e.g. social media) purposes using a wide variety of more or less consistent and adequate consent mechanisms (Axler et al. 2008; Lipworth, Ankeny and Kerridge 2006; Lipworth et al. 2009).

While consent is a central legal and moral principle, public opinion seems to support the view that respect for autonomy is not absolute and that the potential contribution to public wellbeing of scientific research may be sufficiently great to allow consent not to be sought if specific criteria are fulfilled (Lipworth, Forsyth and Kerridge 2011).

Questions about consent become more ethically complicated when the tissue or data that are being used for research are collected in the course of clinical care and stored in, for example, pathology laboratories, electronic health records or administrative databases. The data generated in this way are often referred to as 'real-world data', and their use in research is seen to be at the core of so-called learning health care systems, in which clinical, administrative and research activities are intimately intertwined (Lewis, Lipworth and Kerridge 2017). While there is no a priori reason that consent requirements should be any different in this context, it is increasingly recognised that the need to obtain explicit patient consent for the use of

Box 15: Relevant laws and guidelines on exceptions to consent

Guidelines on exceptions to the consent requirement are found in sections 95 and 95A of the Privacy Act. The guidelines stress that a person's right to privacy can be waived when the public interest in research activities substantially outweighs the public interest in the protection of privacy. This may, for example, be because databanks already exist for which no consent has been obtained or because obtaining consent prospectively would be too onerous.

HRECs are responsible for determining, on a case-by-case basis, whether such waivers should apply. Although HRECs are not bound by previous decisions, some consistency is encouraged by the NHMRC National Statement, which provides clear criteria for opt-out processes and waiver of consent. Factors that need to be taken into consideration include:

- The risk to participants;
- The potential benefits of the research;
- The existence of mechanisms to protect research participants' privacy and the confidentiality of data;
- The likely significance of consent bias if consent requirements are imposed;
- The existence of a plan for returning clinically significant results; and
- The existence of clear governance processes and consistency with state, federal or international law.

When researchers want to allow participants to opt-out of participation in research, they need to show that they will supply adequate information about the opt-out process and adequate time for participants to decline. When researchers wish to seek a complete waiver of consent, they must demonstrate that participants would likely have consented if asked, show that commercial exploitation is unlikely and have a plan for making research information available to participants.

routinely collected clinical or administrative data in research can be resource-intensive. It can also lead to biases as a result of differences between consenters and non-consenters, such as those related to gender, socioeconomic status, or health status. The question of whether, when and how consent should be obtained for secondary research use of clinical and administrative data is still unresolved (Ioannidis 2013; Kaplan 2016).

Box 16: Relevant laws and guidelines regarding research on clinically collected specimens

The NHMRC National Statement notes that, where human biospecimens have been obtained for clinical purposes and have since been retained by an accredited clinical pathology service, the biospecimens may be used for research purposes if they been anonymised or, if identifiable, a waiver of consent has been obtained by the researchers wishing to use the sample.

A common theme in discussions of consent to databank research is that there is an urgent need for new models of consent. Proposed alternatives include dynamic consent – a form of project-specific consent that makes use of web-based platforms (Kaye et al 2015), meta consent – where people specify what kind of consent they would like to give for particular kinds of future research (Ploug and Holm 2015), and portable legal consent (where people donate data for research after signing a standardised consent form, and users sign a contract regarding compliance with particular data use provisions) (Schadt 2012). Alternative methods of governance, such as participatory governance, in which tissue and data donors are direct participants in research governance and engage in collective decision making, are also being explored (Dove, Joly and Knoppers 2012; O'Doherty et al. 2011).

4.2.1.1.3 Incidental findings

Databank research can produce incidental findings that are not directly related to the research question being asked but may have clinical significance. Because research laboratories are not subject to the same quality standards as clinical laboratories, the quality and clinical significance of these findings can be uncertain.

Box 17: Relevant laws and guidelines regarding the right not to know one's information

Privacy laws give individuals the right to know what information is being held about them. In the context of genomics, the right *not* to know is also increasingly recognised to be important. There is not yet any resolution to the question of whether this right not to know can or should be enshrined in law.

The NHMRC National Statement says that information about return of results and incidental findings needs to be part of consent. In recognition of the moral and scientific complexity of deciding whether results should be returned, the National Statement does not demand that criteria be fully specified in advance, but that researchers should have an 'ethically defensible plan' in place. The National Statement declares that 'whenever research using re-identifiable data reveals information that bears on the wellbeing of participants, researchers have an obligation to consider how to make that information available to the participants' (2007, p. 28).

Box 18: Relevant laws and guidelines pertaining to data custodianship

The NHMRC National Statement does not discourage data sharing but does note that 'some uses of data in a databank may be detrimental to people to whom the data relate. Researchers and/or custodians should consider denying or restricting access to some or all of the data for those uses' (2007, p. 29).

There have recently been several inquiries and public consultations on big data in Australia, which suggest that Australia is moving towards a system that is more supportive of data linkage and sharing. For example, a Senate Select Committee on Health recently recommended streamlining data linkage across federal and state health data sets; reviewing privacy regulation and legislation to improve access to de-identified MBS, Pharmaceutical Benefits Scheme (PBS) and other Commonwealth data; and normalising data sharing and open access to de-identified data (Parliament of Australia 2016). A Productivity Commission inquiry recommended 'fundamental and systematic changes … to the way Australian governments, business and individuals handle data', including a new Data Sharing and Release Act; a new National Data Custodian; a suite of sectoral Accredited Release Authorities; broad access to National Interest Data sets; and (of particular relevance to health-related data) new arrangements for higher-risk data to be shared with trusted users (Australian Government 2016).

4.2.1.1.4 Data sharing, control and custodianship

Because databank research involves the long-term storage of data and tissue, these resources can be used repeatedly, and decisions need to be made about who should be able to access the data and material and for what purposes. Although it may be ideal, in terms of autonomy, for research participants to make these decisions on a case-by-case basis, this would require project-specific consent, which is not always feasible or desirable for the reasons described. This brings to the fore the importance of appropriate governance of databanks, including appropriate custodianship of tissue and data (Lipworth et al. 2017).

4.2.1.1.5 Commercialisation and benefit sharing

In part because it is so expensive, databank research is a 'mixed economy', funded and controlled by both public and private entities. While privately funded databanks are not necessarily less ethically robust than publicly funded banks, private control and funding inevitably change the nature of relationships between data donors and custodians (moving away from fiduciary relationships based on trust and professionalism and towards commercial models). Commercialisation also makes it less likely that tissue donors and their communities will benefit from the products of the research (Lipworth et al. 2017).

Box 19: Relevant laws and guidelines regarding rights to tissue

Australians currently do not have property rights in their own tissue, but tissue becomes property when work and skill is applied to it. The legal argument has been made that this misconstrues the research relationship, which is not a therapeutic (consent-based) relationship but a gifting relationship. In this context, consent is an insufficient way of managing the relationship because it fails to account for the realities of, for example, benefit sharing and intellectual property (Stewart et al. 2014).

4.2.1.2 Networking and globalisation of databanks

All the ethical issues discussed above become more complex as databanks become more networked, including across national and international borders. The networking of databanks increases their statistical power, facilitates the sharing of resources and expertise and minimises duplicated investment, but also creates numerous ethical challenges. For example, networking data across national boundaries makes it more difficult to obtain consistent consent from research participants and to ensure that confidentiality is maintained. This kind of networking can also challenge community values, such as trust, custodianship, benefit sharing, equity, respect for cultural difference and individual or community control over the use of tissue and information – values that may be particularly salient to Indigenous communities (Hoeyer 2012; Lipworth et al. 2017; Mason, Lipworth and Kerridge 2016a; Mason, Lipworth and Kerridge 2016b; Smith 2011).

Box 20: Relevant laws and guidelines on international use of samples and data

Biospecimens obtained for research in Australia can be sent overseas for research. HRECs are expected to either approve overseas research projects individually or be satisfied that the tissue will be used in a manner consistent with the original consent. According to the NHMRC National Statement, consent to biobanking needs to include 'whether their biospecimens and associated data may be distributed to other researchers, including those outside Australia' (2007, p. 38).

The National Statement specifies that international samples and data can only be used in Australia if they have been collected in a manner consistent with requirements described in the National Statement and relevant Australian legislation. In addition, the *Australian Code for the Responsible Conduct of Research* states that researchers supported by Australian public funding should make every effort to comply with Australian policy when conducting research outside Australia. Any deviation from the Code must be submitted for institutional approval.

4.2.1.3 Big data research

Although big data research increases the capacity to make fine comparisons, identify rare events, deal with population variability and, in so doing, identify potential molecular targets for multifactorial diseases, it also exacerbates ethical concerns associated with databank research (Lipworth et al. 2017). With respect to privacy, for example, big data analytics have reached a level of sophistication that makes it impossible to

promise complete anonymity, even if all identifiers are removed from a particular segment of data (Scaiano et al. 2016). Data are also collected continuously, in bulk, in a granular form, and are acted on rapidly, which can increase both the likelihood of, and risks associated with, loss of confidentiality (Erdmann 2013; Frizzo-Barker et al. 2016; Schadt 2012; Terry 2012).

Dilemmas regarding return of incidental findings are also magnified in the context of big data research, which is more likely to generate incidental findings simply because of its scale. Matters are further complicated by questions about the validity, reliability and utility of the results of big data research (including, but not limited to, incidental findings). For example, information on genomic variants may be of unknown clinical value, and clinicians and patients could be liable to misread its importance, potentially leading to poor clinical decisions (Fischer et al. 2016; Manrai, Ioannidis and Kohane 2016; Shoenbill et al. 2014). Further, participants' ability to control their data and withdraw from research is complicated by the challenges of erasing or 'forgetting' big data (Newman 2015).

There are also technical challenges associated with the analysis of big data. Some of these are well-recognised statistical challenges that apply to any kind of observational research (e.g. managing biases and confounding factors), but others relate specifically to machine learning and other emerging big data analytics. Importantly, these technical issues have ethical implications. For example, the complexity of analytical models and predictive algorithms may limit the capacity for the public, and even experts, to interpret or question research findings, which may lead them to act on false predictions (Dereli et al. 2014; Fischer et al. 2016; Vayena et al. 2015). People may also lose sight of ethically important contextual nuances that are obscured by big data analyses (Boyd and Crawford 2012; Busch 2014; Mittelstadt and Floridi 2016).

4.2.2 Clinical trials of targeted therapies

Once a potential target for a precision medicine has been identified and a corresponding drug has been produced, it is necessary to assess its safety, efficacy and cost-effectiveness. For common diseases, or rarer diseases in which most or all patients express the relevant molecular target, clinical testing follows the same path – and raises the same ethical issues – as that used to generate evidence about any other therapy. In many cases, however, clinical trials of targeted therapies are complicated by (among other things) the rarity of the disease or molecular target, the need to simultaneously test therapies and companion diagnostics, and the ethical imperative to allow biomarker-positive patients to crossover to active treatment if their disease progresses during a trial. These challenges make it difficult to generate robust evidence of efficacy and safety and to generalise the findings of trials to patient populations (Lewis, Lipworth and Kerridge 2014; Lewis et al 2013).

In response to these challenges, the traditional phases of clinical research are becoming increasingly blurred, and new study designs – such as double randomisation, single arm studies, *n*=1 studies and adaptive and pragmatic trials – are being devised. While these trials are believed to be ethically advantageous in some ways (e.g. better accommodating clinical equipoise and informed consent, and reducing patients' chances of being exposed to suboptimal treatment), they raise their own ethical issues (Hey and Kimmelman 2015). It is beyond the scope of this chapter to consider the ethics of these emerging trial designs in detail, but

one key issue is that there may not be a state of genuine equipoise when patients enter trials (that is, those conducting trials may not be entirely agnostic as to whether patients are likely to benefit from the intervention being tested) or studies may continue beyond the point at which equipoise has been lost. A related ethical issue is that many patients enter these trials not only to contribute to research, but as a means of gaining access to targeted therapies. This turns on its head the ethical assumption that patients need to be disabused of any 'therapeutic misconception' when they decide to participate in research (Meurer, Lewis and Berry 2012).

4.2.3 Observational studies of targeted therapies

New clinical trial designs go only part of the way to solving the problems of evidence generation for precision medicine and, as a result, there is an increasing emphasis on evaluating targeted therapies in the real-world using observational research. As these kinds of studies require collections of data about safety and efficacy, the ethical issues they raise are essentially the same as those raised by databank research. The susceptibility of individuals' health data to breaches of privacy raises key ethical issues about collection, storage and linkage practices, as described in Section 4.2.1. Although in both settings the data used in research might be collected primarily for research purposes or for other – such as clinical or administrative – purposes, clinical studies of targeted therapies almost invariably entail the secondary use of data collected for clinical or administrative purposes. In this context, consent bias can be a major problem, where studies seek to assess the survival of a group of patients for future comparison with newer treatments in similar clinical settings. Assessment of survival is also likely to be confounded if data can only be collected from living patients. Although surviving relatives may assist with data collection, this can be challenging for logistical and emotional reasons (Lewis, Lipworth and Kerridge 2017).

4.3 Ethics of regulating and funding targeted therapies

4.3.1 Regulatory challenges

The challenges associated with generating evidence about targeted therapies affect not only clinical researchers but also regulators, who need to determine whether these therapies are sufficiently safe and efficacious to justify market entry. The key questions here are whether, and to what extent, usual standards of evidence – based on large Phase III randomised trials – should be adjusted for targeted therapies.

As long as these standards remain in place, patients seeking access to targeted therapies either need to rely on their clinicians to prescribe such therapies off-label or seek compassionate access from pharmaceutical companies. While these mechanisms provide much-needed access to targeted therapies for some patients, they raise their own ethical issues in that they tend to be ad hoc, inequitable and, in many cases, driven more by compassion and desperation than by evidence (Ghinea, Lipworth and Kerridge 2015; Lewis, Lipworth and Kerridge 2017; Lewis et al. 2014).

In part as a response to the problems with off-label prescribing and compassionate access, there is currently a large push internationally for accelerated regulatory approval of targeted therapies, whereby regulatory standards are reduced to facilitate timely market entry. The problem with such

programs is that they generally create a disincentive for companies to gather high-quality, standardised data and for patients to participate in trials. This is not just an epistemic issue but also a moral one because it compromises the altruism and social solidarity that form the basis for participation in research. It also has the long-term effect of creating sustained uncertainties and placing patients at risk. In this regard, it is morally significant that medicines, including targeted therapies, approved through accelerated access schemes are more likely to have health warnings related to unanticipated toxicities and to be subsequently withdrawn from the market (Pace et al. 2017a; Pace et al. 2017b; Pace et al. 2017c).

Supporters of accelerated regulatory approval processes for targeted therapies often counter that, once products are on the market, real-world evidence will be generated to determine whether they are sufficiently safe and effective to remain on the market. The problem with this 'solution' is that companies have little incentive to conduct research that could result in withdrawal of products from the market and, even if they do, patients may be exposed to risk for considerable periods of time before products are withdrawn (Pace et al. 2017a; Pace et al. 2017b; Pace et al. 2017c).

4.3.2 Funding challenges

The complexities of funding targeted therapies and companion diagnostics are described in detail in Chapter 7. From an ethical perspective, targeted therapies have two main advantages. First, targeting treatments to those patients who are most likely to benefit and least likely to be harmed can be a more cost-effective and less wasteful approach than funding treatments developed and tested on heterogeneous populations. Second, targeted therapies often provide options for subsets of the population who have few options available to them. Funding these therapies is, therefore, a way of promoting equity.

The problem is that, as with orphan medicines used to treat rare diseases, the companies that produce targeted therapies often charge large sums of money per patient to make a profit. Where resources are limited, this inevitably creates opportunity costs, depriving other patients of interventions that they need or want. This is not necessarily a problem if the targeted therapies being funded are known to be highly effective and costs can be offset through savings elsewhere, but this is not always the case (Lewis, Lipworth and Kerridge 2014; Lewis et al. 2013).

In this regard, a key moral challenge for payers is that, while a subset of patients is likely to respond very well to any new targeted therapy, the science of precision medicine has not yet reached a point where it is always possible to predict in advance who these

Box 21: Relevant laws and guidelines relating to regulation of targeted therapies

The Therapeutic Goods Act plays a crucial role in regulating the supply of health-related products in Australia. The Act is administered by the TGA and regulates the introduction of therapeutic goods into the Australian market. Drugs must satisfy rigorous pre-market assessment standards before receiving marketing approval, requiring evidence of clinical utility, safety and efficacy through clinical trials approved and monitored by HRECs. Fast-track registration may be allowed in limited circumstances where there is unmet clinical need. For devices, including companion diagnostic genetic tests, which are classified as in vitro devices, the stringency of pre-market assessment depends on risk classification.

patients will be. This means that enormous sums of money need to be spent on treating patients who are unlikely to respond, in the hope of helping the few who will. A related challenge is that new targeted therapies are seldom used in isolation and, even with the strongest evidence from trials, it is difficult to assess their likely benefit (and therefore cost-effectiveness) in real-world practice. Of course, none of these economic nuances matter to patients who are desperate for access to treatment or believe that they have a right to access therapies, and who can make strong moral claims for subsidised therapies that can provide even the smallest chance of the smallest benefit (Ghinea, Little and Lipworth 2017; Harper, Ghinea and Lipworth 2017).

Like regulators, payers are under increasing pressure to facilitate early subsidisation of targeted therapies that have not yet been demonstrated to be cost-effective. These programs are referred to as 'coverage with evidence development' or 'managed entry' schemes. The ethical and sociopolitical advantages of such programs are that they 'balance the interests of clinicians and patients, who want early access to new diagnostic tests and medicines; payers, which want to address genuine health needs but do not want to pay more for medicines than they are worth; and pharmaceutical companies, which want to be paid fairly for their products' (Lewis, Kerridge and Lipworth 2015, p. 4114). These programs, however, raise similar ethical issues to those associated with accelerated regulatory approval programs, as well as additional issues related to the need to pay for therapies while evidence is being developed, the barriers to enrolling patients in research when subsidised access is otherwise possible and equipoise cannot be assured, and the psychological distress and inequities that might be a feature of efforts to disinvest from subsidised therapies (Lewis, Kerridge and Lipworth 2015).

4.4 Clinical application of precision medicine

Precision medicine has significant potential to help both individuals and the public by generating more efficient care pathways, facilitating access to new and more efficacious treatments and enhancing the ability to intervene early in disease progression. However, while noting the potential benefits of targeted therapies, it is also important to ensure that hype and scientific hubris do not permeate the clinical space. Like all medicines, targeted therapies can harm as well as help patients, and clinicians need to be just as alert to risk–benefit ratios when prescribing targeted therapies as they are when considering any kind of intervention.

4.4.1 Genetic and genomic testing and molecular diagnostics

The clinical application of precision medicine entails testing omic or other molecular markers to determine whether a patient expresses a pharmacologically relevant molecular target. When the tissue being tested is diseased (e.g. tumour tissue), few ethical issues arise, as the tissue make-up is not considered predictive of any other traits. However, when healthy tissue is tested or screened (e.g. non-tumour tissue in a patient with cancer) or an entire genome is sequenced in the pursuit of an isolated genetic abnormality, the ethical issues are very similar to those that arise in the context of genetic or genomic research, including risks to privacy and associated discrimination (e.g. difficulties in obtaining life insurance) and the management of incidental findings and those of uncertain clinical significance (see Section 4.2.1).

Other issues that arise particularly in the clinical setting include the potential for information from genetic or genomic tests

to have an impact on family members and future generations. Family members can be implicated if, for example, a genetic test indicates findings about relatedness, either by identifying hitherto unknown relatives or indicating non-paternity. Genetic counsellors play a central role in mediating the disclosure and interpretation of such findings. Clinical issues may also arise in relation to direct-to-consumer genomic tests, which may be of dubious quality (Vogenberg, Barash and Pursel 2010); this is also discussed in Chapter 3, where the role of GPs is considered. One issue that perhaps distinguishes testing for diagnostic purposes from testing for the purposes of guiding precision medicine is that the latter might threaten patient autonomy if, for example, public or private insurers begin to coerce patients into having genetic tests as a condition for coverage of medicines (Vogenberg, Barash and Pursel 2010).

4.4.1.1 Confidentiality and discrimination

The collection and testing of patient samples in the clinic raise the risk that the patients' data, including that derived from tissue samples, may be accessed by unauthorised parties. Such breaches of confidentiality are particularly concerning when they lead to the release of genetic information, both because genetic data are always potentially re-identifiable (Chalmers, Nicol and Otlowski 2014) and because genetic information can be both diagnostic and predictive, both personal and familial, and of both immediate and future relevance to individuals (Otlowski and Eckstein In Press). Although processes for protecting the confidentiality of data are constantly evolving, the reality is that, as mechanisms for data protection become increasingly sophisticated, new strategies inevitably emerge that undermine whatever protections exist (Erlich and Narayanan 2014; Gymrek et al. 2013).

Individuals who are discovered to be at risk of certain diseases, or carriers of deleterious genetic variants, can find themselves vulnerable to discrimination by insurers or employers (Barlow-Stewart and Keays 2001; Taylor et al. 2008). Although health insurance in Australia is community rated, under an exemption provided by the *Disability Discrimination Act 1992* (Cth), life insurance is based on individual risk assessment, and applicants are required to disclose all relevant health information including any genetic test results. This includes not only genetic testing undertaken for clinical purposes, but also genetic results obtained through participation in research, notwithstanding that such results are typically not generated in accredited testing laboratories. The stance taken in Australia is in marked contrast to the position taken by many European countries that have legislated to prohibit life insurers from using genetic test information (Otlowski, Taylor and Bombar 2012). In recent years, there have been growing calls to restrict life insurers' access to genetic test information, partly on the grounds that genetic discrimination may discourage people from participating in both genetic testing and genetic research (Keogh et al. 2017). Even where clinical data remain sufficiently aggregated or anonymised that individuals cannot be identified, there is still the potential for group-level harm in the form of profiling, stigma and discrimination (Clark, Barney and Reddington 2016; Rothenberg and Wang 2006).

Box 22: Relevant laws and guidelines on confidentiality and discrimination

The privacy rules governing clinical genetic and genomic testing are similar to those that govern genetic research (described above). Of particular relevance to the clinical setting, guidelines were introduced in 2014 to regulate the disclosure of relevant genetic information to genetic relatives, even without the consent of the index patient (National Health and Medical Research Council 2014b). These guidelines do not create a duty to disclose relevant information to a genetic relative without the consent of the patient; rather, they provide protection from such disclosure breaching the Privacy Act, provided that the guidelines have been closely followed. Although representing an important step forward, these guidelines do not cover health practitioners working in state-based public hospitals. To date, only New South Wales has introduced equivalent state legislation through the *Health Legislation Amendment Act* 2012 (NSW), amending the NSW Health Privacy Principles to make them consistent with the federal guidelines (Otlowski 2015).

Another issue that is particularly relevant in the clinical setting is the regulation of genetic tests. It is prohibited in Australia to make genetic test kits available to individuals for self-testing for the presence of or susceptibility to serious diseases. However, foreign providers of genetic tests who make their services available directly to consumers through the internet are not regulated through this legislation. The NHMRC has produced an information resource for consumers (National Health and Medical Research Council 2014c), as well as a more general statement cautioning about the use of direct-to-consumer genetic testing (National Health and Medical Research Council 2014a).

The legislative regime for the protection of privacy is particularly complex in Australia because of our federal system of government and the limitations on federal legislative power imposed by the Constitution. As a result, there are both federal and state-based privacy statutes. State-based laws govern the privacy of information held by state government agencies, which include public hospitals and many universities. The federal Privacy Act, in contrast, governs federal government agencies and corporations, subject to certain exceptions. To add a further layer of complexity, until 2014 different obligations were imposed on federal government agencies, through a set of Information Privacy Principles, and corporations, through the National Privacy Principles. The *Privacy Amendment (Enhancing Privacy Protection) Act 2012* (Cth) created a new uniform set of Australian Privacy Principles, which primarily create obligations relating to the collection, storage, use and dissemination of, and provision of access to, personal information.

There is, however, still a lack of national consistency in Australian privacy laws. Another problem is that the current federal regime is focused on the protection of information and records, so genetic samples are not protected even though they potentially hold a substantial amount of information about the individual concerned (Otlowski 2013). Additionally, enforcement mechanisms available under the regime are weak, and what protections do exist are lost once information is outside jurisdictional boundaries. The Australian Parliament is currently considering whether to approve an amendment to privacy legislation that would make it a criminal offence to re-identify de-identified government data. While not directly relevant to personal genetic data, this illustrates the seriousness with which the federal government views the protection of privacy.

4.4.1.2 Return of results and incidental findings

Often in the course of clinical care, particularly where genomic testing is employed, information emerges that is not directly related to the question being asked but that has potential clinical significance. The quandary for clinicians is that, while informing participants of such findings might enable them to prevent disease or respond more rapidly when symptoms arise, the significance of findings is not always clear; and people might prefer not to receive such information no matter how clinically 'significant' it might be (perhaps because of the insurance implications discussed above) (McGuire et al. 2013; Wolf et al. 2012).

4.4.2 Big data and predictive analytics in the clinic

Although it may seem on the surface that targeting therapies to individual patients can only improve clinician-patient relationships and facilitate the more general pursuit of personalised medicine, the reality is more complex. For example, it is not at all clear that doctor-patient relationships, and the overall patient-centredness of care, will be enhanced by the presence (even in the background) of artificial intelligence machines. There are also other ethical challenges associated with bringing big data and predictive analytics into the clinic, including:

- Consent – do patients need to be told that their care is being shaped (including resources being allocated) by predictive algorithms?;
- Liability – who is responsible for model failures or for failure to follow a predictive model's recommendation?; and
- Autonomy – can machine-generated decisions be overridden on the basis of individual preferences? (Cohen et al. 2014; Obermeyer and Emanuel 2016).

4.5 Equity

This chapter has focused on the wellbeing of those people who are fortunate enough to be invited to participate in research studies of targeted therapies, to live in countries where targeted therapies are subsidised and to have access to the clinical services through which these therapies might be offered. However, the reality is that the benefits and risks of precision medicine are not distributed evenly, either within or between populations.

4.5.1 Equity in research agenda setting

Much attention has been paid to the capacity for targeted therapies to revolutionise the treatment of monogenic disorders, rare diseases and rare subsets of more common diseases (e.g. molecularly defined cancers). While there is nothing trivial about these endeavours, it is important not to assume that the targeted therapies being developed correspond to the greatest areas of unmet need in the community. It is important to note that precision medicine has not yet addressed many common diseases that may have important social and environmental determinants. This is partly because the science is not yet well enough developed to deal with their multigenic complexity, but it is also because science is less adept at responding to social challenges that may determine health – such as poverty, famine and inequity – than it is at identifying and responding to physically tangible cellular and molecular changes.

Thus, while research in genomics and the pursuit of precision medicine is laudable, it is important that this does not occur at the expense of measures to address national and international social and political determinants of health (Savard 2013). It is also important that precision medicine initiatives themselves focus on areas of genuine unmet need (Pang 2009). These issues are particularly salient in Australia, given the parlous state of the health of Indigenous Australians and other vulnerable groups. As noted in Chapter 5, precision medicine has the potential to close the gap in Indigenous health, but only if the diseases it targets are those that affect the most disadvantaged groups.

4.5.2 Equity of access to subsidised targeted therapies

Even if targeted therapies are relevant to the health needs of disadvantaged populations, this does not mean that access to these therapies will be equitable. In many countries, the price of targeted therapies is well above the median salary, and because these countries are struggling to establish systems for universal health coverage, these medicines are available to only the wealthiest people (Alyass, Turcotte and Meyre 2015). It is noteworthy that it is in these countries that many targeted therapies are tested – such as imatinib for the treatment of chronic myeloid leukaemia – and those who participate in trials do not have subsequent access to ongoing therapy.

Even in high-income countries, such as Australia, where there are national systems for subsidisation of medicines that are known to be effective and cost-effective, the high cost of many targeted therapies is already placing a massive strain on resources. Furthermore, even if people live in countries that give them access to subsidised targeted therapies (that the country can afford), it cannot be assumed that these therapies will be accessible to disadvantaged groups, such as Indigenous Australians and those living in rural and regional locations who may lack access to clinical services.

A commitment to equity requires developing precision medicine in a manner that is consistent with international ethical standards regarding care for local communities, care for research participants and access to therapies for research participants beyond the period of clinical trials. A commitment to equity also requires constant review and reform of health systems and a political commitment to universal coverage and access. This, in turn, demands explicit recognition of the globalisation and networking of research, which creates social and ethical obligations that cross national borders.

CHAPTER 5
INDIGENOUS HEALTH

5.1 Introduction

Aboriginal and Torres Strait Islander (henceforth Indigenous) peoples of Australia are the most disadvantaged group in Australian society. With respect to health, the gap between Indigenous and non-Indigenous outcomes is well documented. The life expectancy of Indigenous people at birth is five to ten years lower than that for the general population (Cooke et al. 2007; The Australian Institute of Health and Welfare 2016), primarily because they experience high rates of chronic disease, and at younger ages than other Australians. Indigenous Australians are three to five times more likely to have diabetes, 2.5 times more likely to have respiratory problems and 1.9 times more likely to die from chronic heart disease; all of which helps explain why the standardised death rate for Indigenous Australians is twice that of Australians of European descent (Australian Bureau of Statistics 2013). This alarming disparity can be largely explained by many historical and sociological factors. Indigenous people are on average more likely to experience racism and social exclusion and less likely to live near and to use health services. Drug and alcohol misuse, smoking, low educational attainment, high unemployment, poor housing and poor nutrition are also common in Indigenous communities (Paradies et al. 2008).

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Views expressed in this chapter do not necessarily reflect the views of these contributors.

Australian governments have committed to reducing the health and social disadvantage experienced by the nation's First Peoples. Investments in precision medicine are unlikely to benefit Indigenous Australians unless specific efforts are made to engage Indigenous people, families and communities and to enhance Indigenous access to health care. Further, efforts to engage Indigenous people and enhance access are unlikely to succeed unless Indigenous people are given the opportunity to directly shape these measures. While addressing these socioeconomic disparities is undoubtedly the most important step towards closing the gap, government initiatives aimed at improving Indigenous Australian health by correcting socioeconomic factors (e.g. 'Close the Gap') largely failed to rectify Indigenous health disparities (Conifer et al. 2017). Genomics and precision medicine may be a part of the solution to overcoming Indigenous health inequalities, if Indigenous people are involved in their implementation.

Twenty-first century biomedicine has started to unravel the complex interactions between genomic and environmental factors that underlie all biological functions. An enhanced understanding of genomics has allowed for better prediction, detection and treatment of certain cancers, rare diseases and many other conditions. However, Indigenous Australians are unlikely to benefit from these advances in the absence of reference data about genome variation in Indigenous populations.

The role of genomics in Indigenous health cannot be understood solely from research on populations of European origin. Information on omic variation (including genomic, epigenomic, metabolomic, microbiomic and proteomic variation) in Indigenous communities is also needed (Moltke et al. 2014). Without research data on population genetic variation and associations with health and disease in Indigenous communities, the potential for precision medicine to contribute to redressing Indigenous health inequalities will remain unclear. The lack of inclusion of Indigenous Australians in genome research is part of a global pattern. A 2016 study found that 80 per cent of the participants in genome-wide association studies worldwide are classified as European, while only 0.05 per cent are Indigenous (Popejoy and Fullerton 2016). Even within these measures, Indigenous Australians are under-represented relative to Indigenous groups in other countries (Kowal et al. 2012).

Research with Indigenous communities in Australia using genome-wide association scans has so far analysed mutations associated with diabetes, rheumatic heart disease and a cancer cluster, while research on genomic associations with end-stage renal disease is still underway (Busfield et al. 2002; Anderson et al. 2015; McWhirter et al. 2015). The small number and scope of these studies mean that any clinical translation is some time away. There is also great interest, but not yet any research, in the role of epigenetics in transgenerational transmission of disease risk related to experiences of trauma (Kowal 2016) and the microbiome in non-communicable diseases, such as obesity, diabetes and cardiovascular disease.

If Indigenous Australians continue to be excluded from the research that leads to advances in precision medicine, any health benefits that accrue from precision medicine may instead widen the health disadvantage. To avoid this scenario, it is crucial that efforts are made to engage Indigenous people, families and communities in precision medicine. The National Aboriginal and Torres Strait Islander Health Plan 2013–2023 includes four principles to support health equity by 2031: health equality, community engagement, partnerships and accountability. Genomics and precision medicine can play a part in this vision, but only if specific efforts are made to include Indigenous people. McWhirter and colleagues (2015) recommend the following steps to allow Indigenous people to benefit equitably from precision medicine:

- Ensure diversity of participants by implementing appropriate protocols at the study design stage;
- Target diseases that disproportionately affect disadvantaged groups;
- Prioritise capacity building to promote Indigenous leadership across research professions;
- Develop resources for consenting patients or participants from different cultural and linguistic backgrounds; and
- Integrate awareness of issues relating to Indigenous people into the governance structures, formal reviews, data collection protocols and analytical pipelines of health services and research projects (McWhirter et al. 2015).

These principles and step make it clear that Indigenous people must be central to any efforts to making precision medicine inclusive, not least in order to ensure that Indigenous approaches to decision making and governance are adhered to. The final part of the chapter addresses options for Indigenous governance of and participation in precision medicine.

In addition to issues of Indigenous governance, attention should be paid to the distinct cultural beliefs and historical experiences of Indigenous Australians. These will influence the engagement of Indigenous people in the field and ensure that benefits are broadly accessible, not restricted to the 'privileged few' (Popejoy and Fullerton 2016).

5.2 Cultural values

Indigenous Australians have unique and diverse cultural viewpoints. Although difficult to generalise, given the diversity of Indigenous peoples, there are two primary ways that genomics and precision medicine may clash with Indigenous belief systems.

First, genomic accounts of population structure may challenge Indigenous peoples' understanding of their origins and relatedness. Historically, Indigenous Australians conceive of themselves as products of a process known in English as 'the Dreaming' – the ongoing mythic work of creator ancestors. There is a potential conflict between this view and the mainstream scientific view that the ancestors of contemporary Indigenous Australians are descended from the first modern humans to leave Africa, reaching the continent of Sahul up to 65,000 years ago. Based on their own deep-time creation myths, many Native Americans have challenged scientific views that their ancestors crossed the Bering Strait 15,000 to 45,000 years ago. In Australia, however, Indigenous attitudes towards genetic accounts of their history have been more favourable (Kowal 2012), perhaps in part because research has bolstered Indigenous claims to remarkably ancient connections to country (Malaspinas et al. 2016; Tobler et al. 2017).

The second way in which genetic research may challenge Indigenous views relates to traditional ideas about the spiritual significance of biological specimens. The different ways that geneticists and Indigenous peoples may conceive of biospecimens and genomics have led to public disputes between Native Americans and scientists in the US, Canada and Brazil (National Centre for Indigenous Genomics 2017). Blood has immense metaphorical value in many Indigenous communities around the world, including Indigenous Australia (Copeman 2009; Carsten 2013). This may deter Indigenous people from participating in the genomic research that is required if they are to benefit from precision medicine. It is impossible to make firm conclusions, however, because of the absence of empirical research on this issue. In the single study of relevance to this, Indigenous participants in a Darwin-based study on diabetes risk who consented to long-term storage of their blood samples tended to be older non-smokers with some non-Indigenous grandparents, whose consent forms were administered by Indigenous staff members (Cunningham and Dunbar 2007; see also Sahota 2014). This suggests that trust in researchers and research institutions is crucial to encourage the participation of Indigenous Australians in genomic research and precision medicine.

5.3 Historical issues

Indigenous peoples' experiences of dispossession, marginalisation and oppression have led many of them to distrust Western institutions and mainstream Australian society in general. Scientific institutions may be particularly suspect, as past researchers have appropriated artefacts, information and biospecimens without consultation, consent or compensation and have used this information to develop systems of racial classification that validated attempts to exclude Indigenous people from mainstream Australian society or, at other times and places, to biologically absorb them into the white majority (see, for example, Anderson 2002; Douglas and Chesterman 2008).

Genetics research has featured in this history of mistrust. An important example was the Human Genome Diversity Project in the mid 1990s, which sought to collect samples from Indigenous groups around the world. Australia did not participate in the project, which Mick Gooda, who was then the Aboriginal and Torres Strait Islander Social Justice Commissioner, referred to as the 'Vampire Project'. In particular, he noted concerns about the possibility of "the cultural, political and social complexity of Indigenous identity and Aboriginal rights being reduced to an arbitrary genetic test" (Human Rights and Equal Opportunity Commission 1996). Aboriginal scholars have also raised concerns that genetics research could revive old ideas about their biological difference from – and inferiority relative to – the white majority (Hook 2009). However, as the Darwin study cited above suggests, it is possible to engage Indigenous people in biomedical studies with free and informed consent, if a rigorous community engagement strategy is developed and maintained (Sharp and Foster 2002; Couzos et al. 2005; Arbour and Cook 2006). As suggested in Section 3.1, engagement efforts for precision medicine need to be capable of accommodating diverse interests and beliefs, to ensure both the viability of the field and the safeguarding of Indigenous (and other patients' and citizens') interests.

5.4 Access to health services

Even if these cultural and historical barriers are overcome, equitable access to precision medicine still requires equitable access to health services. Indigenous Australians lack access to health care services, particularly specialist services (Gruen et al. 2001). Despite having a higher incidence of many genetically determined conditions that may benefit from precision medicine (Condon et al. 2009; Hoy et al. 2012), including some cancers, renal disease and neurodegenerative conditions such as Machado–Joseph disease, Indigenous people are under-represented in patient populations of genetic services (e.g. by about two-thirds in the Northern Territory). This is in spite of evidence of a demand for these services (Garvey and Bernardes 2012). Australia must close the broader gap of health care access if precision medicine is to contribute to closing the gap in health outcomes.

5.5 Options for Indigenous engagement and ownership

Australian researchers and health care providers have an obligation to engage Indigenous people in any research or health care that seeks to benefit their communities. The relevant Indigenous people or community should be provided with the resources necessary to shape these efforts according to their own governance and decision-making processes. One example of this occurring at a national scale is the National Centre for Indigenous Genomics at the Australian National University (Kowal *et al.* 2016). 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. While most precision medicine initiatives will have a broader scope than Indigenous people alone, and therefore may not involve Indigenous governance on this scale, the National Centre for Indigenous Genomics offers practical examples of Indigenous governance that other projects can draw on.

Ensuring that advances in genomics and precision medicine narrow, not widen, the gaps of health disadvantage is an ethical issue. However, there is also much to gain practically from including Aboriginal and Torres Strait Islander Australians in advanced health care. Measures taken to engage Indigenous communities may lead to innovations that have wider relevance. For example, as a result of engaging with Māori communities and elders, the Christchurch Tissue Bank in New Zealand offers participants the option of having their sample disposed of with a Māori blessing (or *karakia*) when it is no longer required for research. This option is taken up by many non-Indigenous biobank participants as well (Morrin et al. 2005). The dynamic consent practices proposed by Australia's National Centre for Indigenous Genomics are another example of innovative practice with potential for wider application (National Centre for Indigenous Genomics 2017). The dynamic consent model allows biobank participants to be informed of how their samples are being used, with the option of opting out of particular projects while maintaining participation in the biobank (Kaye et al. 2015). In this way, the inclusion of Indigenous Australians in genomics and precision medicine can have wider impacts on the practice of 21st century Australian biomedicine.

CHAPTER 6
DATA

6.1 Introduction

The ability to process and interpret complex data has advanced rapidly for genomics, imaging and point-of-care diagnostics. The Human Genome Project took 13 years to map the human genome (completed in 2003); similar results can now be produced in 48 hours for less than US$1,000 (Hayden 2014). Developments in the ability to collect, analyse and share data between individuals and organisations without compromising privacy will support precision medicine by granting health care practitioners and policy makers access to broader, interoperable data sets. These will not only analyse large amounts of data but can cope with data of different levels of accuracy and of different kinds. Data-driven precision health in Australia is underway, powered in part by a big data revolution.

6.2 Data integrity, standards and systems interoperability

For a data set to offer new and reliable insights, controls must be in place during data collection, and collection methodologies must be documented and available to data users. Inconsistencies in data collection and recording impair quality, reliability and, by extension, usability. All data must be collected with respect for the principles of informed consent and used ethically, in terms of both community approvals and legal terms. Implementing widely accepted, shared data integrity standards will speed up data sharing and linkage, in turn catalysing the development of new therapies, technologies

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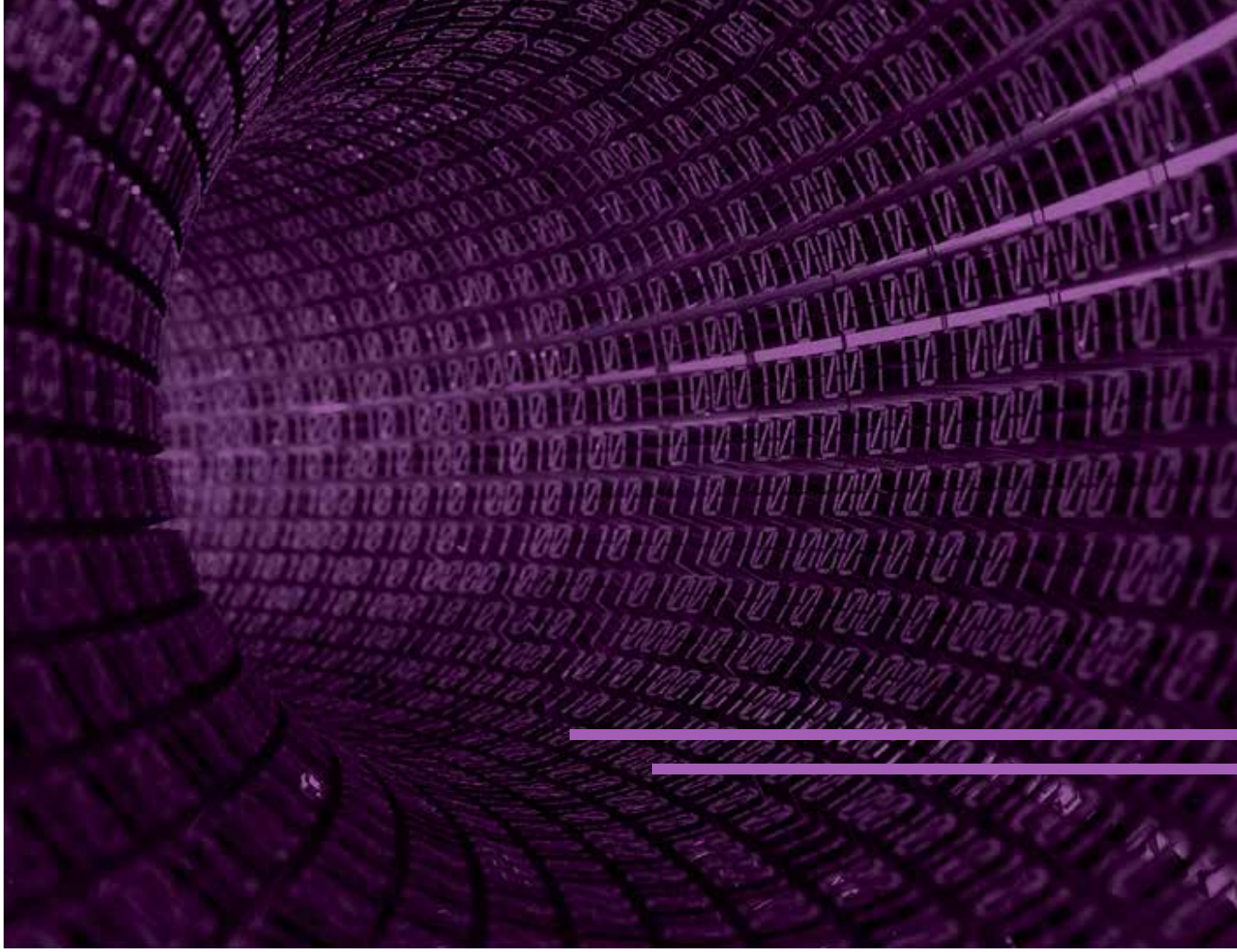

and predictive systems (CSIRO 2017). The use of common metadata registries, such as those conforming with ISO 11179, will facilitate the accurate capture and management of descriptive and structural health metadata (with due regard for assumptions and methodologies used in data capture), which will aid more precise data combination, linkage and re-use. This will govern the ability to apply the conclusions that are obtained from the data.

NATA has put in place data standards to guide the storage of people's genetic information, supporting the future potential for integration of these data while also ensuring a common approach to managing the privacy and confidentiality of this important information. A challenge for the health sector in adopting data-driven technologies will be the need to ensure that, as technologies evolve, the development and implementation of standardised approaches to data management and protection occur in parallel.

Australian health and medical organisations currently adhere to an evolving set of data management standards and requirements. Some of these are set by state and federal governments, such as the NHMRC's best-practice standards and guidance on the Privacy Act supplied by the Office of the Australian Information Commissioner (Australian Government and Office of the Australian Information Commissioner 2017). Others are set by domain experts, such as the Global Alliance for Genomics and Health's *Framework for Responsible Sharing of Genomic and Health-Related Data* and the International Cancer Genome Consortium's global

policies for good research practice. Unifying standards across Australia, particularly in relation to privacy, will support organisational compliance as well as the development of cross-jurisdictional platforms. It is important to facilitate this by simplifying the process of determining which regulations apply to which activities.

Enabling seamless digital records across all care settings (i.e. making health information systems more interoperable) will support access and use of health data. However, achieving interoperability of health data is challenging because of the need to balance the privacy and security of patients' personal data with the utility that can be achieved through data analytics on the combined data. For example, linking data about a single individual across multiple sources (such as multiple clinics) increases risks in terms of privacy and security. New techniques and emerging privacy-preserving record linkage technologies are expected to make this linkage possible by enabling data to be linked without requiring movement of raw personal data across organisation boundaries.

Another emerging challenge is that, as clinician software systems make the inevitable move to the cloud, access to patient data by third-party systems will be under tighter control by software vendors. To ensure consistency of data treatment and to support future linkage potential, standards and obligations for patient data access from cloud-based clinical software (including privacy-preserving access) will need to be in place. However, despite the challenges, interoperability may benefit policy makers, health professionals and patients and aid the implementation of precision medicine (see Table 5).

6.3 Data sharing

Data sharing or integration involves bringing together data held within separate organisations or sources to provide a unified view of the data. Figure 8 visualises the steps involved in bringing data together. Data owners and custodians source, extract, connect and protect data, which is then accessed and used by either authorised or open users to achieve outcomes such as innovation, improved care policy or cost savings for the wider community.

Most Australian states and the Commonwealth have agencies and departments that are developing data sharing and integration frameworks and capabilities. In some cases, these agencies may be suitable to take responsibility for sharing and integrating health data within their jurisdictions (subject to privacy impact assessments and consideration of relevant

Party	Interoperability	Outcome
Government and policy makers	Access information from a variety of interoperable sources	Assist in assessing public health measures, medical outcomes and care delivery outcomes and trends
Health professionals	Interface and share information with other organisations in the health supply chain or with patients	Alleviate delays, activity duplication and information gaps
Patients	Receive and share data on their own health progress and outcomes	Enable a more personalised level of health care

Table 5: How interoperability may benefit policy makers, health professionals and patients

Figure 8: Steps in data integration

Adapted from image supplied by Data61.

legislation). Examples include the NSW Data Analytics Centre (DAC) and Victorian Centre for Data Insights. Additionally, Australian Government initiatives, such as the Data Integration Partnership for Australia, are seeing the development of specialised analytical hubs to support the integration of data for policy development and assessment.

The Productivity Commission's 2017 *Data Availability and Use Inquiry Report* highlighted Australia's health and medical sectors as examples of how mistrust and legal, technical and cross-jurisdictional obstacles are inhibiting data-based opportunities (Productivity Commission 2017). The inquiry recommended establishing:

- A National Data Custodian body responsible for identifying and designating some data sets as being of national interest, with a view to mandating their release; and
- Accredited Release Authorities, tasked with ensuring data sets marked for release are made available with appropriate sharing restrictions (open, secure) and standards (metadata, API).

These developments could make health data sets more widely available, but they rely on strong security measures that vary according to the sensitivity of the data, the level of private or confidential content they contain, and management needs across a variety of scenarios (e.g. data sharing between health providers and patients compared with data sharing across health system operators).

As privacy-preserving data sharing technologies evolve, the patient information software systems used by clinicians will be better able to provide analytics using the data available in the clinic on an individual patient, other patients in the same clinic and aggregated data across many clinics. In treating a patient, clinicians will be able to compare an individual's results and treatment with aggregated data drawn from multiple sources, thus supporting a better understanding of potential treatment options and comparable outcomes.

6.4 Data architecture and infrastructure

At present, the most relevant data sharing and integration models or architectures for potential use in a health context are (NICTA 2015):

- **Point-to-point**, where data are exchanged ad hoc and periodically between organisations, with little consistency in standards, formats and agreements. This is the dominant data-exchange pattern for most Australian government jurisdictions.
- **Centralised**, where data are aggregated and collected by a central intermediary that has responsibility for transforming them to ensure consistency, providing a uniform interface for users of the data. The Australian Bureau of Statistics and NSW DAC are examples of this approach.
- **Federated**, where data are exchanged on a coordinated basis between agencies, based on the use of standards and shared platforms that can process and transform data (e.g. API gateways, data linkage, on-the-fly virtual data set generation). Under this model, the source of data remains with the data custodians, with no persistent data stored on shared platforms or with an intermediary. This is an emerging model exemplified by the Australian Taxation Office's Standard Business Reporting platform and the Australian Government's National Map federated spatial visualisation platform.

An advantage of the use of a centralised data model (described in 6.2 Data Sharing) is that it is easier to manage access to and security of the data because all the data reside in one location. Centralisation also supports use of consistent formats for data, improving the ability to perform analysis on the data. A key risk of a centralised architecture is that it requires moving shared data across business boundaries, including maintaining the data with regular updates from the data custodian. The separation of the data from the data custodian – who is best able to understand the data's context – also presents some risks.

A federated data architecture is a hybrid integration model between the centralised and point-to-point data approaches, where shared data are stored and managed by their original custodian, and a meta-database system is set up to serve as a single share or access point. In practice, when the system receives a query, requests for data are issued to the corresponding data sources and relevant data retrieved at that time. A benefit of this approach is that it enables the data to remain with their custodians (who are best aware of their acquisition and context, confidentiality, privacy and limitations) and supports access to only the most current information at the time of a query, lessening the need for regular sharing or uniformity of data and enabling better accessibility and coordination. A risk of this approach is that it requires sharing of data across organisational boundaries; however, the ability for the custodian to remain responsible for data quality and consistency is a benefit.

The Australian Government seems to be moving towards a more federated approach to data sharing and management. As more organisations – within and beyond government – adopt federated models, the potential for cross-organisation, privacy-preserving data sharing and analytics improves.

Current government-supported initiatives are testing techniques to permit trusted access to high-value data sets while preserving data confidentiality and integrity. One such project allows data platforms to interactively access aggregated data that are confidentialised on-the-fly from sensitive unit record data

sets. Another area with the potential for precision medicine applications is **blockchain** technologies. Blockchains have been widely celebrated as a mechanism for generating and supporting distributed trust on the internet by providing a common register and platform to support information audit and rapid consensus (Hanson et al. 2017). These technologies have the potential to facilitate data sharing and agreement across operators in the health system, with a common audit trail of interactions, approvals and reviews.

6.5 Data ecology

A barrier to implementing data effectively for use in precision medicine is the difficulty of determining what data exist across the health system. This knowledge gap leads to duplication in health data collection, or it may mean that valuable data are not used for decision making or to support cross-population insights. This could be resolved by using data federation techniques to develop sharing platforms, running catalogues of available data and a combination of machine learning and artificial intelligence to make data sets more discoverable and searchable. Such a resource could also have the potential to support the observation of health outcomes data in parallel to other non-health data sets, to explore correlation. For example, the intersections between health outcomes and exogenous factors, such as conflict, migration, natural disasters or climate change, could point to the impact that external factors may have on health (World Bank 2017).

6.6 Data-driven insights

Opportunities for machine learning to support rapid, personalised predictions will continue to increase as more data become available. The ability to draw on a growing field of data sources will allow machine learning to generate insights that are not apparent from single data sets. These data can come from anywhere: from formal sources (e.g. genetic profiling, test data, patient records) to more informal sources (e.g. fitness trackers). Machine learning algorithms will bring the most relevant knowledge from the vast corpus of medical research to the practitioner's fingertips and will be able to place a patient's individual responses in the context of the broader patient population in real time. Ultimately, machine learning technologies will not just process data but also actively collect data to improve their performance. These technologies, driven by artificial intelligence algorithms, will understand when their predictions are uncertain and what additional data will reduce that uncertainty. They will not only suggest tests for an individual patient but also understand what other tests will improve their own predictive performance in the future, so they can continue to learn and improve patient outcomes.

6.7 Data security and privacy

Ensuring the privacy and confidentiality of people's health information throughout the health care system must be a top priority when designing health data sharing or analytics systems. The fear of misuse of personal data, or of access being provided to third parties without consent, means that most people are wary of their data being collected or shared. Indeed, concerns about private or sensitive data being breached or lost have been a barrier to organisational efforts to explore data sharing. Building trust in the systems, architectures and standards that support data handling, sharing and use is essential. The importance of this issue to the community cannot be underestimated; it will

be a deal-breaker if the public does not have confidence in data security and appropriate ethical boundaries on data use.

Strategies for quantifying confidentiality risks do exist, with the most general being based on re-identification probabilities. Various methods are also used to alter or perturb data before release, although each has limitations and all limit the level of insight that can be derived from the raw data in some way. Methods include:

- **Suppression and masking,** where sensitive values are masked or removed before release;
- **Aggregation,** where data are expressed in summary form, reducing disclosure risks;
- **Data swapping,** where data values for selected records are swapped, which discourages users from matching as matches may be based on incorrect data;
- **Perturbation or noise,** where numerical data are protected by adding random data or 'noise' to data sets; and
- **Synthetic data,** where original data values are replaced by values simulated from probability distributions, while still reproducing as many of the relationships in the original data as possible.

Box 23: Social and ethical challenges of machine learning

Precision medicine will require exceptionally high volumes of data, which will entail complex analysis and decision making. Machine learning or artificial intelligence will play a crucial role in deriving insights from this body of data. Better understanding is warranted in the following areas.

Federated machine learning
There is a tremendous opportunity for government and industry to share data sets across organisations, to build more powerful and insightful predictive models. To do so traditionally requires data to be co-located: stored in one secure facility, supported by protected physical and digital infrastructures. This is often difficult for legal, contractual and practical reasons.

Privacy-preserving machine learning
Traditional machine learning methods require data owners to share or expose confidential or potentially sensitive data. This generates serious privacy and competitive implications, as the data may contain trade secrets or private information relating to individuals.

Ethical machine learning
With machine learning playing an increasing role in everyday life (e.g. online search engines), the public is becoming wary of how data – including personal information – are used in the development of predictive models. This includes concerns about data-driven profiling based on data with known historical biases or the use of algorithms that may over-generalise based on attributes such as age, sex and ethnicity. There is also an ethical dimension to the question of accuracy of machine learning and artificial intelligence. Predictive algorithms make predictions with an unfixed, ever-changing degree of certainty. Before those algorithms can be trusted to endorse an action that will affect a patient (such as guiding prescriptions), causality with a high degree of confidence is required.

Security in machine learning
The threat of a potential adversary accessing and exploiting the intricacies of a machine learning model is enormous. Large machine learning models are often extremely complex structures that are notoriously difficult to monitor. This complexity can be exploited by malicious attacks, as it enables attackers to subtly manipulate input data to produce wildly inaccurate predictions without the owners realising a manipulation has occurred.

Techniques are emerging to enable confidential data access without compromising content. For example, confidential computing combines distributed machine learning, homomorphic encryption and secure multiparty computing to enable encrypted queries and responses among third-party data sets, without requiring direct access to raw data. In the future, this kind of approach could enable an individual to map all their health information held on a personal device against a third-party database to receive personalised results, without their data ever being disclosed to another party.

6.8 Australia's data capabilities and capacity

Australia has the capability and capacity to process and analyse the volume of data that will be generated by precision medicine, with potential for the emerging class of commercial secure cloud service providers to develop suitable platforms to support this. These would adapt, or build on, existing services provided for use in commercial data analysis (i.e. those used for market development purposes).

Commercial secure cloud services, with strong privacy and security assurances, are likely to be suitable for use in health data analytics, assuming appropriate privacy impact assessments are undertaken that take into consideration the specific scenarios and infrastructure used in a health context.

To take full advantage of the opportunity that data analytics and integration can provide to Australia's health sector, there will be an increased need for data scientists and data engineers to develop the systems that will be used for large-scale analytics. These professions are in high demand internationally, across both government and private sectors. It follows that increasing suitable training programs, alongside initiatives that will attract skilled data scientists, mathematicians and engineers, will be valuable for ensuring Australia's health system is prepared for precision medicine. There will also be a need for cross-fertilisation of such experts with clinical professionals to unite non-clinical and clinical views on diagnosis and treatment of individuals.

To realise the potential contribution that aggregated data can make to improving individual and community health, advances need to be made in the areas of data integrity and standards, data sharing and interoperability, data security and privacy, and skills development to support the new approach to health care that precision medicine will bring. Some of these advances are important preconditions to the implementation of precision medicine by the health sector, as they are central to community acceptance of the emerging technologies being explored. Used according to best-practice conventions, a precision medicine data ecology can support faster and more informed clinical decision making at the patient–practitioner level and more wide-reaching evaluation of outcomes and health patterns at the population level.

CHAPTER 7
HEALTH ECONOMICS

7.1 Introduction

The development and application of new genetic technologies has the potential to provide significant benefits for health care. For patients, the potential benefits are improved knowledge about the risks of developing disease; the opportunity to mitigate risks through behaviour modification, screening or preventive treatment; and an opportunity to make more informed choices (Salari et al. 2012). For health care providers, there may be increased capacity to predict response to treatment and to target treatments more effectively, leading to greater certainty and potentially better health outcomes for their patients (Patel 2014). Instead of treating 100 people, with 10 per cent showing a response to treatment, 10 people identified through genomic testing could be treated with a 100 per cent response. However, all 100 individuals will require testing initially, and other treatments may be indicated for some of the other 90. This has the potential to decrease the cost of clinical trials and the time-to-market for new drugs. For industry, new technologies lead to new marketable products and potentially new sources of profit (Marketwatch 2014). The emergence of the capacity to identify genetic markers has, in some cases, rescued treatments previously thought to be ineffective or harmful, but which may be effective for a targeted population. For the health system, genetic technologies have the potential to lead to more targeted treatment, reducing health care expenditure on treatments that are unlikely to lead to benefits and improving overall efficiency. However, these new genetic technologies can also have significant costs,

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Views expressed in this chapter do not necessarily reflect the views of these contributors.

and many of the benefits remain uncertain (Deverka et al. 2010). The balance of costs and benefits will differ when considered from different perspectives in the health system and society.

In the short term, there are likely to be increased costs associated with new treatments and tests (Filipova-Neumann and Hoy 2014; Gazouli and Souliotis 2014). From the point of view of manufacturers of health care technologies, genetic technologies have the potential for increased revenue from new tests and treatments. But, in Australia, as in most developed health care systems, the prices paid for new technologies are generally related to the health outcomes gained, and the capacity to target may lead to higher prices for targeted treatments. This may have a direct impact on health expenditure through government-funded programs if there are excess profits or improved outcomes that are not offset by reductions in the number of people treated. Where new technologies are not funded or only partially funded by government, and especially during the period when new and old systems run in parallel, patients will face higher health care costs in terms of insurance premiums or out-of-pocket costs, often at levels that are beyond the reach of average income earners. This raises questions of equity of access to new technologies. It is also worth noting that the information from genetic screening is often indicative rather than definitive. As a result, there may be patients who undergo unnecessary treatment that entails costs and risks but does not provide benefit. Patients may also experience increased anxiety about potential future health outcomes and may choose, as a result, to seek more frequent follow-up and treatment even when this does not confer a health benefit (Hall et al. 1998).

There is also potential for increased anxiety if the ability to identify a risk of disease in an individual has outpaced the development of treatment options for that condition.

This chapter broadly examines the economic implications of these new technologies for the health care system. The gains in health may bring considerable benefits to Australian society, provided the associated costs are reasonable. Direct costs will include charges for genomic and other omic analysis. Even though the cost of DNA sequencing is falling rapidly, and is now in the order of US$1,000 for a complete genomic sequence, including interpretation, it is still considerable if applied to a population. Indirect costs, especially the costs of training existing and new staff in the delivery of genomic information for health benefit, will also be high.

As will be discussed in Chapter 8, both the skills and the equipment used in precision medicine and gene editing are the same as those used in agriculture and veterinary medicine and are relevant to sport and defence. The application of medical research is a highly competitive area of technology and, although Australia has some strengths in biotechnology, it is even stronger in agricultural innovation, where many commercial applications exist.

An estimate of the costs and benefits of precision medicine depends on how health care is funded, how value for the health dollar is determined and how the health technology market is regulated. Australia is a mixed public and private health care system (The Australian Institute of Health and Welfare 2016). This raises the question of what should be covered under universal health insurance (Medicare) and what should be left to private funding. Australia has a well-developed health technology assessment (HTA) approach, but evaluating genetic tests and genomically guided treatments presents new challenges. The rapid development of this technology is leading to lower upfront testing costs, although these may result in increased use of high-cost interventions, which presents challenges for market regulation. Further, the availability of low-cost testing may result in increased demand for treatments that may not yet have demonstrated benefits or for which the capacity for harm remains unknown (Miller et al. 2002). The medical market is becoming internationalised, and the fact that Australian medicine is regarded as safe and well-regulated should allow entrepreneurial medical units to become international centres for genomic diagnosis and treatment.

7.2 Public and private payer systems

Health care in Australia is financed primarily by government, accounting for about two-thirds of health care expenditure (The Australian Institute of Health and Welfare 2016). The other main sources of finance are private health insurance and out-of-pocket expenditure. Funds are then expended through both public and private sectors. Medicare provides subsidies for treatment delivered by private medical practitioners, including diagnostic testing. Private health insurance covers private in-hospital treatment and general (largely dental) and other ancillary services and is prohibited from covering out-of-hospital services provided under Medicare. Over the past decade, there have been a series of initiatives using both subsidies and penalties to encourage the uptake of private insurance (e.g. the Australian Government private health insurance rebate). Slightly less than half the population have private insurance (Australian Prudential Regulation Authority 2017) at a cost of A$6.5 billion in public funding in the form

of rebates (Hawthorne 2016). Consequently, significant public funds have been directed to supporting the private health insurance industry and, by extension, the private health care sector.

The result of these complex arrangements is that any episode of care may be funded through different mechanisms and from different sources. We will consider the application of precision medicine to cancer treatment, as much of its cutting-edge application has occurred in oncology. The use of precision medicine will generally involve initial testing to determine the genetic make-up of the patient and the changes that have occurred in the genome of the tumour. The results of those tests may provide information that will allow the clinician to recommend the most appropriate therapy, particularly where there is a targeted treatment available or where there is information about potential harms of some therapies.

Consider a diagnostic test for a cancer that has an associated genomic marker with a potential targeted medicine. The test may or may not be covered by the MBS, but it may entail a consultation with a specialist, a biopsy and pathology tests, and will likely involve a private provider. The extent to which patients must pay out of their own pocket in the community setting will depend on the fees charged by their provider and the Medicare Schedule Fee. The Extended Medicare Safety Net (introduced in 2004) provides some additional financial protection for those patients who incur unusually high out-of-pocket costs (and higher costs for government) relating to Medicare services delivered in the out-of-hospital sector during a calendar year.

However, many different types of genomic tests are not listed on the MBS. Through their public hospital-linked facilities, state governments have established and funded genetic services that will offer genetic screening, as well as counselling and education. Such services are limited in their physical location, with different funding arrangements across states and territories, and they typically cater to people who have been identified as being at risk of a genetic condition. Any consequent treatment may be provided through a public hospital at no charge or, if the patient has private insurance, they may elect to be treated privately in a public hospital or in a private hospital. Each of these alternatives involves different costs for the patient, the private insurer and the state and federal governments. Subsidies may also distort the distribution of government benefits. These considerations also affect the ethical issues regarding distributive justice and the preferential allocation of resources to those with the greatest clinical needs.

7.2.1 Insurance

Medicare provides universal tax-financed comprehensive insurance, but it does not cover all health care services. This is particularly the case for emerging technologies that have not yet undergone HTA. The process by which new technologies are assessed for public subsidy is discussed in Section 7.4.1. In the context of precision medicine, it is important to note that Medicare has been intended to provide 'medically necessary services', which has not included population-based screening. Major population-screening programs, such as those for cervical cancer, breast cancer and colon cancer, have been funded as separate population health programs. There are some advantages to this approach, as national screening programs can be designed to encompass appropriate counselling, education and follow-up and to provide

a more efficient approach to recruitment, delivery and targeting of services. However, once a condition is detected, further investigation and treatment are deemed medically necessary and covered by Medicare.

The question arises of which genetic information testing and treatment technologies should be publicly funded. An individual pathology test for a specific genetic marker (e.g. for a hereditary disease) is managed through the evidence-based reimbursement decision-making process of the Medical Services Advisory Committee (MSAC). Genomic sequencing (as opposed to genetic testing related to specific risks of an individual) may be assessed through this process. If such an approach to screening becomes widespread, regardless of whether it is funded under Medicare, there will be inevitable consequent costs on Medicare for follow-up and treatment unless the fundamentals of Medicare are changed. There have also been suggestions that changing information can change behaviour in ways that can be difficult to predict, sometimes leading to avoidance and sometimes to seeking additional health care, therefore potentially increasing total costs; however, further studies are required (Macdonald et al. 1984).

Private insurers may choose to cover genomic sequencing, subsequent testing and follow-up through their general or ancillary products. Private insurers are allowed to operate 'health businesses' and some have recently established or acquired interests in dental and optical centres and primary care. Where genomic testing has clear benefits, and the tests are not yet covered by Medicare, this could be a significant challenge to the equity of the Australian health care system. Even when the benefits are not clearly demonstrated, this introduces differential access.

7.2.2 Assessment of risk factors

Genomic testing will provide more precise familial information about individual risk factors. These results may have implications for a person's relatives even if they choose not to be tested. This risk assessment may alter eligibility for private health insurance, other insurance and occupation selection.

Although private health insurance in Australia is community rated (so individual risk should not affect the premium charged), firms do attempt to encourage healthy people ('better risks') to take out insurance by, for example, targeting policies to young people. Genomic testing could provide new approaches to favourable risk selection and while this will improve private firms' profitability, it runs counter to the social goals of community rating for private health insurance. Should firms be obliged to provide cover to individuals with known conditions where the probability of an insurance payout becomes higher, or to provide packages that cover all conditions? There are also questions relevant to the individual's responsibility to disclose risk and, equally, at what point they should seek treatment.

The same issues arise in the context of other insurance, where the markets are not as highly regulated – particularly life insurance and income protection, although we may also include travel insurance.

Finally, more precise information may provide insights into risks associated with certain occupations. In the future, this may benefit the individual in selecting an occupation and could also be valuable to employers in recruiting staff. It is feasible that, just as psychological testing for job attributes has become widespread, employers could seek genomic testing as one basis of candidate selection. This has implications for regulation in terms of mandating the pooling of risks

and the level at which this risk pooling should occur for the population. Further, this raises concerns about an increased risk of discrimination against individuals by employers or insurance providers.

7.3 Cost-effectiveness and resource allocation

The previous section identified how, in Australia's mixed public-private system, the developments of precision medicine can lead to changes in the costs of health care and the distribution of those costs across governments and individuals. The way that these new technologies are financed and funded has a significant bearing on the efficiency, equity and sustainability of the system. It is also important to recognise that the funding mechanism will have consequences; for example, fee-for-service models will generally result in increased volumes of services offered or provided. New technologies generally have high overhead costs associated with the process of discovery and bringing them to market. Funding mechanisms that recompense these fairly and provide incentives for additional advancement, while not allowing providers to capture abnormally high profits, should be considered.

7.4 Costs of implementation

The costs of implementation can be considered in two categories:

- The cost of providing the service based on the technology itself; and
- The need for associated infrastructure.

The cost of any service delivery is a combination of fixed and variable costs. The relationship between the two determines whether there are economies of scale. In many health care services, there are volume-outcome relationships, whereby a minimum level of activity is required to ensure good quality outcomes. Investigation of economies of scale, economies of scope and volume-outcome relationships is required to ensure technical efficiency in the delivery of these services.

It is important to understand that testing in itself does not deliver improved health outcomes, but it can provide information that serves as a basis for further intervention (Cairns and Shackley 1993; Rubin et al. 2014). The information changes the consequences in terms of health care use and costs. Overall, the net costs may be negative or positive (but should be weighed against health gains, as discussed in Section 7.4.1). It is well established that fee for service is associated with increased volumes of services provided and that some of those services will be of little, no or negative benefit. Health reform is seeking new funding approaches that provide more appropriate incentives for practice. Where a service is part of an episode of care, bundling those services may well be a more effective funding mechanism (Dawda 2015). Another consideration is funding mechanisms that will enhance care quality. In the context of precision medicine, such funding mechanisms might ensure that services are better targeted to those who stand to benefit, and that the use of the resulting information leads to the appropriate downstream use of health care. The development and implementation of such innovative funding approaches have not proven easy so far, but will have significant effects on the cost of delivery.

There will also be an associated infrastructure required for the storage of genetic material and the confidentiality of data (see Chapter 6) (McGowan et al. 2014). Storage of information and the capacity to retest will be important because, as more information from research becomes available, there may be changes in the interpretation of results (e.g. there may be retesting of new markers or changes in management based on new information about the existing and known markers). Health information is known to be valuable, and there are increasing risks associated with cybersecurity. There are also medicolegal and ethical implications regarding the responsibility to act on information. For example, if a test identifies a familial risk of a potentially severe condition, should family members be informed even though they have chosen not to be tested?

7.4.1 Ensuring value for money

Australia has a well-developed process for assessing new medical technologies for public subsidy, by way of the health technology assessment process. The need for a rational process, and one that is consistent across funding programs in deciding whether to fund a new technology, is driven by the limited resources available to pay for health care. Australia has introduced formal structures to assess the cost-effectiveness of new technologies, and these are part of both the PBS and the Medicare Benefits Scheme and are in addition to the regulatory structures that are in place to consider the safety and efficacy of new technologies.

There have been a number of reviews of economic evaluation studies in precision medicine (see, for example, Jarrett and Mugford 2006; Vegter et al. 2008; Wong et al. 2010; Beaulieu et al. 2010; Djalalov et al. 2011; Antoñanzas et al. 2012; Assasi et al. 2012; Yang et al. 2013; Buchanan et al. 2013; Simonds et al. 2013; Marzuillo et al. 2014; Miller et al. 2014; Phillips et al. 2014). As precision medicine can vary in its focus, from screening to targeted therapy, and across diseases, it is difficult to reach general conclusions about the cost-effectiveness of the technology. There are inconsistencies in the approach taken in individual studies and in the ratings of quality by reviewers. For example, in an extensive review of cost-effectiveness analyses for colorectal cancer, Frank and Mittendorf (2013) observed significant variability across studies, concluding that the key drivers of the results were: how the costs for the detection of predictive biomarkers were included (not at all, only for patients who received the targeted agent, for all patients); the clinical characteristics of predictive biomarkers (sensitivity, specificity, validity, reliability, timing, prognostic value, testing sequence and incidence); and the data for the targeted agent (based on retrospective subgroup analyses, incorporating heterogeneity of effects, or individualised dosing). However, some general findings about the challenges for economic evaluation emerge.

Although genetic technologies are just another category of new health care technology, and so should be assessed within the same broad HTA framework, there are particular issues that arise in consideration of their cost-effectiveness (Grosse et al. 2008; Deverka et al. 2010). It is important to identify how genomic technologies, and particularly different sorts of technologies (e.g. whole genome sequencing, tests for specific genes or tests for tumour markers), change the treatment algorithm at different points and what the implications are for treatment. The choice of comparative technology against which costs and outcomes are assessed is another issue (Buchanan *et al.* 2013). The choice of comparator for genomically guided cancer care should ideally involve a mix of genomic and non-genomic care. Multiple

comparators may also be of value, particularly when applied to diagnostic tests where there is potential for the use of in-house custom tests of differing cost and analytical validity.

The choice of perspective is key to identifying the scope of outcomes and costs included in the analysis. Choosing a narrow perspective, such as one that emphasises benefits to the health care sector rather than to the economy as a whole, may overlook many of the potential benefits and costs of genomic-based technologies. An example of this is the value that consumers may place on information provided by genetic tests that potentially goes unmeasured or unvalued when the study's perspective is restricted to a health system perspective. Similarly, information may have a negative value if it increases consumer anxiety or concern.

Economic studies of genomically-guided cancer care also require appropriate timeframes to ensure that all downstream costs and benefits are captured. Importantly, economic evaluations of many genomically-guided cancer care technologies are an amalgam of two different technologies: the test and the treatment. This inevitably makes the evaluation more complex and generates more uncertainty about some of the key parameters of the study, such as the sensitivity and specificity of the test results. This makes it important to undertake well-specified sensitivity analyses that can provide information on the importance of such uncertainty to the overall results.

Current HTA approaches rely on clinical evidence produced by clinical trials. Robust trials require large groups of homogeneous patients to achieve statistical significance. In contrast, precision medicine is exploiting the differences between individuals to better target therapy. This produces a challenge in generating scientifically valid evidence. Adding to this complexity, scientific knowledge is expanding at a rapid rate and is likely to change the relationship between genetics, disease progression and therapy. This complex relationship suggests that it is difficult to assess (or predict) the overall impact of genomics on the health care system in terms of health outcomes, costs and delivery.

The decision-making processes for listing pharmaceuticals on the PBS were designed in an era when blockbuster drugs, prescribed to large groups of patients, were commonplace. The additional costs that HTA processes imposed on pharmaceutical companies and governments (such as the costs of producing a health technology report, conducting economic evaluations and undertaking rigorous assessments) were relatively small compared with the overall revenue that could be gained by listing a drug on the PBS. However, the blockbuster era has gone, and the current pharmaceutical market is characterised by more therapeutics for multiple indications and smaller patient groups. This trend is likely to continue with expansion of genomically-guided treatments, where the patient population is getting smaller and the volume of sales for each new therapy is decreasing.

Therapeutics with smaller potential markets may increase the relative costs of undertaking HTA compared with the potential volume of sales. Given that the costs of conducting an HTA is are relatively fixed (i.e. the costs are unlikely to vary much regardless of the sales volume), its expense may begin to put additional pressure on drug prices. These issues may come to the fore with the development of precision medicine. Under circumstances where the target population is small, Australia's current HTA and decision-making processes may become too cumbersome, and alternative priority-setting mechanisms for deciding which technologies to adopt and diffuse may need to be designed.

Box 24: Rare disease economics

Rare diseases are typically complex, debilitating or life-threatening disorders and are a major cause of intellectual and physical disability in childhood. About 8,000 rare diseases have been identified worldwide, and 6 to 8 per cent of the Australian population are affected (Rare Voices Australia 2017). There are an estimated 15,000 new rare disease diagnoses in Australia every year (based on 300,000 births annually), and they account for one-quarter of inpatients in children's hospitals at any one time. As advocates have argued, although rare when considered individually, collectively these diseases have a significant economic and health impact. The rarity of each of these diseases means that diagnosis is often complex, lengthy and can require repeat assessments. Once a diagnosis has been made, many rare diseases have no effective treatment. Improved diagnosis, early intervention and prevention could significantly improve the quality of life of affected patients and reduce the economic burden of rare diseases.

The use of precision medicine to diagnose rare diseases, particularly whole exome sequencing conducted early in the diagnostic pathway, has been shown to increase the diagnostic rate, provide greater accuracy and reduce the cost per diagnosis compared with traditional diagnostic pathways (Stark et al. 2017). Rare diseases are also considered to be good candidates for precision therapeutics that are capable of treating at the level of the gene. Indeed, they have been proposed as good targets of gene editing interventions.

However, the prevalence of individual rare diseases means they pose an economic challenge to traditional models of drug funding. Whereas blockbuster pharmaceuticals are designed to be suitable for broad swathes of the population, the market for a rare disease drug could be as small as a handful of patients. In some cases, this has led to exorbitantly high prices for novel medications. For example, Europe's first approved gene therapy, alipogene tiparvovec (marketed as Glybera and designed to compensate for lipoprotein lipase deficiency, which can cause severe pancreatitis), was made available at a cost of US$1 million per patient; the drug's manufacturer recently announced it would not be seeking renewal for its market licence due to low demand (UniQure 2017). Regulatory measures in some countries, such as orphan drug designations, seek to minimise risk and expedite the work of drug development for rare diseases.

7.5 Regulation of private markets

There are large potential benefits offered by precision medicine, alongside the potential for increased cost pressures on health care budgets. With the rapid development of technology leading to lower costs for genetic sequencing, and the potential for new market-driven opportunities, it is important to ensure appropriate regulations (and incentives) exist to ensure cost-effective use of these new technologies. The policy response will have to address better targeting of genetic tests to population groups, as well as influencing and informing patients and clinicians about appropriate surveillance activities and ensuring that post-market surveillance is part of the infrastructure.

Health care is seen as a growth industry by investors in the Australian economy because Australians are prepared to commit considerable discretionary spending to health, the population is ageing and most health care services are underwritten by government. This provides a context in which private profit can conflict with social objectives. Achieving an economically sustainable precision medicine field will necessitate balancing the cost-effectiveness of new technologies and treatments with effective mechanisms for upholding intellectual property rights, including incentives for the parties developing those innovations.

7.5.1 Pop-up clinics and diagnostic services

New health technologies often provide a niche market for new providers to specialise and develop new customers. This is particularly so when consumers can be recruited directly, without referrals from GPs. A screening test can be useful as a marketing tool and may be offered as a loss leader, particularly if covered by Medicare and thus eligible for bulk billing. People with positive test results can then be recalled for further investigation or treatment. Of course, this provides an incentive to err on the side of classifying more test results as positive and to recoup costs on further tests or treatments.

The development of skin cancer clinics is a case in point. These have proliferated and have been accompanied by a tendency to excise lesions at a rate that is perhaps greater than necessary (The Royal Australian College of General Practitioners 2014). Although such services appear specialised, they are usually staffed by generalist trained doctors rather than dermatologists (House of Representatives Standing Committee on Health 2015).

7.5.2 DIY kits

The market for direct-to-consumer genetic tests, where consumers submit samples and receive information on their genetic profile without the mediation of a GP or other health care professional, has expanded rapidly, facilitated by internet sales and international commerce. Some of the most popular tests are offered through companies such as 23andMe and Ancestry.com, which have been described as offering recreational genomics. 23andMe had to withdraw the links of its ancestry tests to health information after a US FDA warning stated that the company did not have data to justify provision of all the risk analyses it was offering. It has since relaunched with a limited range of health-related advice, concentrating on SNPs associated with high risk of developing several well-characterised diseases, including breast cancer and Alzheimer's disease. The motivation for those taking part in tests offered by 23andMe or Ancestry.com is often an interest in ethnicity or ancestry, but the tests also offer access to a great deal of genetic information, at a low cost.

When direct-to-consumer test companies are based overseas (as is the case for 23andMe), it is difficult to regulate their local use, and they are not subject to NATA accreditation and inspection. However, more than two million people have provided DNA samples to 23andMe, which has also entered into agreements with pharmaceutical companies for the associated data linking gene patterns to health. Even though much of the information offered by the direct-to-consumer companies is accurate and well presented, it cannot give the depth of information tailored to an individual that would be offered by a fully knowledgeable health care provider. As such, the potentially adverse consequences of this form of testing include possible poor

standards of non-accredited providers, variable relevant information, lack of follow-up and counselling services, lack of connection to other health care providers, consequent anxiety for consumers and increased demand on in-country health services (to deal with the results of such testing, regardless of its accuracy or relevance to care). State governments and professional societies in Australia have recognised the need for proper regulation of this market, issuing position statements on the role of direct-to-consumer tests in relation to the health system (see, for example, Australian Medical Association 2012; Office of Population Health Genetics 2013).

7.5.3 Pharmaceutical industry

The pharmaceutical industry has the potential to benefit from the development of targeted treatments, which may command substantially higher prices than established treatments. Currently, the highest returns are made from products for which consumers comprise large segments of the population. Products that will only benefit a small number of patients are less commercially attractive. The industry also bears most of the costs of drug development (although the underpinning basic science is still supported by government in universities and medical research institutes), and these have to be recouped whether the product is for a common or a rare disease. To date, the Australian Government has recognised the need to provide different arrangements for the funding of treatments for rare conditions, including rare genetic conditions, through the Life Saving Drugs Program. The challenge is to encourage inclusion of more therapies that can be directed towards smaller patient groups within the general PBS. It is of note that the prices paid by government are often related to therapeutic benefit for a particular patient group; consequently, the same drug could attract different funding in different patient groups.

The use of economic evidence in determining public funding is a powerful tool for policy makers to increase value for health care expenditure, but decisions are more uncertain where economic evidence is lacking. Clinical and economic evidence takes time to develop, and patients may be denied beneficial treatments in the meantime. One response to this challenge is to provide coverage alongside evidence development, such as through risk sharing arrangements, with the condition that more evidence is collected and with the supplier at risk for a product that proves to be less effective. Thus far, risk sharing arrangements have taken on many forms:

- Agreements that are designed to limit uncertainty regarding costs without considering the health outcome experienced by the patient. For example, a manufacturer pays for a genetic test in order for patients to gain access to a drug that is subsidised on the PBS for individuals with tumours that exhibit specific mutations.
- Price volume arrangements that restrict the financial liability of the payer by placing a cap on their total expenditure. These agreements allow the payer to be reimbursed if the total expenditure exceeds the cap.
- Performance-linked reimbursement arrangements that are designed to limit uncertainty regarding the cost-effectiveness of a new drug in the real-world. For example, under the funding of ipilimumab for melanoma, the funder only pays for the treatment for those patients who respond.

Box 25: Precision medicine health economics questions for further consideration

Insurance

- Where should the responsibility for funding of genomic technologies fall, particularly in a mixed public–private health system such as Australia's?
- Which genomic technologies should be funded or subsidised publicly, and what are the implications of access through the private system in terms of equity and efficiency?

Assessment of risk factors

- What are the implications of genomic technologies, including genetic testing and precision medicine, for private health insurance in Australia?
- Should individuals be required to disclose their testing history to insurers, employers or others?
- Should insurers, employers or others be prohibited from seeking information about testing history from individuals?
- What are the implications for other insurance markets, including life, income and travel insurance?
- Should employers be able to require genetic testing?

Cost of implementation

- Are there delivery system implications (such as economies of scale, volume–outcome relationships) for genomic testing and treatment?
- What are the appropriate funding mechanisms to ensure efficient provision of appropriate and high-quality services?
- Who is responsible for the provision of infrastructure associated with genomic technologies (including storage of genetic information and genetic samples)?
- What are the ethical and legal responsibilities for provision of information to other parties?

Ensuring value for money

- Are the current structures for assessing new technologies, such as MSAC and the Pharmaceutical Benefits Advisory Committee (PBAC), appropriate for assessing new genomic testing and treatment?
- Are structures available for assessing the economics of chronic disease prevention or onset delay?

Pop-up clinics and diagnostic services

- How should the provision of clinics and diagnostic services be regulated to ensure appropriate use of these technologies and to safeguard patient interests?

DIY kits

- Can direct-to-consumer advertising be regulated?
- Can the use of these services be managed to ensure appropriate use of these technologies and to safeguard patient interests?
- Can the quality of laboratories providing genomic profiling be regulated, especially if they are based outside Australia?

Pharmaceutical industry

- How do we ensure that benefits of genetically guided treatment are appropriately shared between the developer of the technology and the taxpayer?
- How do we design payment arrangements for genetically guided treatment to ensure a fair sharing of risks between the developer of the technology and the taxpayer?
- How can we build on existing data collection systems to facilitate monitoring for new risk sharing arrangements?

- Coverage with evidence development arrangements that link population-level payment or reimbursement to prospective data collection.

Despite the obvious attraction, risk sharing agreements have frequently been difficult to implement (Neumann et al. 2011). Some risk sharing arrangements require substantial new capacity to monitor costs and outcomes of new therapies in real-world settings, particularly those that are based on performance-linked reimbursement arrangements that require patient-level outcome measurement. This capacity is often lacking or requires substantial investment.

Thus far, risk sharing agreements have typically been established between the payer and the pharmaceutical manufacturer. However, Ramsey and Sullivan (2014) propose that in the case of genomically guided care, risk sharing agreements between payers and cancer care institutions are worth considering. One of the main reasons for this proposition is that treatment outcomes are not just predicated on the effectiveness of a drug but also on the accuracy of the genomic tests, as well as clinical decisions of who and how to treat. Hence, under traditional risk sharing agreements between payers and manufacturers, the drug company stands to make losses on the basis of decisions that are possibly not in its control. Realigning the agreement between payers and cancer care facilities could address this issue. Under such an agreement, the facility receives greater flexibility to offer patients new therapeutic treatment but bears the financial costs of these decisions if certain predetermined clinical benchmarks are not met. This creates strong incentives within facilities to ensure that the most accurate genetic tests are offered and that treatments are matched to patients most likely to benefit. Despite these potential advantages, such risk sharing agreements would still require a sophisticated data infrastructure to enable outcome measurement, as well as measures to protect facilities from excessive risks.

7.6 Cost-effectiveness of precision medicine

The economic benefits of precision medicine are difficult to assess because they will not only depend on the rate at which the cost of tests comes down, but also on the extent to which the new precision testing can be implemented in practice to reduce the amount of preventable illness. To ensure diagnosis and treatment are considered jointly as part of the cost-effectiveness process, the PBAC and the MSAC will need to review evaluation processes for precision medicine.

Some reviews have found reasonable rates of cost-effectiveness and, to a lesser extent, cost savings (Berm et al. 2016; Verbelen et al. 2016). For example, Verbelen and colleagues (2016) found that a pharmacogenetics-informed treatment strategy was more cost-effective than the alternative in more than half of the studies they reviewed.

Yet other reviews have been less conclusive (Hatz et al. 2014; Phillips et al. 2014; Douglas et al. 2016). For example, Hatz and colleagues (2014b) found that 'personalized medicine in terms of stratifying care by genetic characteristics seems to be neither more nor less economically efficient than conventional medicine'.

A common feature of these reviews and other commentary has been discussion of the challenges in evaluating economic benefits of precision medicine technologies (Antoñanzas et al. 2015; Lu and Cohen 2015; Shabaruddin et al. 2015; Bertier et al. 2016). The challenges span both methodological and data-availability issues. A particular challenge alluded to by Lu and Cohen (2015) is identification of the 'broader impacts on the use and costs of related and/or downstream health services'.

CHAPTER 8
OTHER PRECISION MEDICINE APPLICATIONS AND OPPORTUNITIES

8.1 Introduction

Many of the technologies developed for precision medicine and gene editing are also applicable to agricultural and environmental applications. Data from genomics and other omics, combined with simplified gene editing techniques such as CRISPR, have made it possible to alter the DNA sequence of living cells, giving the ability to alter the genome of any plant or animal. The same technology that is used for large-scale analysis of genetic variants associated with human disease can be applied to crop improvement, animal breeding and veterinary medicine, as well as analysis of environmental diversity. This chapter broadly examines these areas and highlights potential future opportunities for Australia.

8.2 Biotechnology

Australia invests heavily in new ventures in technology, biotechnology and medical devices, with A$10.3 billion invested in R&D in 2017–18 (Department of Industry, Innovation and Science 2017). There are many examples of start-ups that have progressed to initial public offerings, offering both financial and employment opportunities. These ventures are usually 'public-private partnerships', where much of the initial research and development may have taken place at a university, publicly funded research organisation (such as CSIRO) or a medical research institute. A recent example is the development of anti-cancer drugs based on research carried out on the

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oncogene *BCL2* at the Walter and Eliza Hall Institute (see Cory et al. 2017), for which it is envisaged that the value to Australia will come to several hundred million dollars. Forty-five early-stage biotechnology or health technology companies in Australia identify as precision medicine-oriented, and several provide genomic testing and information to practitioners and consumers through pharmacies (Pers. Comms. Dr Carrie Hillyard, 2017).

Much of the technology that underpins precision medicine has been developed in the US or the UK. It would not be easy for Australia to challenge a commercial lead of several years, as well as an intellectual property portfolio that is both comprehensive and nuanced. However, there are still opportunities for Australian involvement, particularly in terms of commercial opportunities, jobs and skills. One example is education and training, where Australian universities and medical research institutes already have a major role in providing training for Australians as well as people from our region in fields as diverse as bioinformatics and genetic counselling.

8.3 Agriculture

Precision genomics, combined with gene editing, is enhancing knowledge about how genes are organised and work in food plants, forest trees, livestock and aquaculture species. This knowledge is leading to new breeding techniques that are being applied to make small, precise changes in genes that are important for productivity, health and environmental protection. The first examples include hornless cattle (see, for example, CSIRO 2017), mildew-resistant wheat (Wang et al. 2014) and altered wood properties in trees (Polle et al. 2013). Recent advances in genome editing, for the most part using CRISPR, have also been applied to alter and accelerate crop breeding cycles, with the potential to develop new varieties in less than five years (Waltz 2016), compared with 7 to 12 years for traditional breeding or an average of 13 years for genetic engineering approaches (McDougall 2011; Scheben and Edwards 2017). Whereas genetic engineered crops are typically subject to multiyear regulatory processes to verify the safety of transgenes (i.e. genes introduced to the crop from different types of organisms), gene editing has benefited from a less cumbersome regulatory process.

The use of precision medicine techniques and gene editing in agriculture may have positive environmental impacts. Using gene editing or gene drive to alter fertility have been suggested as methods to control and eliminate feral animals (such as feral cats) that are destructive to Australian native species (Australian Government 2015) or to control mosquito vectors for diseases such as dengue fever (Kistler et al. 2015). Perhaps the most immediate use of gene editing and sequencing in agriculture will be to improve the health of animal and plant species of economic importance, on both commercial and ethical grounds. Advances that are developed for humans will also help veterinary medicine, if cost-effective, to achieve what might be considered personalised medicine for animals. For instance, many of the genes associated with genetic risk due to selective breeding in dog species have been identified (Hayward et al. 2016), and attempts are being made to breed them out or to change the sequence using CRISPR, either of which would improve the health of the species. Australia has a long and successful history, through CSIRO and biotechnology start-ups, in the field of agricultural and veterinary genomics.

Australia is well positioned to expand into crop and environmental bioinformatics. As bioinformatics is cross-disciplinary, researchers regularly transition between biomedical, environmental and agricultural research, and general support for bioinformatics training in Australia, as well as more general training in genomics, is an effective mechanism to promote the broader biotechnology industry. It is important that universities are encouraged to offer broad-based courses in bioinformatics and related disciplines that can be applied in new areas. Australia has played a major role in sequencing the genomes of several crop species, including wheat and canola, which in some cases were larger and more complex that the human genome (Chalhoub et al. 2014; International Wheat Genome Sequencing Consortium 2014; Golicz et al. 2016; Hane et al. 2017; Montenegro et al. 2017). Local and national access to DNA sequencing capability has supported these advances providing another reason why technology should be distributed and not concentrated in one or two capital cities.

The internationalisation of the market has led to competition and reduced prices for genome sequencing in agriculture, as in other fields, and with advances in new hardware and software, this process is

expected to continue. There remains some uncertainty about the regulation and user acceptance of this technology in Australia, and whether crops developed in this way are, in technical terms, GMOs that come under regulatory surveillance. However, gene editing techniques are already being used to develop crops for the US market that are indistinguishable from conventionally bred varieties and do not contain transgenic material (Scheben et al. 2017). The need for a community consensus on issues such as the production and use of gene technology in agriculture will be important. Careful consideration will need to be given to the regulation of animal or plant varieties that are indistinguishable from similar varieties generated using conventional breeding technologies in use by farmers for hundreds of years.

8.4 Gene technology and the environment

The Australian environment is a unique world heritage resource as a result of the evolutionary isolation of most species after the continent's separation from Gondwana between 50 and 100 million years ago (Veevers and McElhinny 1976). The more recent arrival of Europeans saw a steady introduction of non-native animals and plants, starting with the accidental stowaway rodents from ships. This was followed by deliberate introductions of animals and plants by acclimatisation societies, farmers and other landholders. In the past century, the accidental and deliberate release of unneutered domestic pets by the public has led to feral populations of cats and dogs. Between them, invasive animals and plants have had significant, sometimes catastrophic, impacts on the native fauna and flora of Australia.

Box 26: Precision medicine and innovation in agriculture

The application of genomics to farming has already shaped the industry, in terms of selection and breeding for desirable traits in plants and livestock. The power of personalised genomic capabilities will further enhance innovation in agriculture. For example, genomic analysis is creating further opportunities for increasing farming efficiency and productivity through 'personalised' approaches to soil health. The genomic sequencing of soil microbes from soil samples taken from individual fields on farms is providing insights into soil health and allowing a more directed planting strategy to determine which crops will give higher yields in certain soils (Hartmann et al. 2015). Genomic approaches to soil analysis will also guide the use of fertilisers, pesticides and water.

Personalised genomics will enable personalised nutrition and dietetics for people, as well as animals, creating a greater evidence base to target the use of innovative foods and nutritional supplements. This creates enormous potential in the food technology space, with a consumer-led 'quantified self' approach allowing people to make informed dietary decisions based on their own genomic data. The CSIRO has considerable experience in studies of the impact of diet on health, which may expand by the application of genomic technology, with respect to both the foodstuff and the individual response of the consumer.

Traditional methods to deal with these pests involve chemical poisons (through local or broadcast use of baits) and trapping and shooting of larger animals. For plants, the use of insects as biocontrol systems has had some success, with the alternative being broad-spectrum herbicides. The use of chemicals inevitably has off-target impacts on native species, and the emergence of resistant individuals eventually leads to a re-emergence of pest populations.

There is thus a widely recognised need for innovative control measures for invasive animal and plant species, to ensure the preservation of Australia's many unique ecologies and the threatened species that inhabit those biological niches. CRISPR-based gene drive systems, which could be customised to target any sexually reproducing organism, present new opportunities for pest control (Esvelt et al. 2014).

8.4.1 Gene drives

The CRISPR gene editing tool can be customised to form the engine of a synthetic genetic cassette, known as gene drive, that can duplicate itself during sexual reproduction such that all offspring from a reproductive event will carry the drive system. Theoretically, the gene drive cassette, including a bioactive payload, will spread through a target population over the course of several generations until it is present in all surviving individuals of the target species that are connected biogeographically. Gene drives have been proposed as a tool to control or extirpate an invasive or pest species.

Although the eradication of invasive species can be considered a positive outcome, there are potential unintended ecological consequences that may be related to the loss of a species (Webber et al. 2015). The inherent complexity of ecosystems makes it difficult to predict possible harmful side effects from gene drives towards other species or organisms. As such, they will need to be assessed on a case-by-case basis under controlled or laboratory conditions and not released prematurely into the wild. Further, gene drives can cross geographical borders, which poses challenges regarding who has ultimate responsibility and power to decide on their release (Oye et al. 2014).

More than one million people die annually from vector-borne diseases such as malaria, dengue, yellow fever and Lyme disease (World Health Organization 2016). These diseases are passed to humans through vectors – organisms that can transmit infectious pathogens between living organisms. Common vectors include mosquitoes, ticks, flies and water snails. The spread of vector-borne diseases is influenced by the movement of both human hosts and vectors (Lum et al. 2004), but even current gold standard epidemiological data struggle to understand this.

One of the first organisms to be a priority target was the mosquito species responsible for transmitting malaria. A gene drive cassette was shown to be highly transmissible through a laboratory-contained population of mosquitoes (Gantz et al. 2015). As only female mosquitoes transmit the disease, one suggestion was to interrupt the female development pathway (Hammond et al. 2016). This idea was met with concern because, if unchecked, such a gene drive could ultimately lead not just to local reproductive population collapse but also potentially a global species extinction. Nonetheless, new gene drives are being conceived to control global spread of the relevant mosquito species (Esvelt 2017).

An alternative approach, also using gene drives, is to 'knock in' a gene that stops the mosquito carrying the parasite, thus breaking the cycle of disease spread. This could be useful in Australia, where a different mosquito genus, *Aedes*, is both invasive and a carrier of the dengue virus.

8.4.2 Gene drive for the control of vertebrate pests

Gene drive has also been proposed as a technique to control vertebrate pests, such as mice, rats and rabbits. Modelling suggests that, at least in the case of the mouse, this may be feasible (Prowse et al. 2017). The mouse is a good model system for studying gene drives in vertebrates because of its well-studied genome. Although the technology has potential applications for other pest species (including rats, rabbits, cats and cane toads), there are many important considerations and knowledge gaps to be filled before this can be implemented. Selection of optimal target species, public engagement to discover if these approaches are acceptable and technical development all require focus but also provide an opportunity for public-private collaboration in commercial ventures.

8.4.3 Environmental application of gene editing other than gene drive

Since the 1930s, the cane toad has been marching across northern Australia, damaging ecosystems and decimating certain predator populations with its lethal defensive toxin (Shine 2010). Attempts to mitigate this have shown that the predators affected (including the northern quoll and freshwater crocodiles) can be trained using 'conditioned taste aversion' not to eat cane toads (Ward-Fear et al. 2017). Gene editing could be used to knock out the enzyme that produces the lethal toxin. The resulting non-lethal cane toad should still be distasteful to predators and could potentially be released to protect threatened predator populations (Tingley et al. 2017). As more is understood about the biology of specific pests and their environments, it may be possible that gene editing can be used in ways that do not involve gene drives.

8.4.4 Tracking epidemics

The availability of increasingly cost-effective high-throughput sequencing technologies makes it realistic to implement genomic surveillance as part of infectious disease control and elimination (see Section 2.8). A major challenge now is how to move from sample collection to data output in a timeframe that allows data to influence control programs and patient treatment. Real-time portable sequencers can generate enough sequence data to cover an entire pathogen genome within hours, as shown for the Zika (Quick et al. 2017) and dengue viruses (Yamagishi et al. 2017). However, there is a need for approaches that translate this complex data into actual solutions; this will require novel methods to take advantage of genomic information in an efficient, adaptive and user-friendly manner (Kwiatkowski 2015).

These data must also be accessible across research, public health and clinical settings, which will require computer scientists and bioinformaticians to develop user-friendly computational tools to make use of genomic data.

Box 27: A New Zealand case study

New Zealand, along with many other countries, is considering how new precision technologies might be considered within a scientific, regulatory and societal acceptance framework. The Royal Society Te Apārangi has established an expert panel with a broad disciplinary base to consider the social, cultural, legal and economic implications of revolutionary gene editing technologies. This panel has built on the Society's publication of an evidence update on the range of new gene editing technologies now available and how they are being used internationally (Royal Society Te Apārangi 2016). The panel is using a case study approach covering health, environment and agriculture to comment on this quickly evolving area. Case studies are an effective mechanism for reaching an audience beyond academia and provide practical scenarios of possible applications and challenges to their uptake. The panel has been mindful of the need to meaningfully embed Māori views into deliberations over the use, acceptance, and governance of these technologies.

Much like Australia, New Zealand is subject to the impacts of invasive pests, weeds and diseases, with major implications for natural and productive ecosystems. New Zealand uses a wide range of control methods but has achieved few successful eradications and faces constraints (including animal welfare concerns, pesticide resistance and environmental contamination). Alternative options are therefore being explored.

The New Zealand Government recently announced a policy goal for New Zealand to become predator-free by 2050, with a focus on predators affecting conservation targets (New Zealand Department of Conservation Te Papa Atawhai 2017). While there has been a rapid growth in community-led pest control and demand for effective, safe and ethically approved management tools, large-scale eradication will require new technologies. Gene drives have been proposed as a way of delivering modified reproductive controls (Burt 2003), and the development of technologies such as CRISPR-Cas9 provides the means for targeted reproductive manipulation. In view of possible hype regarding the potential of gene drives, the panel's case studies aim to present a balanced view of both the challenges ahead

The Royal Society Te Apārangi has established an expert panel with a broad disciplinary base to consider the social, cultural, legal and economic implications of revolutionary gene editing technologies

and potential uses of gene drives in targeting invertebrate and vertebrate invasive predators (Dearden et al. 2017).

Vespulid wasps (the German and common wasps) are introduced social insects that have had a severe impact on birds, native invertebrates and tourism experiences. Current eradication tools are of limited effectiveness, although they have strong public support. Gene drives are a possible strategy, but one that is impeded by limitations in knowledge of wasp embryology, social insects' genetic transfer mechanisms and undeveloped containment methods for population studies, as well as unexplored cultural (especially Māori) views of human relations with the natural world, animal welfare, ethics and regulation. **Introduced mammals**, such as the brushtail possum, are also high priorities for control measures that do not rely heavily on toxins. Here, challenges include the low reproductive rate of marsupials and complexities of manipulating oocyte production.

Gene drives may also offer potential for management of **invertebrate pests**, such as the Argentine stem weevil – a major pasture pest for which parasitic biological control is breaking down (Tomasetto et al. 2017) – or the Australian sheep blowfly. However, there are concerns about the reversibility of gene drives and the risks of transferring modified genes to places where pests are native. Gene editing also offers opportunities for floral management by, for example, editing in disease resistance to native plants. Recent outbreaks of myrtle rust in native plants may provide a pathway to social acceptance for enhanced natural selection.

The hype and excitement around these advances needs to be tempered by aligning public expectations and scientific, cultural, regulatory and societal challenges. Scenario-based engagement may encourage pragmatic debate and, if publicised well, increase public engagement. As the New Zealand expert panel recognises the need to frame the debate within national cultural, economic and environmental criteria, additional papers are being prepared on regulatory constraints and engaging with Māori.

8.5 Forensic science

One field in which genomics has already been significant is forensic science. DNA evidence is now central to many police investigations. While the purpose of precision medicine does not overlap with the use of DNA by the police, there are legitimate research drivers in the context of using genomics and related sciences for health that could also be of value in preventing crime. However, genomic data that could be accessible for health reasons should not be accessible by the police for criminal investigations; the forensic services should be separate from the use of DNA for the prevention and treatment of disease. There are significant ethical issues associated with the use of individual health data and biospecimens in criminal contexts (see, for example, M'Charek 2008). A discussion of these issues is beyond the scope of this report, but it is a matter for empirical investigation.

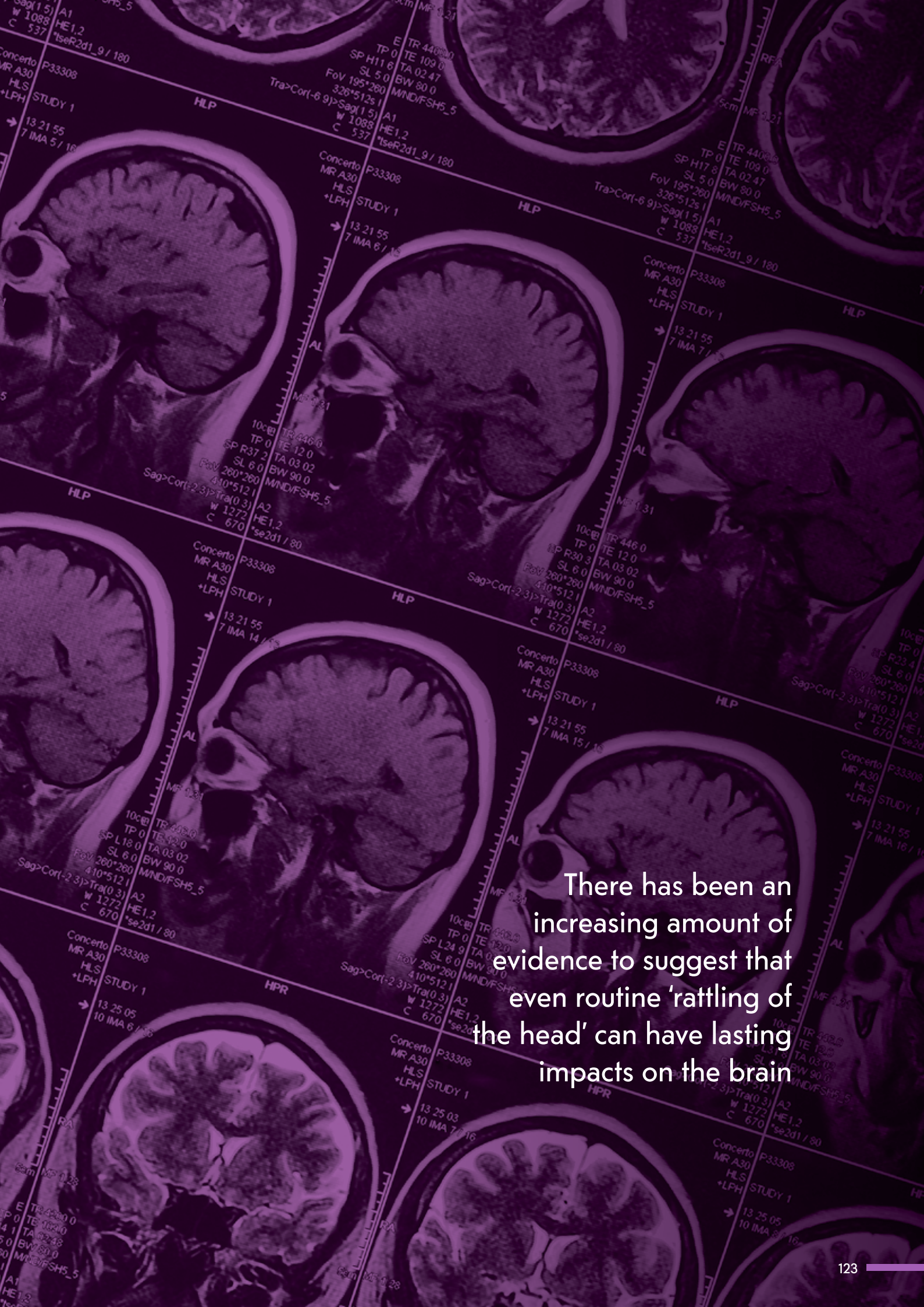
There will nevertheless be overlaps. For example, it is legitimate for health reasons to study genes that are involved in cleft lip and palate, but these genes are also involved in how a face looks and the parameters of the face that can be measured (Dixon et al. 2011). These studies may in the future mean that a DNA sample and its sequence may be used to predict what a person looks like; not only hair, eye and skin colour, but potentially the shape of the face and its features. This is legitimate medical research that could also be of interest to law enforcement. It is important that the community is reassured that there are lines that separate these very different functions.

There are several university degrees in forensic science (e.g. at Deakin University, Griffith University and the University of Tasmania) that make full use of the concepts and practice of precision medicine: genomics, proteomics, microbiomics, metabolomics and epigenetics. This may provide opportunities for Australia to be viewed as a major provider of tertiary skills-based education in all aspects of precision medicine, forensic science and related fields.

8.6 Trauma and personalised medicine: defence and sport

There is considerable interest in the consequences of repeated mild trauma, especially in the context of concussion-related traumatic brain damage to Australian Defence Force personnel and to professional sportsmen and sportswomen in contact sports such as Australian rules and rugby league football. There has been an increasing amount of evidence to suggest that even routine 'rattling of the head' can have lasting impacts on the brain (Head injuries in sport must be taken more seriously [editorial], *Nature*, 2017, 548, 371).

The role of brain trauma in causing brain damage and dementia is dependent on individual response. While many of those subject to concussion, whether from sport or from an improvised explosive device, will develop neurological problems, many will not. This is the type of problem for which personalised medicine approaches could be of great value. There is a case to be made that serving defence force personnel and professional sportspeople should be among those who are given the opportunity to participate in any pilot program offering genome sequencing, as these people will be followed up for any sign of chronic traumatic encephalopathy. DeKosky and colleagues (2013) have suggested that whole genome sequencing of patients with chronic traumatic encephalopathy from traumatic brain injuries could provide comprehensive genetic profiles of individuals who develop chronic traumatic encephalopathy, as well as those with identical traumatic brain injury histories who remain cognitively intact.



There has been an increasing amount of evidence to suggest that even routine 'rattling of the head' can have lasting impacts on the brain

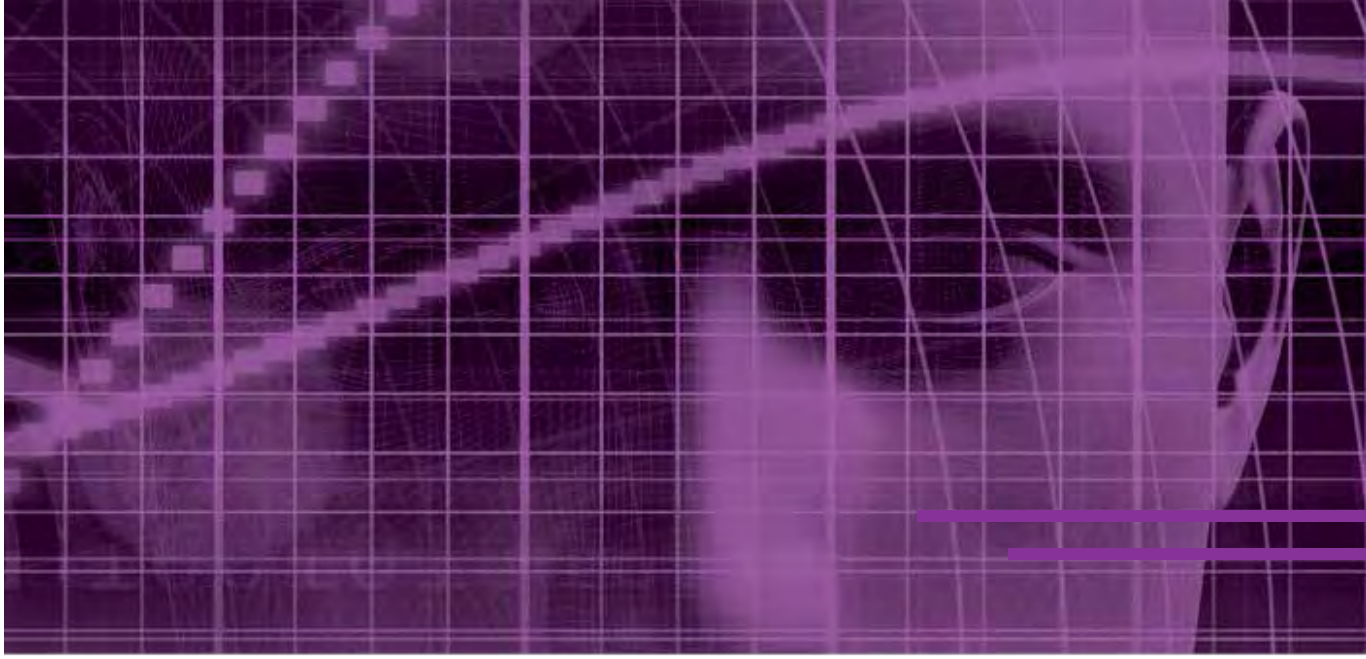
CONCLUSION

Precision medicine is already underway in Australia and is set to evolve in exciting directions in the near future. This report has mapped these directions, identifying the opportunities precision medicine opens up, as well as the challenges that accompany them. In many ways, Australia is well equipped to advance precision medicine: we enjoy a world-class health system; expertise across genomics, primary care, data and ethics; and a strategic position as a regional leader that is also linked to key global networks. However, in addition to the expected ups and downs of scientific research, precision medicine will pose ethical, economic and logistical challenges. Navigating these successfully and sensitively will be a defining task for the field.

Some forms of precision medicine are already commonplace. Oncologists order genome sequencing of tumour tissue with the aim of determining the best course of treatment for their patients; laboratory scientists routinely use CRISPR gene editing to test the effects of genetic variants and pharmaceuticals; epidemiologists sequence DNA from bacteria and viruses to trace and halt the evolution of potential pandemics; and Australian facilities sequence patients' whole genomes by the day.

While the core of precision medicine is genomics, other omics are also key, and as the field develops it will benefit from the insights of diverse disciplines, such as public health, epidemiology, computer science, immunology, primary and specialist medicine and the social sciences. Clinical expertise, in particular, will be fundamental in bringing precision medicine to patients. There is a historical tendency for Australian research to be carried out in silos; knowledge exchange across institutions, disciplines, geographical locales and public-private sectors will be central to making precision medicine work in and for Australia. This kind of connectivity can be facilitated through appropriate regulation (e.g. permitting and safeguarding the movement of data and samples), funding structures (e.g. consortium-based funding) and technological support (e.g. data ecologies). The National Health Genomics Policy Framework provides a valuable roadmap for integrating genomics into the health system. Like this report, the framework highlights the need for a highly skilled workforce, for sensitivity in addressing social and ethical questions and for genuine, ongoing public consultation. This will be a valuable resource for guiding precision medicine in years to come.

Part of making precision medicine not only socially acceptable but also valuable is the task of ensuring it meets the needs of the whole Australian public, while safeguarding their interests and allaying any concerns that may arise. This will involve engaging with the current state of Australian society, especially the inequities that affect Indigenous Australians; and it will involve investment in research that examines the cultural significance, ethical grey zones and social value of precision medicine.



A patient's view of precision medicine

In closing, consider a speculative scenario for the precision medicine clinic of the future, contrasted with medicine today. **Today,** a patient will wait until they feel a lump, for instance, then will see a primary care doctor, who will refer them to a specialist, who may note that they are overweight or smoke or do not exercise – but will only provide treatment for the patient's cancer and will do so using consensus data, which, to some extent, are 'trial and error' because each patient can react differently to a particular drug. **In the future,** a patient will arrive at the hospital or practice with their whole genome already on file, accessible across institutions and perhaps even from their own personal device. The data will have been used to ensure that appropriate advice on weight loss, hypertension (with the right drugs) and smoking (with the right biomarkers) has already been provided to them. For a patient living with chronic disease, their GP has prescribed medication according to their personal pharmacogenomic data. The development of their condition, including response to medication, can be traced by relatively non-invasive, serial measurement of proteomic biomarkers. If cancer is found, the patient is treated according to both their own genomic profile and that of their tumour; they have an increasing range of therapies, both approved and in clinical trial contexts, available to them.

Advances in the clinic will be underpinned by strong programs of basic research, where gene editing has accelerated the pace of discovery and innovation. Data sharing and point-of-care testing make precision medicine advances available to patients living in rural and remote regions. The data are shared internationally to maximise patient benefit, but individuals are still protected by dedicated regulatory provisions that safeguard patients' personal information. Education and training programs that keep pace with technological developments will ensure practitioners have the necessary skills and expertise for precision medicine advancements. Healthy patients can acquire epigenetic and biomarker data on their risk of developing diseases such as diabetes, which can subsequently be mitigated through personalised lifestyle, medical and environmental measures, as advised by their GPs, specialists and genetic counsellors, and by highly professional educational material. Ongoing engagement ensures that as community perspectives on precision medicine develop, they are folded back into the precision medicine portfolio, producing a health future that meets community expectations and is socially and medically of a world standard.

APPENDIX A INTERNATIONAL PRECISION MEDICINE INITIATIVES

A.1 Global actions, alliances and initiatives

A.1.1 Global Alliance for Genomics and Health

The Global Alliance for Genomics and Health (GA4GH) is a collaborative public-private partnership established in 2013 to accelerate progress in human health through responsible sharing of genomic and clinical data (Global Alliance for Genomics and Health 2017a). GA4GH comprises organisational members from 500 institutions in 45 countries, including 28 organisational members from Australia, among them CSIRO, Australian Genomics Health Alliance and the Murdoch Children's Research Institute.

In October 2017, GA4GH's vision for global genomics in the next five years was launched by Francis Collins, Head of the US National Institutes of Health (NIH):

- **In 2022, genomic data on tens of millions of individuals are responsibly accessible via GA4GH standards.** The vast majority of these data have been generated through health care approaches.
- **Genomics data that can be shared responsibly *are* shared responsibly,** meaning every qualified clinician, researcher and corporate entity around the globe shares and has access to the maximal data set that is privacy-preserving within the context of the relevant and localised consent and authorisation policies.
- **Genomic and phenotypic data are integrated in clinical records** and form a 'health care learning system'.
- **GA4GH collaborates and coordinates** with the many other global, national, regional and enterprise activities within the genomics and health ecosystem and regularly engages policy makers to ensure ongoing funding of genomic testing and sustainability.

GA4GH is comprised of work streams that address key aspects of genomics: two Foundational Work Streams (Data Security, and Regulatory and Ethics) and various Technical Work Streams (Clinical and Phenotypic Data Capture, Cloud, Data Use and Researcher Identities, Discovery, Genomic Knowledge Standards, Large Scale Genomics). The GA4GH Work Streams collaborate with real-world genomic initiatives (GA4GH Driver Projects) to identify the standards most needed by the international genomics community to share data. The Driver Projects in turn implement and evaluate the frameworks, tools and standards produced by the Work Streams.

Examples of Driver Projects include:

- Beacon Project: an open internet search engine that enables the presence of specific gene mutations to be queried across a growing network of shared genetic data sets.
- BRCA Challenge: combines information on sequence variation, phenotype and scientific evidence on *BRCA* genetic variants from around the world, with the aim of increasing understanding of breast cancer and other cancers.
- Cancer Gene Trust: an online network that brings together somatic cancer genomic and clinical data from medical institutions worldwide and makes the data publicly accessible for cancer research.
- Matchmaker Exchange: a federated platform to facilitate matching of rare disease cases with similar phenotypic and genotypic profiles (Philippakis 2015).
- Australian Genomics, Genomics England and the US Precision Medicine Initiative *All of Us:* national genomic medicine implementation programs which will facilitate iterative development and testing of data sharing tools, ethical standards and data security approaches.

The national genomic medicine Driver Projects also collaborate through the GA4GH Partner Engagement initiative to facilitate two-way dialogue with key communities worldwide and enable all national genomic medicine initiatives to share best-practice. GA4GH, in partnership with Genomics England and Australian Genomics, has established a consortium of 15 national genomics initiatives, which meets six-monthly to promote sharing of data, resources and experience.

A.1.2 Global Genomic Medicine Collaborative

The Global Genomic Medicine Collaborative (G2MC) is a non-profit organisation that arose from the 2014 Global Leaders in Genomic Medicine Summit and which now sits under the administrative remit of GA4GH. The G2MC aims to develop genomic medicine projects with global participation by producing educational platforms, community engagement and dissemination strategies; create a registry of projects with the aim of facilitating translation and collaboration; provide a policy forum for genomic medicine; and directly address Stevens–Johnson syndrome and toxic epidermal necrolysis. These goals are addressed by seven working groups, covering communication, education, evidence, IT, bioinformatics, pharmacogenomics and policy, and a steering group that oversees these. Several members of Australian Genomics play roles in G2MC, such as Professor Robyn Ward, who is currently Co-Chair.

A.2 Africa

A.2.1 Human Heredity and Health in Africa Initiative

The concept for the Human Heredity and Health in Africa (H3Africa) Initiative was developed during a Frontiers Meeting of the African Society of Human Genetics, the US NIH and the Wellcome Trust in 2009, which identified the need for a large-scale research program in Africa. H3Africa was announced in 2010 and is supported by the NIH and the Wellcome Trust. The aim of the initiative is to enhance understanding of disease susceptibility and drug responses in African populations through innovative genomics research in a pan-continental network of laboratories.

H3Africa manages biospecimen collection from 22 African countries through its Biorepository Program at three biorepositories in Uganda, Nigeria and South Africa. The data from these specimens are available for genomics research. In addition to this program, H3Africa runs personalised medicine training events and produces guidelines and policy documents (Human Heredity and Health in Africa 2013).

A.3 Asia

A.3.1 BGI

BGI (previously known as the Beijing Genomics Institute) is a Chinese company based in Shenzhen. BGI has established large-scale DNA sequencing infrastructure at the QIMR Berghofer Medical Research Institute in Queensland, and has signed collaborative agreements with several Australian research institutions.

A.3.2 GenomeAsia 100K

GenomeAsia 100K is a non-profit organisation that aims to create reference genomes and identify key alleles for the Asian population. The initiative is hosted at Nanyang Technological University in Singapore, with support from founding partners Macrogen and MedGenome. The first stage of the project aims to sequence 10,000 people to generate reference genomes from all major Asian ethnic groups. This will be followed by sequencing of 90,000 additional people. Genomic data will be combined with clinical, microbiome and phenotype information to allow greater analysis of disease causation. The initiative was announced in 2016, with an aim to complete the database by 2020 (Genome Asia 100K 2017).

A.3.3 China Precision Medicine Initiative

Announced in March 2016, the China Precision Medicine Initiative is a US$9.2 billion 15-year initiative run by the Chinese Academy of Sciences to fund Chinese precision medicine research. The initial project will involve collection of genetic data from 2,000 people and will be carried out by a cross-disciplinary team coordinated by the Beijing Institute of Genomics (Russell 2016).

A.3.4 Japan's Initiative on Rare and Undiagnosed Diseases

Launched in 2015, Japan's Initiative on Rare and Undiagnosed Diseases (IRUD) aims to provide diagnoses for people with medically unidentifiable conditions, using genome sequencing technologies. The project includes children and adults who experienced childhood-onset symptoms (Otake 2015). Patients are assessed by multidisciplinary teams drawn from across 34 IRUD clinical centres. Additional project foci include identifying novel, mutation-specific therapeutics and integrating data with global networks and databases.

A.3.5 Indian Department of Biotechnology Human Genetics and Genome Analysis program

The Indian Department of Biotechnology (DBT) is driving genomics research and engagement in India through its Human Genetics and Genome Analysis program (Department of Biotechnology 2017). In 2013, the Indian Government, through DBT, commenced its five-year plan to promote human genomic and genetic research. Its strategy involves acquisition of genomic technologies, the creation of five new

genomic research centres and establishment of technology transfer organisations and incubators to commercialise new genomic technologies (Padma 2016). The major outputs to date include establishment of 21 genetic diagnosis and counselling units, implementation of a consortium project at several Indian medical research institutes and the formation of three advisory taskforces:

- Task Force on Genome Engineering Technologies and their Applications;
- Task Force on Human Genetics and Genome Analysis; and
- Priority areas of Human Genetics and Genome Analysis Task Force.

The DBT also established the National Institute of Biomedical Genomics (NIBMG) in 2010, which was the first institution in India solely devoted to biomedical genomics. NIBMG aims to accelerate genomic medicine by conducting and communicating leading genomics research, establishing world-leading infrastructure and facilitating faster uptake of novel genomic technologies through greater operational understanding. Its key outputs include workshops, conferences, policy documents and publications in scientific journals (National Institute of Biomedical Genomics 2017).

A.4 Europe

A.4.1 International Consortium for Personalised Medicine

The International Consortium for Personalised Medicine (ICPerMed) began in 2016, as a result of several workshops run by the European Commission, and is funded by the EU's Horizon 2020 Research and Innovation Program (ICPerMed, 2017). It is a platform of more than 30 European and international organisations created to encourage collaboration in personalised medicine research, funding and implementation. The high level of participation of personalised medicine groups allows ICPerMed to map the work taking place throughout Europe, which enables it to develop frameworks for infrastructure, resources and regulatory procedures to facilitate the development of personalised medicine.

The ICPerMed Action Plan was published in March 2017 and identifies 22 research activities and 8 research-supporting activities that are ready to be implemented at national, European and international scales (Aaviksoo 2017). This forms the basis of the work program for ICPerMed members and stakeholders to 2020. The activities identified span data (sharing, security, access, extraction, use), methods and technologies (disease classification, preclinical models, translation, clinical validation, cohorts, clinical trials) and people (digital literacy, patient engagement, evaluating engagement).

A.4.2 European Personalised Medicine Association

The European Personalised Medicine Association (EPEMED) was founded in 2009 to accelerate adoption of personalised medicine in Europe by providing recommendations on regulations and reimbursement, promoting the creation and application of advanced diagnostic tests, and designing education and training programs for personalised medicine stakeholders (The European Personalised Medicine Association 2017a).

To deliver on these objectives, EPEMED has produced white papers, public fora, research studies and activities led by subcommittees that focus on regulatory, economic and educational issues associated with personalised medicine in Europe. In April 2017, EPEMED announced it will

direct its remaining funds towards funding personalised medicine research through scholarships or fellowships and grants over five years, rather than continuing to produce high-level recommendations and programs (The European Personalised Medicine Association 2017b).

A.4.3 Biobanking and Biomolecular Resources Research Infrastructure – European Research Infrastructure Consortium

The Biobanking and Biomolecular Resources Research Infrastructure – European Research Infrastructure Consortium (BBMRI-ERIC) is a European network of distributed personalised medicine infrastructure. BBMRI was established in 2008 with funding for three years from the European Commission. In December 2013, BBMRI was awarded ERIC status to facilitate collaboration of biobanks and biomolecular resources into a pan-European collaborative facility (BBMRI-ERIC 2017). BBMRI-ERIC is increasing access to quality biobank and biomolecular resources to facilitate high-quality precision medicine research throughout Europe.

BBMRI-ERIC members are Austria, Belgium, Czech Republic, Estonia, Finland, France, Germany, Greece, Italy, Latvia, Malta, the Netherlands, Norway, Poland, Sweden and the UK. In mid 2017, there were 1,379 biobanks or biomolecular resource centres throughout Europe listed in the BBMRI-ERIC directory (Holub 2016).

A.4.4 European Alliance for Personalised Medicine

The European Alliance for Personalised Medicine was established in 2012 with the aim of improving public health research and the regulatory environment for personalised medicine. Its key actions include running educational events for personalised medicine stakeholders and summer school for health care professionals, and publishing guidelines and recommendation documents (European Alliance for Personalised Medicine 2017).

A.4.5 France Genomic Medicine Plan

The France Genomic Medicine Plan 2025 was commissioned by the Office of the Prime Minister in 2015 and published the following year. The plan centres on three targets: first, to develop a leading reputation through the export of French expertise in genomics and precision medicine; second, to prepare to integrate genomics into care pathways for common diseases, as well as cancers and rare diseases; and third, to set up a national genomics framework. A key part of the second target is the aim of sequencing up to 235,000 genomes per year by 2020, followed by the expansion of genomics across the medical landscape (Levy 2016).

A.4.6 Individualised medicine (Germany)

Individualised medicine is a priority area of health research in Germany, as set out by the Federal Ministry of Education and Research. This work will aim to improve diagnostics and therapeutics for patients, and is integrated through all six German Centres for Health Research (German Federal Ministry of Education and Research 2017).

A.4.7 Multiscale Complex Genomics project (Spain)

The Institute for Research in Biomedicine in Barcelona is now home to the EU Horizon 2020-funded Multiscale Complex Genomics project, which focuses on three-dimensional

genomics and data infrastructures. The rationale behind the project is that unidimensional sequencing is insufficient to interpret genomic information, and that 3D or 4D simulations are needed instead. This effort aims to bring the biology community closer to big data. Six other institutions around Europe are collaborating on the project (Anonymous 2015).

A.4.8 Genome of the Netherlands

Part of the BBMRI, Genome of the Netherlands is a national effort to produce population-level information on DNA sequence variation, using whole genome sequencing. The Dutch study is distinctive, as the participants are 250 family trios (comprising parents and offspring) drawn from across all of the Netherland's provinces, who are selected as a representative sample of regional genetic variation (Boomsma et al. 2014). The analysis has yielded findings on the founding of the contemporary Dutch population (The Genome of the Netherlands Consortium 2014).

A.4.9 Faroe Genome Project

The Faroe Genome Project (FarGen) is the Faroe Islands' national genome project. Closely allied with the country's public health system, the project initially aims to sequence the genomes of 1,500 citizens. However, its stated aim is to collect sequence data from as many individuals as are willing to participate (Faroe Genome Project n.d.). The project intends to produce a Faroese reference genome and to roll out findings into diagnostics and care.

A.4.10 SardiNIA

Initiated in 2001, SardiNIA aims to sequence 2000 Sardinian genomes to identify variants associated with age-related disease. A cohort of almost 7,000 people has been genotyped, with more than 2,000 of those receiving whole genome sequencing. Recently, transcriptome data have also been analysed from a subgroup of this cohort (Pala et al. 2017).

A.4.11 The Estonian Biobank

Established in 2001, the Estonian Biobank is based at the University of Tartu's Estonian Genome Centre. It currently maintains genomic samples and data from more than 50,000 Estonians and forms the cornerstone of the Estonian government's recent drive towards precision medicine (Leitsalu and Metspalu 2017).

A.5 United Kingdom

A.5.1 Innovate UK and Precision Medicine Catapult

The Precision Medicine Catapult (PMC) program was a network of collaborative research centres designed to increase innovation in key areas and to help drive economic growth for the UK. The PMC was established in 2015 and was based in Cambridge. Its aim was to harness UK expertise to become a world leader in developing precision medicine tests and therapies (University of Glasgow 2015). Activities ranged across clinical trials, device and diagnostic development and regulatory and reimbursement issues, as well as harnessing big data and bioinformatics.

In June 2017, Innovate UK announced that some aspects of the scientific aims of the PMC would be transferred to the Medicines Discovery Catapult, and the PMC has now closed. The funding for the PMC is instead being directed into providing funding for grants for businesses and precision medicine regional centres of excellence throughout the UK (Innovate UK 2017).

A.5.2 100,000 Genomes Project

The 100,000 Genomes Project was launched in late 2012 by the Department of Health and is run by Genomics England. The project aims to sequence the genomes of 100,000 NHS patients and combine this genetic information with medical records. Participants are patients in the NHS with a rare disease and their families, and patients with cancer (Genomics England 2017a).

The main goals of the project are: to create an ethical and transparent program based on consent; to benefit patients and set up a genomic medicine service for the NHS; to facilitate new scientific discovery and medical insights; and to encourage the development of a UK genomics industry. As of August 2017, the 100,000 Genomes Project had sequenced 32,642 genomes (Genomics England 2017b), using Illumina whole genome sequencing technologies. The project has driven the establishment of the infrastructure required for the delivery of diagnostic genomics services in England, including a centralised sequencing facility, standardised bioinformatics and analysis pipeline and 13 Genomic Medicine Centres (Genomics England 2017b).

A.5.3 Cancer Research UK Genomics Initiative

The Cancer Research UK Genomics Initiative commenced in 2011 and provided funding for genomics research in cancer. The initiative is funding nine projects for two years, all of which include genome sequencing and subsequent analysis of the genomic data. Data from each of the projects are published in an open-access database so they are available for genomics researchers worldwide (Cancer Research UK 2011).

A.5.4 Transforming Genetic Medicine Initiative

The Transforming Genetic Medicine Initiative (TGMI) is a £5.3 million four-year program funded by the Wellcome Trust. It was established in June 2016 to undertake collaborative research, development and promotion required for large-scale genome sequencing to be integrated into mainstream medicine. The TGMI has four key aims:

- To build a gene-disease map that provides information on the association between genes and disease in humans;
- To develop a clinical annotation reference system to provide standards and tools for consistent recording and reporting of genomic data;
- To develop techniques that allow access of data from multiple sources worldwide to deliver fast, automated, large-scale, high-throughput gene analysis required for successful genomics; and
- To develop processes that maximise the research and clinical utilities of genetic testing.

TGMI works to deliver projects, tools and resources. Its key outputs to date include a sequencing data set and gene data analysis software (Transforming Genetic Medicine Initiative 2017).

A.5.5 Deciphering Developmental Disorders

The Deciphering Developmental Disorders (DDD) project is a collaboration between the NHS and the Wellcome Trust Sanger Institute. The project brings together experts from each of the UK's 24 regional genetics services and has completed exome sequencing of 33,000 people, including children with

developmental disorders and their parents. A 27 per cent diagnostic yield was obtained, and the data contributed to the discovery of more than 30 new genetic disorders (Wright et al. 2015). The DDD study promotes the sharing of variants through the DECIPHER database to improve rare disease diagnosis globally.

A.5.6 The Scottish Genomes Partnership

The Scottish Genomes Partnership was established in 2015 and builds on the country's long history of pioneering genetics research. The partnership consists of 12 collaborators around Scotland, who are currently conducting a population study (VIKING) of the richly phenotyped Shetland population, research into cancer genomics and rare diseases, and a partnership with Genomics England. The group work out of sequencing facilities based in Edinburgh and Glasgow and have sequenced 1028 genomes to date (Scottish Genomes Partnership 2017).

A.5.7 Genomics for Precision Medicine Strategy (Wales)

The Welsh Government is currently drafting a precision medicine strategy to improve the health of, and health care for, the people of Wales. The aim is to develop an internationally recognised public health genomics system with Welsh leadership that will operate through a strengthened NHS and strategically chosen partnerships (Welsh Government 2017).

A.6 United States

A.6.1 Precision Medicine Initiative

The Precision Medicine Initiative (PMI) was launched by President Obama in his 2016 federal budget with an investment of US$215 million. The initiative is run by the NIH in conjunction with the FDA and the Office of the National Coordinator for Health Information Technology (The White House, 2016).

The key component of the PMI is the NIH All of Us Research Program, which is an initiative to gather genomic data from one million or more people living in the US to accelerate precision medicine. Participant enrolment for anyone over the age of 18 years living in the US is planned to commence during 2018, and children will be able to participate in the coming years. The project will include healthy individuals and those with rare as well as common diseases. These participants will share biospecimens and longitudinal health data to further the understanding of genetic and environmental factors in determining health outcomes (Precision Medicine Initiative Working Group 2015).

Through a series of funding awards, the NIH has established the essential elements of the All of Us Research Program. Funding has gone towards the establishment of biobanks, data and research centres, health care provider organisations (to collect data), participant centres, participant technology systems centres and communications and engagement (National Institutes of Health 2017).

A.6.2 Million Veteran Program

The Million Veteran Program (MVP) is a national voluntary research program funded by the Department of Veterans AffairsOffice of Research and Development. The program collects genomic and health information from veterans receiving care in the Veteran Affairs health care system. The Department of Defence also partners with the Department of Veterans Affairs to facilitate the enrolment of active-duty participants into MVP. Data will be used to gain a better understanding of disease and military-related illnesses (Office of Research and Development 2017).

A.6.3 California Initiative to Advance Precision Medicine

The California Initiative to Advance Precision Medicine (CIAPM) was announced in April 2015 and received US$13 million funding from the California state government. CIAPM is a collaborative initiative between the state, the University of California and several public and private organisations.

The aim of the initiative is to provide the infrastructure and resources necessary to support precision medicine activities in California. The program is building an inventory of the state's precision medicine initiatives, including research projects, clinical studies, databases and analysis platforms. In addition to this, CIAPM funded two precision medicine demonstration projects in 2015 and a further six projects in 2016 (California Initiative to Advance Precision Medicine 2016).

A.6.4 Innovative Genomics Institute and Initiative

The Innovative Genomics Institute (IGI) was created in 2014 as the Li Ka Shing Centre for Genetic Engineering, from a donation from the Li Ka Shing Foundation. The centre expanded in 2016 and relaunched as the Innovative Genomics Institute.

The Innovative Genomics Initiative is a partnership between the University of California, Berkeley, and the University of California, San Francisco, utilising the IGI. The focus of the initiative is to fully understand CRISPR-based genome editing and apply this to improve health care. Achievements to date include improving the efficiency of gene replacement and initial work towards a treatment for sickle cell disease.

To complement its research, the institute also runs conferences, workshops and public engagement on genome engineering (Innovative Genomics Initiative 2017).

A.6.5 Personalized Medicine Coalition

The Personalized Medicine Coalition (PMC) is an educational and advocacy organisation that was launched in 2004 by 20 organisations representing all sectors of the health care system. PMC brings together researchers, patients and health care providers to promote the understanding and uptake of personalised medicine technologies, services and products by addressing regulatory, reimbursement and clinical adoption issues critical to the field's advancement. Its key outputs to date are a number of policy documents and public events (Personalized Medicine Coalition, 2017).

A.6.6 National Human Genome Research Institute

The National Human Genome Research Institute was launched in 2007 as an outgrowth of the National Center for Human Genome Research (established in 1989). The institute was involved in the Human Genome Project and its Ethical, Legal and Social Implications program.

As of 2011, the group's vision for genomic medicine had emphasised the importance of bioinformatics and computational biology, education and training, and the role of genomics in society (Green and Guyer 2011). Current research covers cancer genetics; comparative genomics; computational and statistical genomics; medical genetics; metabolic, cardiovascular and inflammatory disease; social and behavioural research; and translational and functional genomics (National Human Genome Research Institute 2014).

A.7 Mexico

A.7.1 National Institute of Genomic Medicine

The National Institute of Genomic Medicine (INMEGEN) was established in 2004 by a consortium consisting of the National Autonomous University of Mexico, the National Council for Science and Technology, the Ministry of Health and the Mexican Health Foundation. INMEGEN's key actions focus on genomic research, education and outreach, technology development and development of the institute through strategic alliances. Its main outputs include a postgraduate course in genomic medicine, a number of scientific publications and educational workshops (Instituto Nacional de Medicina Genomica 2013).

A.8 Canada

A.8.1 Personalized Medicine Initiative

The Personalized Medicine Initiative (PMI) was established in 2014 with the goal of introducing technologies for personalised medicine into the Canadian health care system. PMI is a collaborative community, with members from all the technological, preclinical and clinical health care communities in British Columbia, and receives funding from clinical, academic, government and industry partners.

PMI holds weekly meetings at which the perspectives of personalised care stakeholders in government, industry, health care and academia are presented. PMI also sources funding, prepares teams and assists in project management for a range of genomic projects, supports product commercialisation for new technologies, and runs an annual summit on personalised medicine (Personalized Medicine Initiative 2017).

A.8.2 Genome Canada

Genome Canada is a not-for-profit organisation funded by the Canadian Government, founded in 2000. It supports large-scale genomics research projects and provides Canadian scientists with access to the most advanced technologies and expertise, through a network of Science and Technology Innovation Centres. Genome Canada's aim is to advance genomics through research translation, facilitating collaboration and investing in large-scale precision medicine science and technology (Genome Canada 2017).

Genome Canada also supports and funds the Precision Medicine Policy Network, which brings together top Canadian genomics researchers to address four key policy themes:

- Research ethics;
- Health economics and HTA;
- Knowledge transfer and implementation in health care systems; and
- Intellectual property and commercialisation.

Key outputs from the Precision Medicine Policy Network include publications in scientific journals, presentations, workshops and policy documents (Precision Medicine Policy Network 2017).

A.8.3 Orion Health Canada

Orion Health Canada has developed a care coordination tool that allows patients to digitally create, update and share their personalised care plan, which can be accessed by all a patient's health care providers. Using this tool, caregivers receive up-to-date patient data, allowing them to monitor the patient's past and present health care information in one location, and enabling greater collaboration between health care providers (Orion Health, 2017).

A.8.4 Genomics Research and Development Initiative

The Genomics Research and Development Initiative (GRDI) was established in 1999 to fund genomics research in eight federal science departments and agencies, covering areas such as health, agriculture, forestry, aquaculture and environment. The GRDI has provided funding for a number of health genomics research projects to date, on topics such as foodborne illnesses, immunotoxicogenomics and developing safer stem cell treatments (Government of Canada 2017).

A.8.5 Care for Rare

Care for Rare is an Ontario-based initiative that has recruited 4,000 patients with rare diseases. The project unites 21 research groups throughout Canada, which have collectively provided diagnoses for 1,500 patients and discovered 150 new rare disease genes. A number of patient organisations are affiliated with the group, which is also partnering with pharmaceutical companies to translate findings into clinical therapies (care4rare.ca).

A.9 New Zealand

A.9.1 Precision Driven Health Initiative

The Precision Driven Health Initiative was established in March 2016 by Orion Health, the University of Auckland and Waitemata District Health Board, with support from the Ministry of Business, Innovation and Employment. The initiative is investing NZ$38 million over seven years to provide world-leading research in precision medicine. It is also encouraging precision health research through funding of postgraduate scholarships, summer research scholarships and travel grants (Precision Driven Health 2017).

Precision Driven Health focuses on four key themes:

- Making new data sources available to broaden the scope of precise health care;
- Using a range of big data sources for predictive modelling in a health care setting;
- Using disparate data sources, analyses and technologies to enable precise health care; and
- Leveraging technology to encourage self-management of health care.

A.9.2 Orion Health, Medtech and CSC

In late 2015, Orion Health, Medtech and CSC announced they were collaborating to deliver an innovative precision medicine solution for New Zealand. The organisations stated they would be working together to link hospital and primary care data in a single

digital platform, with the aim to integrate this information with genomics, microbiomics, proteomics and other new health data in the future to provide a truly personalised health care system for New Zealanders (Orion Health 2015).

A.10 Middle East

A.10.1 The Nancy and Stephen Grand Israel National Center for Personalized Medicine

The Nancy and Stephen Grand Israel National Center for Personalized Medicine (G-INCPM) was established in 2012 by the Weizmann Institute of Science. It is named after Nancy and Stephen Grand, who donated US$50 million to establish the centre. G-INCPM is a collaborative research facility comprising genomics, protein profiling, drug discovery and bioinformatics research platforms, and is accessible by Israeli academic and industry researchers. The centre aims to support personalised medicine by providing access to cutting-edge infrastructure for researchers and promoting a culture of collaboration and knowledge sharing (G-INCPM 2014).

A.10.2 Saudi Human Genome Program

The Saudi Human Genome Program was launched in December 2013 and, with funding of SAR300 million, aims to sequence the genomes of 100,000 Saudi Arabian people to identify the genetic basis for a range of diseases. The first phase of the project involved standardising sequencing laboratories. This was followed by a period of training and knowledge transfer to increase the national genomic skills base, which will support the ultimate aim of genome sequencing and data analysis. Saudi leaders focused US$40 million on a pilot project to diagnose patients with single-gene diseases, who are recruited by physicians at Saudi research institutions (Kaiser 2016; Saudi Human Genome Program 2013).

A.10.3 Qatar Biobank

The Qatar Biobank was launched in 2012 in collaboration with the Ministry of Public Health and Hamad Medical Corporation. The project aims to establish a national biobank for biological samples and health information to enable research into advancing precision medicine in Qatar, by recruiting more than 60,000 participants by 2019. The project's pilot phase concluded in February 2016 with the official opening of the Qatar Biobank. Qatar Biobank recorded 2006 participants in the first three years of the project (Qatar Biobank 2017).

A.10.4 Kuwait Genome Project

The Kuwait Genome Project aims to sequence the genomes of three subgroups of the Kuwaiti population: Bedouin, Persian and Saudi Arabian. Early results suggest these three groups form genetically distinct clusters, and the project has generated a reference genome for the Persian ancestry group (Thareja et al. 2015). The Kuwaiti Government has received significant international criticism after announcing mandatory DNA sequencing of all permanent residents of Kuwait as a national security measure (Minister 'okays' top panel's report on proposal to amend the DNA Law 2017).

APPENDIX B
COMMERCIAL INITIATIVES

B.1 Commercial companies

B.1.1 Caribou Biosciences

Caribou Biosciences is a California-based gene editing company that was founded in 2011 by Dr James Berger, Dr Jennifer Doudna and Dr Martin Jinek. Caribou is using CRISPR-Cas9 gene editing technology, which Dr Jennifer Doudna co-invented, with applications in human and animal therapeutics, agricultural biotechnology, biological research and industrial biotechnology (Caribou Biosciences 2017).

B.1.2 Color Genomics

California-based Color Genomics was founded in 2013 by Othman Laraki, Taylor Sittler, Nish Bhat and Elad Gil and provides a physician-ordered genetic test to assess hereditary cancer risk. Color Genomics also contributes anonymised data to public genomic databases to assist in genomic research (Color Genomics 2017).

B.1.3 Counsyl

Counsyl is a DNA testing and genetic counselling service founded in 2007 by Ramji Srinivasan, Dr Eric Evans and Rishi Kacker, with US$102 million in funding from private investors (Counsyl 2017). The company's first genetic testing product was launched in 2009, and today it has three different tests:

- Foresight Carrier Screen: targeted at couples who are planning to have children to assess if they carry certain genetic diseases;
- Prelude Prenatal Screen: tests a baby in utero for chromosome conditions such as Down syndrome; and
- Reliant Cancer Screen: assesses an individual's risk of developing nine different cancers.

B.1.4 CRISPR Therapeutics

CRISPR Therapeutics is a gene editing company founded by Dr Rodger Novak, Dr Emmanuelle Charpentier and Shaun Foy in 2013, with initial funding from Versant Ventures. The company was established in Basel, Switzerland, and subsequently opened R&D operations in Massachusetts, USA, and business operations in London, UK. CRISPR Therapeutics licensed the foundational CRISPR-Cas9 patent estate for human therapeutic use from its scientific founder, Dr Emmanuelle Charpentier, who co-invented the application of CRISPR-Cas9 for gene editing (CRISPR Therapeutics 2017).

B.1.5 deCODE Genetics

deCODE Genetics was established in 1996 by Dr Kari Stefansson to map the unique

genomes of the Icelandic population. This population was chosen because there are relatively few ancestors that account for the current Icelandic population, meaning biomarkers of genetic disease are more easily found than in other more heterogeneous populations. The company's work has provided genetic information for Alzheimer's disease, type 2 diabetes, cardiovascular disease and schizophrenia, among other health issues (deCODE Genetics 2017).

B.1.6 DNA Solutions

DNA Solutions was established in 1997 and operates out of Melbourne. It supplies home DNA tests for paternity and other kinds of relatedness, including tests accepted by the Department of Immigration and Border Protection. It also offers a small range of animal DNA tests, including sex identification for birds (DNA Solutions n.d.).

B.1.7 DuPont Pioneer

DuPont Pioneer is an agricultural biotechnology company that was founded in 1926 and is headquartered in Iowa, USA. DuPont Pioneer is using CRISPR-Cas9 gene editing technology to maximise productivity and profitability of a range of agricultural products. The first commercial product DuPont developed was waxy corn hybrids, which are expected to be available to grow in the US within four years, pending trials and regulation (PRWeb 2016).

B.1.8 EasyDNA

EasyDNA is an international firm, with four Australian offices, that offers DNA testing for paternity and other relationship determination. It also supplies some health-related genetic testing (primarily for dietary intolerances), ancestry testing and prenatal testing (EasyDNA 2017).

B.1.9 Editas Medicine

Massachusetts-based Editas Medicine is a discovery-phase genome editing company founded in 2013. It aims to use CRISPR-Cas9 technology to develop curative gene editing techniques, with a focus on eye, muscle, blood, lung and liver diseases, as well as cancer (Editas Medicine 2017).

B.1.10 Fitgenes

Fitgenes was founded by Paul and Leigh Beaver and has been operational since 2008. It provides health advice and training to medical and allied health practitioners, based on genomic analysis of disease-causing pathways. Fitgenes has accredited some 900 practitioners around Australia.

B.1.11 Foundation Medicine

Foundation Medicine was founded in 2010 and is based in Massachusetts, USA, and launched its first product, FoundationOne, in 2012. Foundation Medicine focuses on identifying genetic risk of developing cancer and now has four genome tests, including the first FDA-approved companion diagnostic assay for the treatment of ovarian cancer with rucaparib (Foundation Medicine 2017).

B.1.12 Futura Genetics

Futura Genetics is a Canadian company founded in 2014 by Auro Pontes and Efi Binder. It provides a genetic test that can be used worldwide and is designed to assess an individual's risk of developing each of the 28 most common conditions, including cancer, Alzheimer's disease and obesity (Futura Genetics 2017).

B.1.13 Genus plc

Genus plc is a biotechnology company founded in 1994 and headquartered in Basingstoke, UK. It focuses on the application of gene editing to the porcine, dairy and beef sectors. Genus is currently working with the University of Edinburgh to demonstrate how CRISPR can remove a molecule in pigs that makes them susceptible to porcine reproductive and respiratory syndrome (Genus 2017).

B.1.14 Intellia Therapeutics

Intellia Therapeutics a genome editing company founded in 2014 by Dr Nessan Bermingham, and has its headquarters in Massachusetts, USA. The company's aim is to develop techniques to cure diseases using CRISPR-Cas9 genome editing technology. Intellia's in vivo programs focus on liver diseases, and its ex vivo focus is on receptor T cells and haematopoietic stem cells (Intellia Therapeutics 2017).

B.1.15 myDNA

myDNA, previously known as GenesFX, is a Melbourne-based genetic interpretation company founded in 2007 by Associate Professor Leslie Sheffield. myDNA comprises a team of pharmacologists and molecular and clinical geneticists who provide gene testing and interpretation to explain the relevance of genetic data to the individual and their doctor, with a focus on medication and diet (myDNA 2017).

B.1.16 National Measurement Institute Bioanalysis Research Group

The National Measurement Institute's Bioanalysis Research Group is a government body that commercially supplies a range of products and services related to biological measurement. These include genotype analysis, DNA reference material and standards, and DNA-based testing of stockfeed.

B.1.17 Rosetta Genomics

Rosetta Genomics was established in 2000 by Dr Isaac Bentwich and is headquartered in New Jersey, USA, with offices in the US and Israel. Rosetta develops diagnostic tests to differentiate between various types of cancer to enable accurate diagnosis and prognosis and improved patient care (Rosetta Genomics 2017).

B.1.18 smartDNA

smartDNA was established in 2009 by Dr Margaret Smith and Simone Walsh. It offers genetic and microbiome tests through accredited practitioners, with a focus on wellness and nutrition genomics.

B.1.19 Verge Genomics

Verge Genomics was founded in 2015 by Alice Zhang and Jason Chen, with US$4 million in private funding. Based in California, Verge uses genomic data to develop better drugs to treat brain diseases, including Alzheimer's disease, amyotrophic lateral sclerosis and Parkinson's disease (Verge Genomics 2017).

B.1.20 Veritas Genetics

Veritas Genetics was founded in 2014 by Professor George Church, Mirza Cifric, Dr Preston Estep and Dr Jonathan Zhao and is headquartered in Massachusetts, USA. In March 2016, Veritas launched its gene-testing kits for US$999, which includes screening, analysis and genetic counselling. In addition to whole genome sequencing, the company tests for several types of cancer and for hereditary diseases in newborns and pregnant women (Veritas Genetics 2017).

B.1.21 23andMe

California-based 23andMe was founded in 2006 by Anne Wojcicki, Linda Avey and Paul Cusenza and launched its Personal Genome Service one year later. In April 2017, 23andMe had genotyped more than two million customers worldwide and was granted first-ever FDA approval to market direct-to-consumer Genetic Health Risk reports, including tests for Parkinson's and Alzheimer's diseases. In addition to providing genomic services to customers, 23andMe also contributes its customers' genomic data, with the individual's permission, to a number of scientific studies; on average, one customer contributes their genomic data to more than 200 studies. 23andMe has published more than 75 peer-reviewed studies in scientific journals and has produced a number of white papers on its discoveries (23andMe 2017).

In late 2013, the FDA banned 23andMe from offering genetic screening for health information because the company had not provided evidence of the accuracy of its detection methods or standard error information (Gutierrez 2013). 23andMe recommenced providing consumers with genomic-based health information again in late 2015, after gaining FDA approval (23andMe 2015).

Box 28: US CRISPR-Cas9 patent dispute

The application of CRISPR-Cas9 for gene editing was invented by Jennifer Doudna and Emmanuelle Charpentier (University of Vienna) in 2012 at the University of California (UC), Berkeley. They used the tool to cut and rearrange viral DNA. In 2013, Feng Zhang, a bioengineer from the Massachusetts Institute of Technology and Harvard's Broad Institute, created a procedure for using CRISPR-Cas9 specifically for eukaryotic (including human) cells. Both teams filed for patents – UC first and the Broad Institute shortly after – the latter opting for an expedited review process. The Broad Institute was awarded the patent first.

UC lawyers filed for an 'interference' proceeding in January 2016 in an effort to reverse the Broad Institute's patent, arguing that the use of CRISPR-Cas9 in eukaryotes overlapped with the UC invention. In February 2017, patent judges ruled that the Broad Institute's invention was distinct from that of UC and the patent would stand (Ledford 2017). The UC legal team appealed the ruling in April 2017 (Sanders 2017). Charpentier, Doudna and their respective organisations were granted patents by the UK's Intellectual Property Office in March 2017 (Doudna Cate et al. 2017), the European Patent Office in July 2017 (Jinek et al. 2017) and, more recently, by China's State Intellectual Property Office (Paganelli 2017).

APPENDIX C
MOLECULAR DIAGNOSTICS FACILITIES

The following table presents all the NATA- and RPCA-accredited laboratories in Australia that currently offer molecular testing (of any type) on non-research patient samples.

Laboratory name	Hospital	Suburb	State
Sullivan Nicolaides Pathology		Bowen Hills	QLD
Pathology North	Royal North Shore Hospital	St Leonards	NSW
NSW Health Pathology	Concord Hospital	Concord	NSW
St Vincent's Pathology (SydPath)	St Vincent's Hospital	Darlinghurst	NSW
NSW Health Pathology	Royal Prince Alfred Hospital	Camperdown	NSW
Douglass Hanly Moir		Macquarie Park	NSW
QML Pathology		Murarrie	QLD
NSW Health Pathology	South Eastern Area Laboratory Services	Randwick	NSW
The Children's Hospital at Westmead	Westmead Hospital	Westmead	NSW
SA Pathology	Flinders Medical Centre	Bedford Park	SA
SA Pathology	Royal Adelaide Hospital	Adelaide	SA
SA Pathology	Women's and Children's Hospital	North Adelaide	SA
Alfred Pathology Service	Alfred Hospital	Melbourne	VIC
PathWest Laboratory Medicine WA	Royal Perth Hospital	Perth	WA
PathWest Laboratory Medicine WA	Fiona Stanley Hospital	Murdoch	WA
PathWest Laboratory Medicine WA	QEII Medical Centre	Nedlands	WA
Melbourne Health Shared Pathology Service	Royal Melbourne Hospital	Parkville	VIC
Peter MacCallum Cancer Centre		Melbourne	VIC
ACT Pathology	The Canberra Hospital	Garran	ACT
St Vincent's Pathology	St Vincent's Hospital Melbourne	Fitzroy	VIC
Victorian Infectious Diseases Reference Laboratory	Doherty Institute	Melbourne	VIC
Mater Pathology	Mater Hospital	Brisbane	QLD
Pathology Queensland	Royal Brisbane and Women's Hospital	Herston	QLD

Laboratory name	Hospital	Suburb	State
Austin Pathology	Austin Hospital	Heidelberg	VIC
Monash Pathology	Monash Hospital	Clayton	VIC
Adelaide Fertility Centre Pty Ltd		Dulwich	SA
NSW Health Pathology	Liverpool Hospital	Liverpool	NSW
Pathology South	Royal Hobart Hospital	Hobart	TAS
Genea Ltd		Sydney	NSW
Western Diagnostic Pathology		Myaree	WA
Victorian Clinical Genetics Services Ltd	Royal Children's Hospital	Parkville	VIC
Australian Clinical Labs		Clayton	VIC
Pathology North	John Hunter Hospital	New Lambton Heights	NSW
St Vincent's Hospital Melbourne		Fitzroy	VIC
Griffith University		Nathan	QLD
Genomics Research Centre Diagnostic Clinic		Kelvin Grove	QLD
Garvan Institute of Medical Research		Darlinghurst	NSW
Australian Red Cross Blood Service		West Melbourne	VIC
Genomics for Life Pty Ltd		Newmarket	QLD
Hudson Institute of Medical Research		Clayton	VIC
Genomic Diagnostics		Heidelberg	VIC
Cancer Genetics Diagnostic Laboratory	Royal North Shore Hospital	St Leonards	NSW
Viafet		Penrith	NSW
Genome.One Pty Ltd		Darlinghurst	NSW
Virtus Health Specialist Diagnostics		Spring Hill	QLD
GenSeq Labs Pty Ltd		South Yarra	VIC
Clinical Laboratories (WA) Pty Ltd		Subiaco	WA
Monash Reproductive Pathology and Genetics		Clayton	VIC

The following table presents NATA- and RPCA accredited laboratories in Australia that currently offer molecular testing (of any type) using next-generation sequencing methods.

Laboratory name	Suburb	State
Sullivan Nicolaides Pathology	Bowen Hills	QLD
South Eastern Area Laboratory Services (SEALS)	Randwick	NSW
The Sydney Children's Hospitals Network	Westmead	NSW
SA Pathology	Adelaide	SA
SA Pathology	Bedford Park	SA
SA Pathology	North Adelaide	SA
PathWest Laboratory Medicine WA	Nedlands	WA
PathWest Laboratory Medicine WA	Murdoch	WA
Peter MacCallum Cancer Centre	Melbourne	VIC
SA Pathology	North Adelaide	SA
St Vincent's Pathology	Fitzroy	VIC
Mater Pathology	South Brisbane	QLD
Pathology Queensland	Herston	QLD
Austin Pathology	Heidelberg	VIC
Victorian Clinical Genetics Services Limited	Parkville	VIC
Australian Clinical Labs	Clayton	VIC
Pathology North	New Lambton Heights	NSW
Genomics Research Centre Diagnostic Clinic	Kelvin Grove	QLD
Genomics for Life Pty Ltd	Newmarket	QLD
Genomic Diagnostics	Heidelberg	VIC
Genome.One Pty Ltd	Darlinghurst	NSW
St John of God Pathology	Subiaco	WA

GLOSSARY

Amino acid	Small organic molecules that are coded for by DNA and that combine to make up proteins
Amplification	The process of copying a segment of DNA or RNA to create a greater mass of the desired sequence
Anatomical pathology	The study of how disease affects the body at both a macro (e.g. organs) and micro (e.g. chemical) level; often diagnostic
Antibody	A type of immune protein produced by white blood cells that can recognise and neutralise harmful pathogens (e.g. viruses, bacteria)
Autologous	Of a patient's own body (e.g. autologous cells)
Bacterium	Single-celled microorganism; some bacteria are disease-causing
Big data	Data that are collected or combined in such a large quantity that they cannot be stored, analysed or used by traditional methods; data science and machine learning are thus key to much big data processing
Biobank	A repository of biospecimens
Bioinformatics	The collection and use of biological data, using computers, and usually drawing on interdisciplinary expertise
Biomarker	An indicator of some physiological process, often disease-related, that can be measured to assess a patient's state of health
Biospecimen	A biological specimen, such as tissue, DNA, urine or blood
Biotechnology	The use of living organisms to create products (e.g. genetically modified viruses, disease-resistant crops and the CRISPR gene editing system)
Blockchain	A digital, public record of online transactions
Carrier screening	Genetic testing to determine if a person has a certain mutation; different diseases are screened for before, at and after birth
CAR-T cells	Chimeric antigen receptor T cells. Immune cells that have had a synthetic receptor added to make them more specific to a certain kind of disease cell
Cardioprotective	Protective of the heart
Cas9	An enzyme that originated in bacteria but is now widely used with CRISPR for gene editing; it is capable of cutting double-stranded DNA at a specific site, guided by a specifically selected RNA sequence
Cell culture	Refers to both cells grown under controlled, laboratory conditions and the process of growing them
Cell line	A cell culture derived from a single cell, sharing the same genetic material
Chemoprotective	Protective of healthy tissue from the toxicity of chemotherapies

Citizens' jury	A method of public opinion gathering based on courtroom practice, wherein a randomly chosen and representative group of people are invited to discuss an issue of significance at length, hearing from expert witnesses, with the aim of producing policy recommendations at the end
Clinical genetics	The diagnosis and treatment of genetic diseases in human patients, as opposed to laboratory-based genetics research
Clinical trials	An established system for proving the safety and efficacy of new pharmaceuticals and medical devices, usually consisting of Phase I, II and III trials
Clostridium difficile	A bacterium that lives in the intestines and causes diarrhoea
Cohort (cohort study / human cohort)	Usually refers to a large group of people being followed in longitudinal research to track how changes in health over time correspond to a range of factors
Consensus conference	A public-opinion gathering strategy wherein conveners select a number of non-expert citizens who have applied to participate, provide them with preparatory materials and hold a conference of some days, including expert Q&As, after which the citizens prepare a final report
CpG methylation	The addition of methyl molecules at the CpG site (CpG refers to a specific order of bases: cytosine, phosphate, guanine)
CRISPR	A series of repeated DNA segments found in bacterial genomes, which can be harnessed for gene editing of a wide range of organisms
Curcumin	A component of turmeric, which is a member of the ginger family
Direct-to-consumer test	Genetic testing that individuals can acquire without the mediation of a health practitioner (e.g. by buying online)
Dysbiosis score	A measure of microbial imbalance
DNA	Deoxyribose Nucleic Acid. A molecule made up of a string of nucleic acids in the form of a twisted ladder (the double helix), which contains all of an organism's genetic material
DNA methylation	The addition of methyl groups to DNA, modifying the DNA's expression
Epidemiology	The study of disease origins and patterns; genetic epidemiology is the study of how a disease spreads and evolves
Epigenetics	Chemical modifications of DNA (including methylation) that regulate gene expression without altering the DNA sequence
Epigenome	The total of an individual's or organism's epigenetic modifications
Exome sequencing	The process of determining the DNA sequence of the 'coding' regions of the genome (i.e. those that produce proteins, the exome)

Gene	A piece of DNA that 'codes' for a protein
Gene drive	A molecular technique that drives the inheritance of a particular gene with the aim of affecting a whole population; it is reliant on a rapid reproductive rate
Gene editing	A molecular tool for making precise changes to an organism's DNA
Gene expression	The process by which a gene becomes a gene product (e.g. a protein)
Gene panel	Targeted sequencing of genes associated with specific groups of rare diseases or cancer
Genetic counselling	A profession tasked with providing information in non-directive ways to patients and families affected by genetic disease and diagnosis
Genetics	The study of the form and function of genes
Genome	The total genetic material of an organism or individual
Genome sequencing	The process of determining the DNA sequence of the whole genome
Genomics	The study of the structure and function of the genome
Genotype	An individual's unique genetic make-up; the genotype works alongside epigenetic and environmental factors to shape the phenotype
Genome-wide association study	Large-scale scanning of whole genomes for genetic variants associated with disease
Germ cells	The reproductive cells of an organism, also called the gametes
Germline	Refers to either the cells from which the germ cells originate or the genetic content of those cells that can be transmitted to subsequent generations
Gnotobiotic	An organism that has been bred completely free of germs, then deliberately colonised with defined microbes
Helicobacter pylori	A bacterium found in the digestive tract that can cause stomach and small intestine ulcers
Heterozygous	When two different alleles of a gene are carried
HLA-typed T cells	Immune cells with known human leukocyte antigens on their surface
Homeostasis	A state of equilibrium within an organism or biological system that is achieved by continual adaptation in the face of changing external conditions
Homozygous	When both alleles of a gene are carried
Human genome	The total genetic variation occurring in the human species
Immunomodulation	Modification of the working of the immune system, often referring to suppression
Immunotherapies	A class of therapeutic products that work by modifying the action of the immune system
Imprinting	Epigenetic alterations determined by parental gene expression
Machine learning	The ability of computers to process and adapt rapidly and independently to large quantities of data, without being explicitly programmed to do so; fundamental to big data

Mass spectrometry	A technique that uses a magnetic field to determine the mass of an ionised molecule, from which its identity can be inferred
Metabolites	Small molecules produced through metabolism
Metabolomics	The study of metabolites in cells, biofluids, tissues or organisms
Metagenomics	The collection and analysis of genomic material taken directly from the environment, as opposed to using a reference genome, which allows researchers to work with the actual genetic diversity of a given context, at an aggregate level
Microbes	Microorganisms, including bacteria and viruses, that typically multiply rapidly and can be disease-causing or beneficial
Microbial	Of microbes
Microbiome	The whole community of microbes, including their genetic material, living in or around an organism
Microbiomics	The study of interactions and processes of a microbial community and the individual 'host'
Microorganism	A microscopic living organism
Molecular	Of molecules
Monoclonal	Derived from a single cell
Mutation	An alteration in the sequence of a gene, potentially resulting in disease; mutations can be inherited or acquired
Off-target effects	A side effect of gene editing, where a change is made at an unintended site in the genome; in humans, this can potentially cause disease
Omics	An umbrella term that includes the fields of genomics, proteomics, metabolomics, microbiomics and transcriptomics, which are united by each studying a specific kind of biological product (e.g. proteins, microbes)
Opportunity cost	The concept that selecting one alternative takes away from others (e.g. where a finite amount of money is available, choosing to fund one thing leaves less funding for others)
Pathogen	A disease-causing microorganism
Pharmacogenomics	The use of genomic information to inform prescription or avoidance of pharmaceuticals
Phenotype	An individual's observable characteristics, resulting from the interaction of genotype, epigenetics and environment
Phylogenetics	The study of how a group of organisms evolved and are related, usually achieved by measuring genetic or morphological changes; in this context, phylogenetics can track how, for example, drug-resistant viruses evolve
Proteome	All of the proteins being expressed in a given cell or organism at a given time
Proteomics	The study of the proteome
Recombinant DNA	DNA from different sources that has been combined
Resistance	An organism's ability to withstand damage from, for example, disease or pharmaceuticals (e.g. as in antibiotic-resistant infections)

Retinoic acid	A metabolite of vitamin A that plays an essential role in growth and development
Risk stratification	The division of patients into groups according to likelihood of developing a given disease
RNA	Ribonucleic acid. A single-stranded molecule essential for turning DNA into proteins
SNP	Single Nucleotide Polymorphism. A distinctive change in a single base pair of the DNA occurring in less than 1% of the population; some SNPs have no effect, some cause disease and some are indirectly associated with disease without being causative
Somatic cells	Body or tissue cells
Squamous cell carcinoma	A common form of skin cancer arising in the middle and outer layers of skin
Sulforaphane	A compound found in cruciferous vegetables
TALENs	Transcription Activator-Like Effector Nucleases. A gene editing tool that can be engineered to target and cut DNA at specific sites
Technology assessment	A family of approaches to evidence and opinion gathering among a range of stakeholders, which is typically problem-oriented and participatory (and different to Australia's health technology assessment process)
Transcription	The first stage of gene expression, in which DNA is unravelled and an exact copy made in the RNA
Transcriptome	A record of gene expression in a cell or organism at a given time
Transcriptomics	The study of the transcriptome
Translation or translational research	Research focused on converting laboratory or preclinical studies on human cells or animals into clinical settings with human patients
Trastuzumab	A monoclonal antibody approved for the treatment of some breast and stomach cancers
Tumour typing or characterisation	The process of determining genetic or other features of a tumour that can indicate the best treatment pathway
Wellderly	Healthy elderly
Zinc finger nucleases	Synthetically made restriction enzymes that can target and cut certain genomic regions; used as a gene editing tool

ABBREVIATIONS

ADPKD	Autosomal dominant polycystic kidney disease
AEHRC	Australian e-Health Research Centre
API	Application programming interface
APoE	Apolipoprotein E
APPN	Australian Point of Care Practitioners Network
CAR-T	Chimeric antigen receptor-T Cell
CD19	Cluster of differentiation 19
COAG	Council of Australian Governments
CRISPR	Clustered regularly interspaced palindromic repeats
CSIRO	Commonwealth Scientific and Industrial Research Organisation
ctDNA	Circulating tumour DNA
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DNA	Deoxyribonucleic acid
EU	European Union
FDA	Food and Drug Administration (US)
FTE	Full-time equivalency
GC	Guanine–cytosine
GMO	Genetically modified organism
GP	General practitioner
HASS	Humanities, Arts and Social Sciences
HER2	Human epidermal growth factor receptor type 2
HLA	Human leukocyte antigen
HPV	Human papillomavirus
HREC	Human research ethics committee
HTA	Health technology assessment
IEC	International Electrotechnical Commission
ISO	International Organization for Standardization
LMICs	Low- to middle-income countries
MBS	Medicare Benefits Schedule
MOOC	Massive open online course
MSAC	Medical Services Advisory Committee
NATA	National Association of Testing Authorities, Australia
NHS	National Health Service (UK)
NHMRC	National Health and Medical Research Council
NIH	National Institutes of Health (US)
NSW DAC	NSW Data Analytics Centre
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PCR	Polymerase chain reaction
PET-CT	Position emission tomography and computed tomography
PoCT	Point-of-care testing
R&D	Research and development
RCPA	Royal College of Pathologists of Australasia
RNA	Ribonucleic acid
SNP	Single-nucleotide polymorphism
STEMM	Science, technology, engineering, mathematics and medicine
TALEN	Transcription activator-like effector nucleases
TGA	Therapeutic Goods Administration
VCGS	Victorian Clinical Genetics Services
WHO	World Health Organization

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EXPERT WORKING GROUP

Professor Robert Williamson AO FRS FAA FAHMS

Professor Bob Williamson became Professor of Molecular Genetics and Biochemistry and Pre-Clinical Dean at St Mary's Hospital Medical School, University of London, in 1976, where he remained until 1995, when he moved to Melbourne as Director of the Murdoch Institute and Professor of Medical Genetics. He retired in October 2004 and is now an Honorary Senior Principal Fellow of the Murdoch Institute, the University of Melbourne and Monash University.

Professor Williamson has more than 400 refereed career publications, including about 40 in *Nature*, *Nature Genetics*, *Cell* and *The Lancet*. He was involved in the first cloning of the human globin genes, their mutations causing thalassaemia and the identification of genes for cystic fibrosis, Friedreich's ataxia, craniofacial abnormalities, heart disease and Alzheimer's disease. More recently, he has taken a major interest in national science policy and medical and scientific ethics, has advised several state premiers, health ministers and ministers for innovation, and is still advising research groups wishing to use stem cells to treat genetic disorders.

He is a Fellow of the Australian Academy of Science (where he was Secretary for Science Policy from 2009 to 2013), a Fellow of the Royal Society and an Officer of the Order of Australia.

Professor Warwick Anderson FAHA FASSA FAHMS

Professor Warwick Anderson holds an appointment as an Australian Research Council (ARC) Australian Laureate Fellow and Professor in the Department of History and the Centre for Values, Ethics and the Law in Medicine at the University of Sydney. Additionally, he has an affiliation with the Unit for History and Philosophy of Science at the University of Sydney and is a Professorial Fellow of the School of Population Health at the University of Melbourne.

As an historian of science, medicine and public health, focusing on Australasia, the Pacific, South-East Asia and the US, Professor Anderson is especially interested in ideas about race, human difference and citizenship in the 19th and 20th centuries. Occasionally he writes programmatically on postcolonial science studies and more generally on science and globalisation.

Dr Stephen Duckett FASSA FAHMS

Dr Stephen Duckett is Director of the Health Program at Grattan Institute. He has a reputation for creativity, evidence-based innovation and reform in areas ranging from the introduction of activity-based funding for hospitals to new systems of accountability for the safety of hospital care. An economist, he is a Fellow of the Academy of the Social Sciences in Australia and of the Australian Academy of Health and Medical Sciences.

Professor Ian Frazer AC FRS FAA FTSE FAHMS

Professor Ian Frazer is a clinician scientist, trained as a clinical immunologist in Scotland. As a professor at the University of Queensland, he leads a research group working at the Translational Research Institute in Brisbane on the immunobiology of epithelial cancers. He is recognised as co-inventor of the technology enabling the HPV vaccines, currently used worldwide to help prevent cervical cancer. He heads a biotechnology company, Admedus Vaccines, working on new vaccine technologies, and is a board member of several companies and not-for-profit organisations. He is current President of the Australian Academy of Health and Medical Sciences a member of the Commonwealth Science Council and has most recently been appointed chair of the federal government's Medical Research Future Fund.

Professor Frazer was recognised as Australian of the Year in 2006 and was a recipient of the Prime Minister's Prize for Science, and of the Balzan Prize, in 2008, and was elected Fellow of the Royal Society of London in 2012. He was appointed Companion of the Order of Australia in the Queen's Birthday Honours list in 2013.

Dr Carrie Hillyard FTSE

Dr Carrie Hillyard is currently Chairman of Fitgenes, a company dedicated to preventive health care, Chairman of FizzioFit Pty Ltd and Deputy Chairman of the Mater Medical Research Institute. Previously, she was a co-founder of venture fund CM Capital Investments and a director of several of its investee companies and led its Life Sciences group for over 10 years. She has commercialised products from laboratory bench to market and was an inventor of a number of patented technologies. Her previous experience was in medical and diagnostics research in the UK and Australia.

Dr Hillyard has also mentored entrepreneurs, assisted with commercialisation and licensing and served on government, public and private company boards, including membership of the former Industry Research and Development Board and ANSTO. She has a PhD from London University, was elected as a Fellow of the Australian Academy of Technology and Engineering (ATSE) in 1997 and a Fellow of the Australian Institute of Company Directors in 2012. She was awarded a Centenary Medal in 2003, the inaugural Women in Technology Biotechnology Star award in 2006 and the AusBiotech Excellence award in 2008. Carrie currently Chairs the ATSE Queensland Division and will be an incoming Director of the ATSE Board.

Professor Emma Kowal

Professor Emma Kowal is Professor of Anthropology in the Alfred Deakin Institute for Citizenship and Globalisation and the School of Humanities and Social Sciences at Deakin University. She is a cultural anthropologist who previously worked as a medical doctor and public health researcher in Indigenous health settings before completing her PhD in 2007. Her research interests include Indigenous–state relations and settler colonialism, racism and anti-racism, and science and technology studies.

She has authored more than 100 publications, including her monograph, *Trapped in the Gap: Doing Good in Indigenous Australia*. She has received 22 grants and consultancies, including three four-year fellowships from the NHMRC and the ARC.

Professor Kowal has held visiting positions at Yale University, the University of California, Berkeley, the Max Planck Institute for the History of Science, Berlin, Nanjing University, China, and the Universidade Federal de Santa Catarina, Florianopolis, Brazil. She is an editor of the international journal *Postcolonial Studies*, past convenor of the Asia-Pacific Science, Technology and Society Network and member of the National Committee for History and Philosophy of Science of the Australian Academy of Science. She is an award-winning researcher and educator, receiving the 2014 Academy of the Social Sciences in Australia Paul Bourke Award for Early Career Research, a 2015 Thomson Reuters Women in Research Citation Award and a 2013 National Citation for Outstanding Student Learning.

Professor John Mattick AO FAA FRSN FAHMS HonFRCPA

Professor John Mattick is the Director of the Garvan Institute of Medical Research. He spent much of his career at the University of Queensland, where he was Foundation Director of the Institute for Molecular Bioscience, the Australian Genome Research Facility, the ARC Special Research Centre for Molecular and Cellular Biology and the ARC Special Research Centre for Functional and Applied Genomics. He is internationally known for pioneering a new view of the information content of the human genome; specifically that, rather than being largely 'junk', it encodes an extensive and malleable RNA regulatory system that guides the epigenetic processes of development and cognition.

Professor Mattick's honours and awards include the inaugural Gutenberg Professorship of the University of Strasbourg, the Order of Australia and Australian Government Centenary Medal, Honorary Fellowship of the RCPA, the International Union of Biochemistry and Molecular Biology Medal, the Human Genome Organisation Chen Award for Distinguished Achievement in Human Genetic and Genomic Research, and the University of Texas MD Anderson Cancer Center Bertner Memorial Award for Distinguished Contributions to Cancer Research, previous winners of which include several Nobel Prize winners and other pioneers of molecular biology.

Professor Mattick was recently named by the NHMRC as the one of the all-time high achievers in Australian health and medical research. He has overseen the development of the Garvan Institute into one of the largest centres for human genome sequencing and analytics in the world, including new software for the automated conversion of unstructured text in electronic health records into machine-readable ontologies, together with the establishment of one of the world's first clinical genomics companies, Genome.One.

Professor Catriona McLean FAHMS

Professor Catriona McLean directs the Department of Anatomical Pathology, the Victorian Neuromuscular Service and the Solid Tumour Division of the Molecular Pathology Unit for Alfred Health and the Victorian Brain Bank, Florey Neurosciences. She is also the pathologist for the Victorian Melanoma Service and the Australian National Creutzfeldt–Jakob Disease Registry. With expertise in pathology and neuropathology, she has published more than 350 research papers in the fields of dementia and cancer.

As inaugural director of the NHMRC Australian Brain Bank Network, Professor McLean has enabled accurate provision of pathologically characterised tissues to national and international researchers, supporting more than 600 papers. She has innovated and implemented an online pathology medical curriculum and initiated and developed the post-fellowship neuropathology national curriculum. Professor McLean has international, national, state and university awards for education, research supervision, research and her contribution to the field of pathology.

Professor Kathryn North AM FAHMS

Professor Kathryn North is Director of the Murdoch Children's Research Institute and the David Danks Professor of Child Health Research at the University of Melbourne. She is trained as a physician, neurologist and clinical geneticist and, in 1994, was awarded a doctorate for research in neurogenetics. She completed a postdoctoral fellowship in the Harvard Genetics Program.

Professor North is a national and international leader in genomic medicine. In 2014, she was appointed as Co-Chair of the Global Alliance for Genomics and Health – a collaborative network of 500 organisations across 45 countries funded by the NIH and the Wellcome Trust (ga4gh.org). Commencing in 2016, she leads an NHMRC-funded national network of more than 70 institutions – the Australian Genomics Health Alliance. The goal of Australian Genomics is to provide evidence and practical strategies for the implementation of genomic medicine in the health system.

Professor North has received a number of awards, including the GSK Australia Award for Research Excellence (2011), the Ramaciotti Medal for Excellence in Biomedical Research (2012) and Member of the Order of Australia (AM) for service to medicine in the field of neuromuscular and neurogenetics research (2012). In 2012, she was appointed Chair of the NHMRC Research Committee, and in 2014 was appointed as a Foundation Fellow of the Australian Academy of Health and Medical Sciences. She chairs the International Advisory Board of the Great Ormond Street Institute of Child Health (UK) and is a member of the Board of the Victorian Comprehensive Cancer Centre.

Mr Adrian Turner

Mr Turner is the CEO of Data61, a CSIRO entity that is the largest data innovation group in Australia. He is a successful and influential Australian technology entrepreneur who has spent 18 years in Silicon Valley. He is also co-Chair of the Australian Cyber Security Growth Network and a member of the Board of Directors for the AEHRC. Most recently, he was Managing Director and Co-Founder of Borondi Group.

Previously, Mr Turner was co-founder and CEO of smartphone and Internet of Things security company Mocana Corporation, had profit and loss responsibility for Philips Electronics connected devices infrastructure and was Chairman of the Board for Australia's expatriate network, Advance.org. He is also author of the ebook, *Blue Sky Mining, Building Australia's Next Billion Dollar Industries*.

PEER REVIEW PANEL

This report has been reviewed by an independent panel of experts. Members of this review panel were not asked to endorse the Report's conclusions and findings. The Review Panel members acted in a personal, not organisational, capacity and were asked to declare any conflicts of interest. ACOLA gratefully acknowledges their contribution.

Professor Susan Dodds

Professor Susan Dodds is Dean of Arts and Social Sciences and Professor of Philosophy at the University of New South Wales, Sydney, Australia. She is also an Adjunct Professor in Philosophy at the University of Tasmania and Chief Investigator and theme leader of the Ethics, Policy and Public Engagement theme of the Australian Research Council funded Centre of Excellence for Electromaterials Science (ACES) CE14010012. She is the author of nearly 100 refereed journal articles or book chapters and is co-editor (with Rachel A. Ankeny) of *Big Picture Bioethics: Developing Democratic Policy in Contested Domains* (Springer, 2016) and (with Catriona Mackenzie and Wendy Rogers) *Vulnerability: New Essays in Ethics and Feminist Philosophy* (OUP, 2014).

Susan was a member of the Australian Health Ethics Committee (AHEC), 2012-2015 and a member of the Clinical Ethics Capacity Building sub-committee, Return of Genetic Results sub-committee, the Health Resource Allocation sub-committee and was the AHEC member in common for the Gene Technology Ethics and Community Consultative Committee (GTECC). She is currently a member Genetics and Genomics Working Committee (NS Chapter 3.5). She was has also served as a member and Chair of the National Enabling Technologies Strategy (NETS) Stakeholder Advisory Council, until 2012.

Professor Nick Martin FAA FASSA FAHMS

Nick Martin graduated with honours in Genetics from the University of Adelaide in 1972 and obtained his PhD in genetics at the University of Birmingham. In 1978 he returned to a Research Fellowship at the Australian National University where he founded the Australian Twin Registry. After 3 years in the US he returned in 1986 to the Queensland Institute of Medical Research where he heads the Genetic Epidemiology Laboratory and continues longitudinal studies with twins of a wide range of complex traits of medical and behavioural interest. He also is involved in several large studies of cognition and brain imaging (EEG and MRI). His research over recent years has moved to genome wide association studies (GWAS) to locate genes influencing complex traits including anxiety, alcoholism, and dizygotic twinning. He developed methods for multivariate analyses and the analysis of gene–environment interactions. Most recently he has initiated projects to recruit large patient samples for GWAS of anorexia, depression and other psychiatric disorders. He has published over 1200 papers and is a fellow of the Australian academies of Science, Social Science, and Health and Medical Science.

Professor James McCluskey FAA FAHMS

James McCluskey is Deputy Vice Chancellor Research at The University of Melbourne. He trained in Perth as a physician and researcher at the National Institutes of Health (USA). He has held academic positions at Monash University, Flinders University and the Australian Red Cross Blood Service in Adelaide, South Australia. He established the SA unrelated bone marrow donor registry.

He has published more than 300 scientific articles on how genes control immunity, recognised by the Rose Payne Award from the American Society for Histocompatibility and Immunogenetics (ASHI), The Ceppellini award from the European Federation for Immunogenetics. Jointly with Jamie Rossjohn he won the International Roche Organ Transplantation Fund Recognition Prize for Excellence in Organ Transplantation Research, an Australian Museum Eureka award for scientific Research, the GSK Research Excellence Award and the 2016 Victoria Prize for Life Sciences.

He is a member of Faculty of Science, Royal College of Pathologists Australasia, a Fellow Australian Academy of Science, Fellow of the Australian Academy of Health and Medical Sciences, Fellow of the Royal Australian College of Physicians and Fellow of the Royal College of Pathologists Australasia.

He led the development, funding and establishment of the Peter Doherty Institute for Infection and Immunity ($207 million). He is a founding member of Australian Friends of ASHA Slums (the Australian branch of Asha India) launched in November 2012. He led a team that won a USD$50 million grant from The Atlantic Philanthropies to help to establish a new Fellowship program focused on leadership to effect social change.

EVIDENCE GATHERING

Workshops and meetings were held across Australia during this project. Many people have contributed their time and expertise to the project through written submissions, meetings with members of the Expert Working Group and participating in the workshops.

The views expressed in this report do not necessarily reflect the opinions of the people and organisations listed in the following sections.

Workshops

The ACOLA Precision Medicine Project held three workshops:

- Initial scoping workshop: held in Melbourne on 30 November 2016 to discuss the scope of the horizon scanning project;
- Second scoping workshop: held in Canberra on 18 July 2017, with key stakeholders and the Expert Working Group; and
- Synthesis workshop: held in Melbourne on 22 August 2017, with key stakeholders and the Expert Working Group to synthesise the submissions received (below).

Stakeholders consulted at workshops

We thank the following stakeholders for their time and participation in the ACOLA Precision Medicine Project workshops:

Adam Wright

Andrew Sinclair

Anne-Marie Lansdown

Amber Beavis

Augustus Yip

Cheryl George

David Abbott

Erica Kneipp

Jason Tong

Krisztian Baranyai

Kylie Tattersall

Richard Beasley

Robyn Ward

Rosalie Viney

Shane Porter

Sharyn McGregor

Sue Meek

Sylvia Metcalfe

TJ Higgins

Will Howard

Written submissions

As part of the evidence-gathering to support the development of the report, a call for input was sent to experts in the field. The development of the report has been made possible through their generous contributions, and the Expert Working Group would like to thank the following people.

Current precision medicine capacity – Australia

John Mattick, Kathryn North, Andrew Sinclair, Zornitza Stark, Maud Dumont, David Bunker, Marcel Dinger, Sean Grimmond, David Burt, John Christodoulou and Tiffany Boughtwood

Current precision medicine capacity – International

The Australian Academy of Technology and Engineering (ATSE)

Sequencing

Dave Burt, Yuanyuan Cheng and Ken McGrath

Gene editing

Tanya Medley and Melissa Little

Epigenetics

Tanya Medley and Richard Saffery

Omics

David James and Samantha Hocking

Microbiomics

Mark Morrison and Philip Hugenholtz

Point-of-care testing

Catriona McLean and Robyn Ward
Rosy Tirimacco

Infectious disease

Mark Walker, David Paterson, Paul Young,
Mark Schembri, Scott Beatson
and Alexander Khromykh

Pathology and imaging

Catriona McLean, Andrew Gill,
Sarah-Jane Dawson and Tom Barber

Immunotherapy

Rajiv Khanna

Primary care and complex disease

Ingrid Winship

Age-related disease and mental health

Robert Williamson

Wellness

Carrie Hillyard and Grant Morahan

Professional development

Sylvia Metcalfe, Amy Nisselle,
Belinda McClaren and Clara Gaff

Public engagement

Matthew Kearnes, Declan Kuch,
Nicola Marks, Georgia Miller, Wendy Russell,
and Niamh Stephenson

Consumer engagement

Avnesh Ratnanesan, with Daniel Damiano,
Matthew Tice, Matt Riemann, Yang Jiao
and Kiran Nair

Ethics

Wendy Lipworth and Ian Kerridge

Regulatory and legal

Dianne Nicol and Margaret Otlowski

Indigenous health

Emma Kowal, Elizabeth Watt, Laura Weyrich,
Margaret Kelaher and Ray Tobler

Data

Adrian Turner, Cheryl George,
Bill Simpson-Young, Stephen Hardy,
Chelle Nic Raghnaill and Jane Polak Scowcroft

Health economics

Rosalie Viney and Jane Hall

Stephen Duckett and Greg Moran

Biotechnology

Krystal Evans and Bob Williamson

Agriculture

Dave Edwards and TJ Higgins

Genomics and vector control

Alyssa Barry and Karen Day

Environmental application of gene editing

Mark Tizard

Gene editing in the environment
– the New Zealand experience

David Penman and Peter Dearden

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We gratefully acknowledge the expertise and contributions from the many experts that have helped shape and develop the report. Further information of these contributions can be found in 'evidence gathering'.

Our special thanks to the Department of Health and the Office of the Chief Scientist, who provided valuable contributions.

The EWG put a great deal of time, effort, and insight into coordinating the report's conceptualisation and production.

The ACOLA Secretariat, and in particular Dr Lauren Palmer, Dr Angus Henderson, and Dr Courtney Addison, have provided support to the EWG and project management.

HORIZON SCANNING

ACOLA
AUSTRALIAN COUNCIL OF LEARNED ACADEMIES