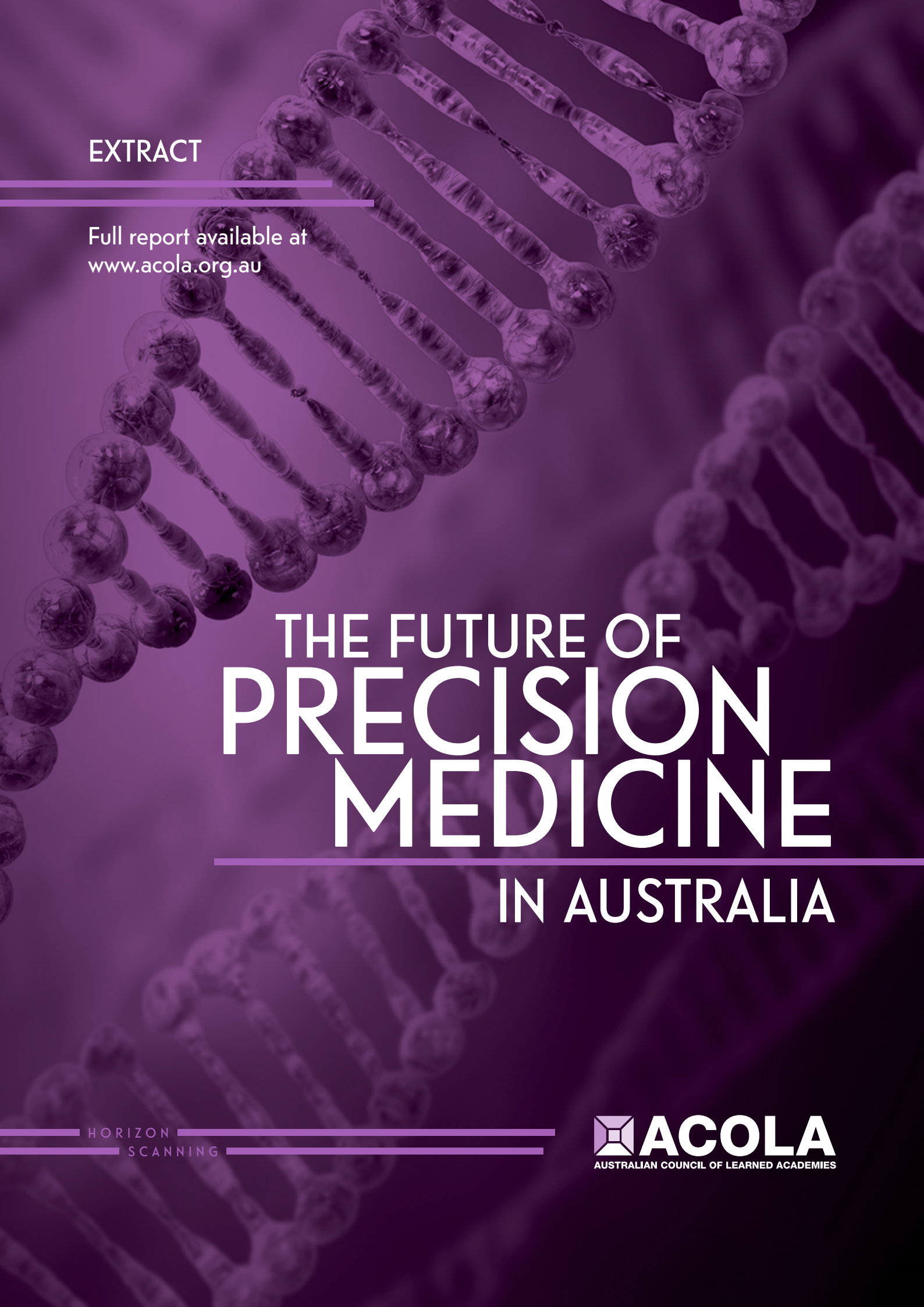

EXTRACT

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THE FUTURE OF PRECISION MEDICINE IN AUSTRALIA

HORIZON SCANNING

ACOLA
AUSTRALIAN COUNCIL OF LEARNED ACADEMIES

EXPERT WORKING GROUP

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EXTRACT

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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.

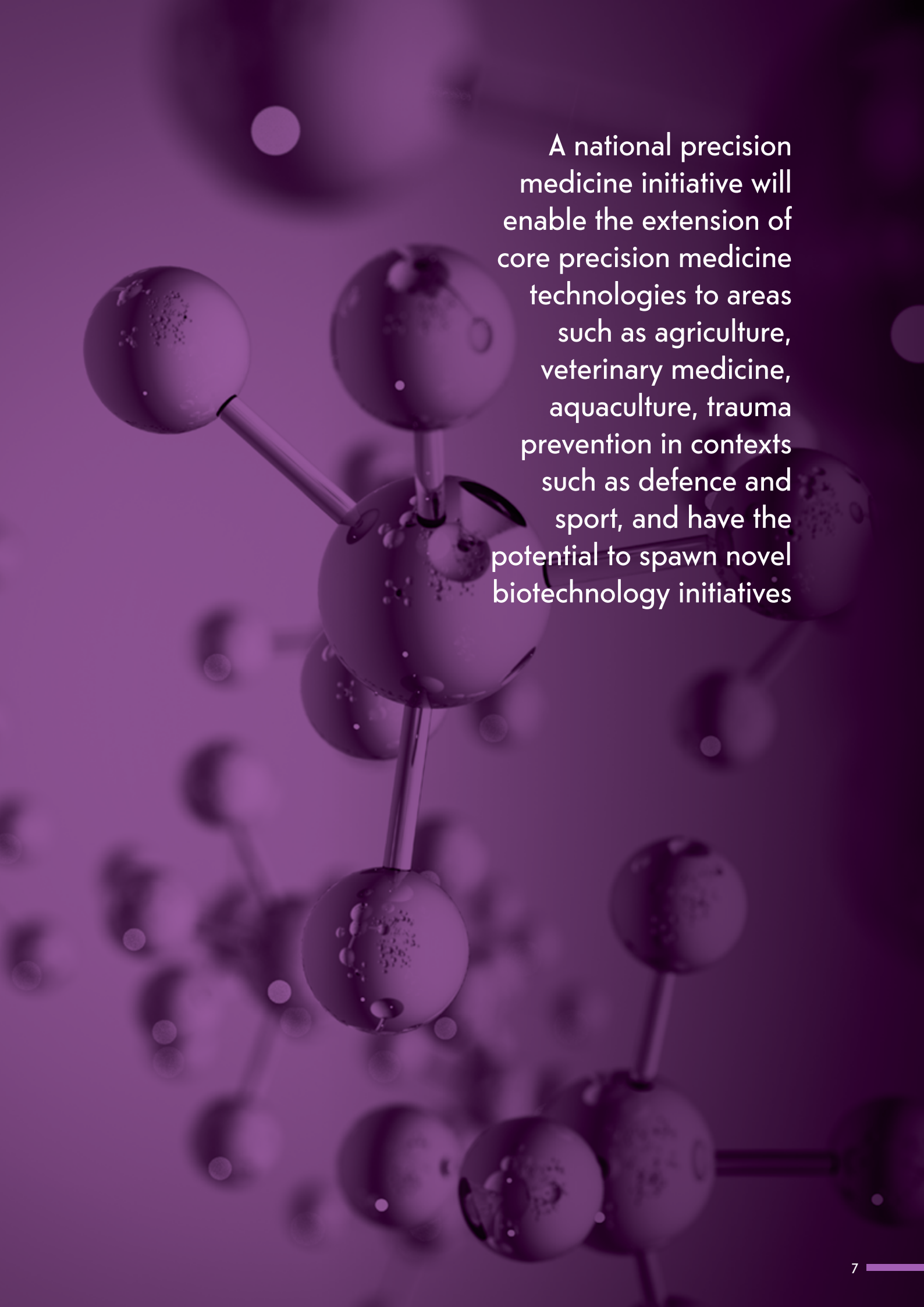
Building a broad capacity is essential: wide-scale omics information aggregated into big data can inform basic research, which, in turn, will lead to improved understanding of fundamental disease mechanisms and interventions that could lead to improvements in prevention through public health. Storage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

Advances in precision medicine, and the technologies that support it, are poised to reshape health care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