NSW HEALTH

Genomics Strategy

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FOREWORD

A recent article in genomics, an online magazine for consumers interested in the transformative potential of such technologies, raised the simple but profound question in terms of curing cancer[1]: **are we there yet?**

> *Today, we are able to predict and prevent some inherited forms of cancer. Targeted treatments, based on the molecular profile of the tumour itself, are extending the lives of cancer patients. Novel therapeutic strategies are being developed that harness a patient's immune system[1].*

This question matters for all of us: cancer is now the largest burden of disease in Australia, and cancer is essentially a disease of the genome. Genomics plays a role in 9 of the 10 leading causes of death, including heart disease, stroke, diabetes and Alzheimer's disease[2]. The answer was correspondingly profound: not yet, but how far have we come and the future is bright.

The application of genomic knowledge is transforming the way we deliver healthcare. NSW Health recognises that harnessing this knowledge and integrating it into the NSW health system will improve the health of the people of NSW, both at an individual and population health level.

The NSW Health Genomics Strategy is the beginning of a long term commitment NSW Health is making to ensure the potential benefits of genomics are incorporated into the NSW Health system effectively and efficiently. This Strategy seeks to bring together the key genomics policy issues and proposes a way forward to address the choices and challenges that we may face in this fast evolving area of healthcare.

By working collaboratively and recognising existing strengths and opportunities for innovation as a group of engaged stakeholders, we will position NSW Health as a proactive system at the forefront of genomic technology in healthcare, both nationally and internationally, for the benefit of the NSW population.

Finally I would like to offer my sincere thanks to those who have engaged in the development of this Strategy. Your enthusiasm, expert knowledge and commitment to clinical care in this field have been invaluable in setting the future direction of genomics in NSW.

Elizabeth Koff
Secretary, NSW Health

[1] McCarthy, J. (2015), "Are we there yet?" online magazine called "Genome" (cited 2017 May 19). Available from http://genomemag.com/are-we-there-yet/#.WR4IiOWGNeW

[2] Leading Causes of Death (Internet). Centers for Disease Control and Prevention (cited 2017 May 19). Available from https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm

CONTENTS

1 | EXECUTIVE SUMMARY

The past decade has delivered major advances in our understanding of the human genome and the association between genetic variation and disease.

Genetic testing is not new: genetic services have played an important role in diagnosis and medical care over many years. However, a much broader array of tests are now becoming available, including comprehensive gene panel tests and tests based on sequencing exomes or whole genomes.

These new genomic tests are opening up new and exciting avenues for disease diagnosis, prognosis and ultimately treatment. This reflects the long anticipated maturing of human genomic technologies as well as the development of new and related technologies (e.g. proteomics). The pattern of progress is evident across the various disease areas, as well as rare childhood conditions, with some areas advancing faster than others. At the same time, new questions are emerging – scientific and ethical questions, as well as practical questions in terms of how and when these medical advances can be made more widely available.

NSW scientists and researchers are working at the forefront of this field. With a range of world class medical research institutions and a strong public health system, we have an opportunity to lead in the development and application of clinical genomics: to move it from the margins to mainstream healthcare over the coming decades and to shift the paradigm from disease management to prevention. Doing so will enhance current services provided by the NSW health system with the continued aim of delivering the best possible outcomes for patients and their families.

However, given the novel and disruptive nature of the technology and ethical dilemmas it raises[3], there is no well-defined path for achieving this. NSW Health must develop its own path – hence the need for this Strategy.

Strategic Vision for genomics in NSW

The scope of the NSW Health Genomics Strategy is clinical genomics, defined as the emerging discipline that involves using genomic information about an individual, a cancer or an infectious organism as part of clinical care (e.g. for diagnostic and/or therapeutic decision-making) and the health outcomes and policy implications of that use[4]. Whilst the focus is genomics, including the study of genetic material, there are other emerging 'omics technologies, such as transcriptomics (gene expression), metabolomics and proteomics that are developing in parallel. It is envisaged that this Strategy will have applicability to these fields and that these can be advanced through a common framework.

Genomics can provide greater accuracy in determining disease risk, assessing diagnosis and prognosis, and informing the selection of therapeutic options for care. Improved precision in care may avoid unnecessary treatments and provide savings for the healthcare system and the economy at large. Applications of genomic technology in this way are commonly referred to as precision or personalised medicine.

[3] These include incidental findings, confidentiality and reproductive responsibility. For an introduction to these issues, see: https://theconversation.com/the-genomic-revolution-is-coming-and-with-it-some-big-dilemmas-42101

[4] Based on NIH National Human Genome Research Institute. https://www.genome.gov/27527652/genomic-medicine-and-health-care/ (accessed 14/3/17).

The vision for NSW Health genomics

By 2025, NSW Health will be recognised as a leader in the development and use of appropriate genomic technologies in healthcare and public health for the benefit of the NSW population. NSW will be seen as the preferred partner for industry in (gen)omics research, education and training, with effective translation into clinical practice and public health initiatives. This will attract talent and investment to NSW to help realise the promise of genomics.

The NSW Health Genomics Strategy articulates a shared vision for genomics in NSW. It describes pathways to implementation and makes recommendations as to how NSW can remain responsive to this transformation in healthcare and position itself as a recognised leader in this field. To achieve this, NSW will build on current partnerships with service providers, clinicians, researchers, industry and consumers. Working together, we can achieve the NSW vision for clinical genomics.

Achieving the vision in NSW will require:

- Leadership and collaboration of engaged stakeholders who share a common vision for clinical genomics;
- A co-ordinated approach to avoid fragmentation and duplication of resources;
- Mechanisms to support integration of new developments in clinical genomics into the NSW Health system;
- Accessible pathways for patient care across rural, regional and metropolitan NSW;
- Infrastructure for data systems to support clinical care;
- Workforce planning and training for genomic services into the future;
- Consideration of legal, ethical and privacy concerns in line with the National Framework: *Integrating genomics into healthcare for Australians*.
- Engaging primary healthcare providers; and
- Provision of clear, accessible information for consumers.

Realising this vision for health genomics will require a new level of connectedness and collaboration across stakeholders through a multi-stage journey. Three key phases have been identified:

1. **Strengthening the foundations** (next 2 years): foster existing collaborations and develop a strong and integrated network that is proactive in extending evidence-based genomics services across NSW
2. **Enhance disease management and prevention** (next 2-7 years): deliver enhanced healthcare using genomics for the benefit of the NSW population and participate in knowledge exchange nationally and internationally
3. **Towards precision medicine** (7 years and beyond): remain adaptive and agile to meet population needs while adopting genomics technologies that maximise health outcomes.

NSW Health has developed the Strategy through extensive consultation with key stakeholder groups including: service providers, clinicians, researchers, consumer groups and other policy makers. This has provided an opportunity to identify current innovations in health genomics across the State as well as highlighting the many challenges and opportunities facing us.

The following recommendations respond to the challenges articulated by stakeholders during the consultation and are the first steps to realising the vision.

RECOMMENDATIONS	
1	*Establish a Governance Committee to guide the strategic direction for clinical genomics in NSW and provide leadership at a State level, including appointing a suitable subject matter expert to co-chair this Committee in conjunction with an appropriate NSW Health executive.*
2	*Enhance the mechanisms for assessing the clinical need, validity and utility of new developments in genomics and prioritise their potential for translation into the NSW public health system.*
3	*Develop new service delivery models linked to clinical pathways that incorporate genomic and digital advances to provide safe and equitable access across NSW.*
4	*Work with relevant parties to define the information standards, protocols and enabling infrastructure required to integrate genomics into mainstream healthcare.*
5	*Work with relevant NSW stakeholders and national bodies to identify future workforce requirements, including awareness and genomic literacy within NSW Health, and develop a plan to address these needs.*
6	*Work with key stakeholders, including general practitioners and Primary Health Networks, to engage the community regarding clinical genomics, to build and sustain public confidence. This includes working with consumers as equal partners to develop services that reflect their needs and preferences in line with ethical, legal and professional standards.*

The establishment of collaborative governance arrangements, including an implementation plan, will support the achievement of the recommendations.

2 | THE PROMISE OF GENOMICS

This chapter provides a brief introduction to genomics and its application to healthcare. Genomic medicine is developing rapidly and its capacity to transform individual and collective patient care is becoming clearer. This includes the development of personalised or precision medicine, which will mark a fundamental change in the way healthcare is delivered.

> *The goal of getting your genome done is not to tell you what you will die from, but it's to learn how to take action to prevent disease.*
>
> ***George M. Church***

2.1 What is genomics?

Major advances have been made over the last 25 years in our understanding of the human genome and the association between genetic variation and disease. Genetics is the study of heredity, and genetic testing is not new. Genetic services have played an important role in diagnosis and medical care for many years with around 4,000 inherited diseases, including cystic fibrosis and Huntington disease, now understood to be caused by a single gene. In recent years there has been a growing awareness of diseases which are associated with several genes as well as being influenced by lifestyle and environmental factors.

Genomics, defined as the study of genes and their functions, and related techniques, provides insight into these complex dynamics[5]. Genomic testing typically requires the analysis of hundreds and thousands of genes at the same time – hence the need for sophisticated computer-based analyses. Accordingly, modern genomics includes the development of technology to support such advances. This includes the related 'omics technologies, such as proteomics (all the proteins in a cell or organism), metabolomics (all the metabolites) and transcriptomics (the study of gene expression). Over time, such technologies are opening the way to new diagnostic tests and therapies based on identifying gene mutations and manipulating the genome (e.g. gene therapy). For simplicity, the terms "genomics" or (gen)omics will be used throughout this document to encompass these related technologies.

Such technologies are enabling major advances in clinical genomics. Clinical genomics refers to the use of genomic information about an individual, a cancer or an infectious organism to inform clinical care (e.g. for prevention, diagnostic and/or therapeutic decision-making). In addition, there are health outcomes and policy implications of its use[6]. This field is rapidly developing and has profound implications for an individual's healthcare and for health systems.

[5] The **main difference** between genomics and genetics is that genetics scrutinises the functioning and composition of the single gene whereas genomics addresses all genes and their inter relationships in order to identify their combined influence on the growth and development of the organism. Genomics and World Health: Report of the Advisory Committee on Health research, Geneva, WHO (2002).

[6] Based on NIH National Human Genome Research Institute. https://www.genome.gov/27527652/genomic-medicine-and-health-care/ (accessed 14/3/17).

> *Your genome sequence will become a vital part of your medical record, thereby providing critical information about how to optimise your wellness.*
>
> ***Leroy Hood***

In particular, the speed and trajectory of the technology presents unique challenges. New sequencing technologies such as massively parallel sequencing (MPS) made it possible to do large-scale sequencing, up to and including whole human genome sequencing (WGS). Through advances in methods and tools, the cost of testing has fallen dramatically. This, coupled with the availability of high speed computing to support sophisticated analysis, is making it feasible for genomics to become a part of routine healthcare. This is compounded by rising consumer interest in, and demand for, genomic services, as well as the increasing availability of tests being offered by providers. These tests may be for specialised disease specific purposes or generic risk assessment, wellness or ancestry analysis.

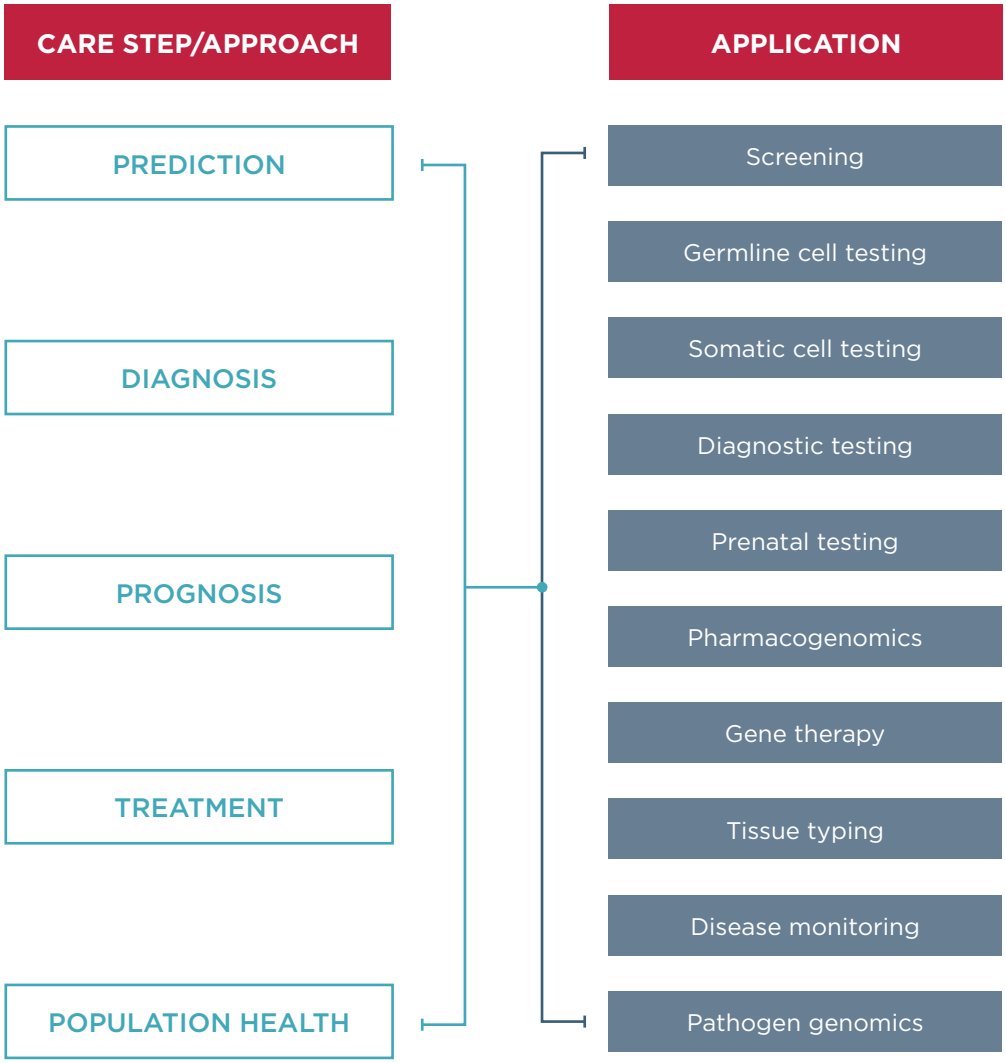
However, as one stakeholder noted, "just because it's available doesn't mean that it's necessary or good". Effective and appropriate applications must be determined. Additionally, the generation of data must be matched by the development of interpretative skills to generate robust, clinically-relevant findings. It will be necessary to guide the application of these new technologies across the health system to benefit patients and minimise potential harms, including over-diagnosis and over-treatment; data misuse; discrimination and stigmatisation.

This requires careful consideration – hence the purpose of this Strategy.

2.2 Applying genomics to inform and guide healthcare

Genomics adds to the existing array of tests and therapeutic options available to health stakeholders. Medical applications of genomics include prediction, diagnosis, prognosis, disease monitoring and treatment, as well as the identification of pathogens as shown in the following diagram:

Figure 1 **Health applications of genomics**



Genomic technologies can be used by clinicians from all specialities to diagnose patients who have high risk genetic errors causing disease. This includes prenatal screening for genetic diseases through new non-invasive methods. Genomic technologies are also increasingly being used to understand the contribution of both rare and common genetic factors to the development of common diseases, such as hypertension, diabetes and cancer. This provides opportunities to assess predisposition to disease, potentially prompting more focused clinical monitoring and lifestyle changes. Variants in germline cancer predisposition genes will become more prevalent as our understanding grows, placing greater burden and demand on familial cancer services and allied health professionals such as genetic counsellors and psychosocial services. Following diagnosis, it is also opening up new treatment options, including more targeted therapies (based on identifying the genetic drivers of disease and providing drugs or other substances which target that pathway), and gene therapy including the emerging field of gene editing (adding, removing or replacing sections of the DNA sequence).

In addition, genomic technologies enable the genomes of microorganisms that cause human infection to be sequenced to identify the exact organism causing symptoms, help to trace the cause of infectious outbreaks, and give information as to which antibiotics are most likely to be effective in treatment. Further applications continue to emerge, such as the use of genomics to identify drug resistance in clinically relevant bacteria, viruses and fungi,[7] or the emerging area of human gut virome and bacterial microbiome analysis.

[7] Antimicrobial resistance is a major global health crisis – see National Antimicrobial Resistance Strategy 2015-2019. In addition, genomics provides a powerful tool for monitoring viral infections and outbreaks.

2.3 Transforming healthcare: the promise of precision medicine

On one level, genomics is additive to the existing health system. On another level, it can be transformative. As discussed in the previous section, genomic medicine has the capacity to enable precision or personalised medicine for individuals[8].

Precision medicine involves a fundamental shift in the way that healthcare is organised and delivered:

Traditionally, medicine has been built around clinical teams specialising in a particular organ system working back from a patient's symptoms to arrive at a diagnosis. Personalised medicine turns this approach on its head. It recognises that complex diseases should no longer be considered as a single entity. One disease may have many different forms, or "subtypes", resulting from the complex interaction of our biological make-up and the diverse pathological and physiological processes in our bodies. These will not only vary between patients who have the same disease but also within an individual patient as they get older and their body changes[9].

Early examples of personalised medicine can be seen in cancer care, since all cancer has a genetic base. Genomic or molecular diagnosis provides insight into this genetic base and may support more accurate tumour diagnosis and highly targeted treatments. This is being applied across an increasing range of cancers, including breast, brain, colon and skin cancer (melanoma). Stratifying patients and cancers in this way provides a path to major advances in disease management and prevention.

At the same time, the challenges associated with realising this promise should not be overlooked. For example:

- the relationship between genome and phenotypic (or observable) data is complex and gene therapies may yield unexpected side effects;
- not all people with a particular genetic change or mutation will develop features of the disorder; accordingly genomic testing could potentially lead to over-diagnosis in the absence of appropriate controls;
- genomic information is dynamic such that new discoveries may necessitate recontacting individuals to amend advice as new information becomes available; and
- the value of genomics in terms of disease risk prediction has not yet been definitively established for situations beyond specific examples. Probability and relative risk are difficult for most people to understand, and current data suggests that individuals don't change their behaviour much even when they become aware of being in a high-risk group[10].

Accordingly, the promise of precision medicine cannot simply be assumed, nor should the current diagnostic capabilities of genomic technology be overstated. Significant further clinical, public health and health service research is required. Further work to confirm disease related phenotypes and genotypes will also continue to remain vital to diagnosis; hence the need for close, ongoing cooperation between clinicians and medical researchers to further the development of clinical genomics.

[8] Building on our inheritance: Genomic technology in healthcare. United Kingdom 2012. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213705/dh_132382.pdf (accessed 14/3/17).

[9] Improving outcomes through personalised medicine, NHS England, 2016.

[10] Hollands GJ, French DP, Griffin SJ, et al. The impact of communicating genetic risks of disease on risk-reducing health behaviour: systematic review with meta-analysis. BMJ. 2016; 352:i1102.

2.4 Responding to the challenge

The potential benefits of precision medicine are widely recognised. In light of this, a growing number of countries including the USA, England, Germany, France, Canada, China and India are formulating policy and research programmes to support the development of genomic medicine and the adoption of more personalised approaches to healthcare[11, 12, 13, 14, 15].

Figure 2 (see following page) summarises the major national and international initiatives currently underway. These include the UK's 100,000 Genomes project launched in 2012 and the more recent Precision Medicine Initiative in the USA, as well as several collaborative international initiatives including the Global Alliance for Genomics and Health, and the Global Genomic Medicine Collaborative. Australian organisations have established links with or are active in a number of these, including Cancer Breakthrough 2020 (previously known as the Cancer Moonshot program).

Australian governments are also responding. This ranges from nationally funded programmes, such as the Australian Genomics Health Alliance – a broad array of key organisations working at the forefront of genomics research – through to state grants and initiatives (e.g. NSW, Victoria and Queensland).

[11] Genomics England. https://www.genomicsengland.co.uk/about-genomics-england/how-we-work/ (accessed 14/3/17).

[12] Ministry of Social Affairs and Health Finland 2016. http://stm.fi/en/article/-/asset_publisher/tyoryhma-valmistelemaan-genomikeskuksen-perustamista (accessed 14/3/17).

[13] National Cancer Institute USA. https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative (accessed 14/3/17).

[14] Genome Canada Strategic Plan 2012- 2017. http://www.genomecanada.ca/sites/genomecanada/files/publications/gc_strategic-plan-full-version.pdf (accessed 14/3/17).

[15] All of Us Research Program, National Institute of Health. https://www.nih.gov/research-training/allofus-research-program (accessed 14/3/17).

Figure 2 **Select International Genomics Initiatives**

GENOME CANADA (CANADA)

- Vision to harness the transformative power of genomics to deliver benefits to Canadians
- Invested $1.2 billion (GC & partner) in 77 large-scale projects since its establishment in 2000

GENOMICS ENGLAND 100,000 GENOMES PROJECT (UK)

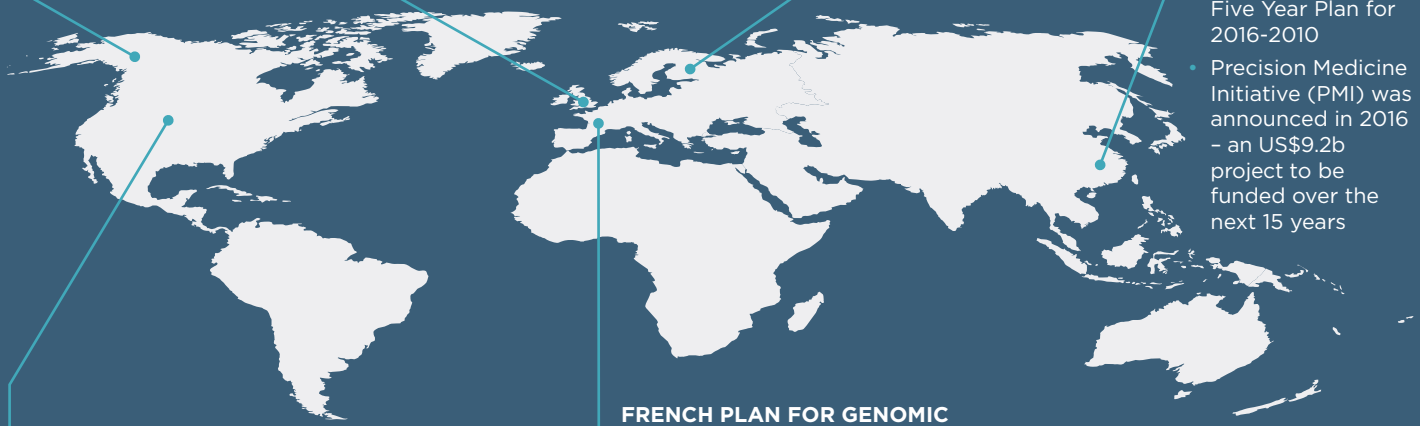
- Launched in late 2012 with a vision to bring the predicted benefits of genomics to NHS patients
- Focus on people that are affected by rare disease (both patients and their families) and cancer
- Aiming to sequence 100,000 whole genomes from NHS patients by 2017
- £300 million worth of cash injection from public and private sources

MINISTRY OF SOCIAL AFFAIRS AND HEALTH (FINLAND)

- National strategy published in 2015
- Announcement to set up a national genome centre and cancer centre with €17 million budget proposed over the next 3 years

PRECISION MEDICINE INITIATIVE (CHINA)

- China's congress confirmed plans to make precision medicine part of its Five Year Plan for 2016-2010
- Precision Medicine Initiative (PMI) was announced in 2016 – an US$9.2b project to be funded over the next 15 years



PRECISION MEDICINE INITIATIVE (USA)

- National initiative set out to enable a new era of medicine through research, technology, and policies that empower patients, researchers, and providers to work together toward development of individualised care
- US$130 million enacted for FY16 and US$230 million requested for FY17
- Committed to sequence 1 million person cohort

CANCER MOONSHOT INITIATIVE (USA)

- Established in early 2016 – led by Vice President Joe Biden
- Aiming to unite the entire cancer ecosystem to catalyse innovation, accelerate progress and disseminate knowledge

FRENCH PLAN FOR GENOMIC MEDICINE 2025 (FRANCE)

- Aimed at positioning France as a leader among the major countries involved in genomic medicine within the next ten years
- Plan to invest €670 million over the next 5 years

GLOBAL ALLIANCE FOR GENOMICS AND HEALTH (GLOBAL)

- Comprises 427 organisational members from 41 countries
- Goal is to create a common framework of harmonised approaches to enable the responsible, voluntary, and secure sharing of genomic and clinical data

THE GLOBAL GENOMIC MEDICINE COLLABORATIVE (GLOBAL)

- An action collaborative among global leaders in the implementation of genomic medicine in clinical care
- Seeks to improve global health by catalysing the implementation of genomic tools and knowledge into healthcare delivery globally

2.5 Australian Genomics Policy Framework

The need for national harmonisation across all jurisdictions in the use and regulation of genomic technology is widely recognised.

To address the need for national harmonisation, the Commonwealth Department of Health is finalising the National Health Genomics Policy Framework.

This seeks to provide a shared framework for integrating genomics into the Australian health system, including identifying and recommending national policies and measures to support this. The Framework reflects a commitment from Commonwealth, state and territory governments to work together to foster consistency of action and approach across jurisdictional boundaries so that the potential benefits of genomics are harnessed in an efficient, effective, ethical and equitable way for the good of all Australians.

There are a number of intersecting areas of NSW and Commonwealth policy where strategic directions will need to remain consistent. They include:

- Ethical, legal, social and regulatory issues;
- A skilled and literate genomics workforce;
- Sustainable investment in clinical genomics; and
- Effective and appropriate collection, management and utilisation of genomic data.

NSW Health is committed to working closely with the Commonwealth to ensure local strategies to develop clinical genomics in NSW align with national policy.


190
280
370
460
550
640
650

3 GENOMICS IN NSW: PART OF THE PLAN

The NSW Government is committed to building a 21st century healthcare system that delivers the "right care, in the right place, at the right time", as articulated in the NSW State Health Plan[16].

Clinical genomics, with its potential to enable precision medicine, will become an increasingly important focus for healthcare providers and policy makers. This Strategy aligns with the NSW State Health Plan priorities (Table 1 below) to maximise the potential of genomic technology for the benefit of the NSW population.

Table 1 **Links with NSW State Health Plan**

NSW STATE HEALTH PLAN PRIORITIES	DESCRIPTION
Direction One: Keeping People Healthy	Supporting people to live healthier, more active lives and reducing the burden of chronic disease
Direction Two: Providing World-class Clinical Care	Providing timely access to safe, quality care in hospitals, Emergency Departments and in the community
Direction Three: Delivering Truly Integrated Care	Creating a connected health system, so that patients get the care they need, where and when they need it, by connecting State health services with other health services

Some of the foundations for achieving this are already in place or being put in place through prior investment decisions. Accordingly, NSW has a strong base to build upon in clinical genomics. This chapter highlights some of the capabilities that already exist: capabilities that mean NSW Health is well positioned to progressively incorporate genomics into everyday care for the benefit of NSW consumers, communities and the health system as-a-whole. These include:

- Clinical innovation and exemplars;
- World class translational research;
- State-wide networks;
- Advanced information and communication technology (ICT);
- Collaborations and partnerships.

[16] NSW State Health Plan: Towards 2021. NSW Ministry of Health 2014. http://www.health.nsw.gov.au/statehealthplan/Pages/default.aspx

3.1 Clinical innovation and exemplars

Clinical genomics in NSW is improving the health of the NSW population through innovative clinical care, underpinned by strong research evidence. NSW has a number of established services where advanced testing techniques are being applied by leading specialists for disease surveillance, to identify genetic variations and enhance current diagnostics.

At a population health level, NSW services are at the forefront of genomic testing as a part of disease surveillance to protect the community. For example, during a community outbreak of legionellosis in metropolitan Sydney in March-April 2016, near real-time genome sequencing of bacteria by the NSW Pathogen Genomics Partnership provided critical evidence to help NSW Health Protection identify and rapidly contain the source of the infection. Additional examples in the Appendices further illustrate how genomics is being applied in NSW to assist in disease control and prevention.

Genomics is also changing the management of cancer in NSW, as shown in the case study at Appendix A. Precision oncology based on genomic tumour analysis provided both greater therapeutic effectiveness and tolerability for a patient of the Hereditary Cancer Clinic at the Prince of Wales Hospital[17]. This is showing great promise and is progressively being extended to a wider set of cancers.

Advances in genomics have been particularly significant for patients with rare diseases, where diagnosis has traditionally been both inconclusive and protracted. For example, clinicians within the Department of Neurogenetics at Royal North Shore Hospital were able to provide a definitive diagnosis for a patient who had spent more than a decade seeking answers in relation to her condition (see Appendix B[18]). Such encounters can make a significant difference for patients and families who have endured "diagnostic odysseys" over many years. Some genetic conditions may be partially receptive to treatment; early diagnosis of certain genetic mutations may enable earlier intervention, thereby ameliorating the progressive impact of the condition on learning and development.

Finally, diagnosis of inherited rare diseases can assist in identifying other patients and family members with similar genetic variants, facilitating early diagnosis and treatment where appropriate. New models of care are required to support this, including genetic counselling both prior and post-testing. An example of such a model is described in Appendix C: here research clinicians at the Centenary Institute's Genetic Heart Disease Clinic in Sydney Local Health District (LHD) have developed networked, specialised multidisciplinary models of care for families with inherited cardiac diseases[19]. This service is relatively well developed, having been applied and extended over several years, and could provide a model for application in other disease areas.

[17] Lemech CR, Williams R, Thompson SR, McCaughan B, Chin M. Treatment of Breast cancer 2 (BRCA2)-mutant follicular dendritic cell sarcoma with a poly ADP-ribose polymerase (PARP) inhibitor: a case report. *BMC Research Notes*. (2016) 9:386

[18] http://www.smh.com.au/articles/2007/04/05/1175366380306.html?page=fullpage#contentSwap1

[19] Ingles J, James C. Psychosocial care and cardiac genetic counselling following sudden cardiac death in the young. *Progress in Pediatric Cardiology*. 2017. Accepted March 2.

3.2 World-class translational research

From the growth of the Internet through to the mapping of the human genome and our understanding of the human brain, the more we understand, the more there seems to be for us to explore.

Martin Rees

NSW is developing leading genomic research and technological capabilities through a number of world class medical research institutes. These include:

- The Children's Medical Research Institute;
- The Children's Cancer Institute;
- The Garvan Institute of Medical Research and The Kinghorn Cancer Centre - a partnership between The Garvan Institute and St Vincent's Hospital;
- The Victor Chang Cardiac Research Institute;
- The Hunter Medical Research Institute;
- The University of Sydney, including The Centenary Institute;
- The University of NSW, including the Ramaciotti Centre for Genomics;
- Cancer Medical Research Institute, including ProCan (The ACRF International Centre for the Proteome of Human Cancer).

Translational research is a key focus for these centres: aligning world class research with rapid translation to the clinic to improve patient outcomes. The quality of this work is reflected in the number of competitive research grants secured over the past decade (e.g. National Health and Medical Research Council (NHMRC), Australian Research Council (ARC) and international grants).

A good example of this is the work happening at Westmead to address retinal dystrophy disease. Genetic retinal disease is the more likely cause of blindness than diabetes related eye disease in younger populations, affecting about 1 in 3,000 people. NSW researchers and clinicians are working collaboratively to identify the genetic basis for these diseases and develop diagnostic tests to identify people at risk of developing the disease, potentially leading to earlier interventions.

Understanding genetic retinal disease – The Children's Hospital at Westmead

Research undertaken by the Children's Medical Research Institute and The Children's Hospital at Westmead (CHW), together with the University of Sydney's Save Sight Institute, has identified and developed testing for over 150 retinal dystrophy disease genes. These genomic tests are now available to clinicians and their patients across NSW through Sydney Genome Diagnostics, part of the Western Sydney Genetics Program at CHW. This establishes the basis for effective genetic information for patients affected by these conditions.

While a genetic diagnosis is now available for 60 to 70% of patients with retinal disease, further genomic studies are underway in collaboration with the Garvan Medical Research Institute to find disease genes for the 30 to 40% of patients for whom a genetic diagnosis is not yet available. In addition, advances in genomics in this area have opened the door to current research by the Children's Medical Research Institute and the Save Sight Institute using a combination of genome engineering, new vector technologies and stem cell therapies to develop treatments for these diseases.

Outstanding examples of such translational research are not limited to individual patient care but extend to wider public health, such as helping to identify and manage potential outbreaks of foodborne disease:

Pathogen genomics
– Western Sydney Local Health District

Despite public health efforts, rates of foodborne salmonellosis (gastroenteritis) in Australia are climbing, costing over $37 million yearly. NSW Health led the investigation and control of a national outbreak in fruit, supported by the NSW Pathogen Genomics Partnership using genome sequencing to "fingerprint" strains of bacteria. The Partnership was established in 2015 between NSW Health Pathology, the Centre for Infectious Diseases and Microbiology at Westmead Hospital, and the University of Sydney Marie Bashir Institute for Infectious Diseases and Biosecurity.

The capacity to identify, track and deal with such multi-jurisdictional and international outbreaks through the rapid sequencing of infectious organisms has become critical to protecting the health of communities, the quality and safety of traded goods and the economic benefits that flow from such trade. NSW has leading capabilities in this area. For more information please refer to Appendix D.

Another excellent example being led out of NSW is the translational research around childhood cancer. Researchers and clinicians in NSW are jointly leading a national translational research initiative to develop a holistic diagnostic platform to identify and recommend personalised treatments for the most aggressive childhood cancers.

Tackling childhood cancer
– Collaboration between Kid's Cancer Centre, Sydney Children's Hospital Randwick, & Children's Cancer Institute

Advances in technology are leading to an exponential increase in our understanding of the molecular pathogenesis of cancer and to the subsequent development of targeted therapies for specific patient populations selected according to the genetic, proteomic, and biologic characteristics of the cancer cells. Targeted therapy has the potential to improve survival and decrease treatment-related toxicity.

Zero Childhood Cancer Program, the most ambitious childhood cancer research initiative ever undertaken in Australia, is a joint initiative of scientists and clinicians at Children's Cancer Institute and the Kids Cancer Centre, Sydney Children's Hospital, Randwick. This multicentre prospective study will assess the feasibility and clinical utility of a diagnostic service which encompasses tumour molecular and proteomic profiling, in vitro drug screening and in vivo drug modelling to identify personalised therapy for children and adolescents with high-risk malignancies.

The goal is to develop a genomic profiling and drug testing platform in Australia that can provide a comprehensive analysis of cancer cells from individual patients, leading to recommendation of personalised cancer therapy that has the potential to improve patient outcomes and reduce treatment-related toxicities.

3.3 State-wide networks

A distinctive feature of NSW Health and affiliated public health agencies is the development of state-wide networks, with national and international links, to support ease of access and consistent delivery of quality health services across the state. Accordingly, NSW has a number of established state-wide services that provide a platform for developing clinical genomics services in line with the NSW government's commitment to access and equity. These include:

The Agency for Clinical Innovation (ACI) works with clinicians, consumers and managers to provide expertise in service evaluation and redesign, specialist advice on models of care, implementation support and continuous capability building. The ACI consists of clinical networks, taskforces and institutes that provide a unique forum for people to collaborate across the NSW Health system. By bringing together leaders from primary, community and acute care settings the ACI promotes an integrated health system.

The Clinical Genetics Network at the ACI provides expert advice on genetic services and assists in the development and implementation of new or improved models of care to improve health outcomes for people living in NSW. This network of clinicians includes: clinical geneticists, genetic counsellors, consumers, molecular geneticists, health policy makers and other interested health professionals. The role of the network includes the review and updating of state-wide policies and guidelines and development of patient consent forms and consumer information.

The Centre for Genetics Education is a state-wide education service. The Centre is dedicated to providing health professionals who are non-genetics trained with the skills and knowledge to manage the impact of genetic and genomic technologies on their practice. Based at the Royal North Shore Hospital in Sydney, the Centre's educational activities aim to promote appropriate and equitable access to genetic services for people across the State.

Patient support groups: clinical genomics includes the psychological and emotional ongoing care of patients and their families. Patient groups play an important role in facilitating support for those affected directly or indirectly by genetic conditions. NSW Health provides funding to **Genetic Alliance Australia** who provide peer support and information for individuals and families affected by a rare genetic condition/rare disease.

NSW Health Pathology (NSWHP) provides expert pathology and forensic services for the State's health and justice systems. It is the largest public pathology provider in Australia operating approximately 60 laboratories and 200 pathology collection services in public hospitals and community health settings. It employs around 4,000 staff and conducts more than 61 million tests per year.

As partners in research and innovation, NSWHP is helping to protect and improve public health and safety. Its state-wide structure enables rapid translation of new technologies, scientific knowledge and processes to help improve patient outcomes. So far it has established three specialty services to cover rare diseases, cancer and pathogen genomics with each including translational research to promote future development.

NSWHP has played, and is continuing to play through its new Genomics unit, a leading role in a number of clinical genomics initiatives:

- A NSWHP laboratory was the first in Australia to receive accreditation to provide a next generation sequencing (NGS) assay for screening of genes associated with breast cancer in 2013;
- State-wide, it currently performs over 80,000 genetic and genomic tests annually, such as clinical exome sequencing for rare disorders, gene panels for rare cancer syndromes and tumour profiling through to sequencing infectious organisms;
- NSWHP Genomics played a major role in assisting Genome.One, a wholly owned subsidiary of the Garvan Institute, to obtain accreditation for Australia's first whole human genome sequencing test;
- Through its Forensic and Analytical Science Service, it is also examining the use of genomics to help solve crimes and determine the causes of unexplained death.

Looking ahead, NSWHP has the potential, in partnership with NSW Health clinical services, to play a key role in ensuring appropriate genomic testing is offered by NSW Health.

3.4 eHealth: information technology solutions

Our intuition about the future is linear, but the reality of information technology is exponential, and that makes a profound difference.

Ray Kurzweil

NSW Health is well advanced in the development and deployment of enabling ICT infrastructure across the State. This includes:

- The largest hospital deployment of an Electronic Medical Record (eMR) system in the country. In NSW, clinicians in more than 143 hospitals – or 80% of the total bed base, have access to an eMR, allowing them to order tests, schedule surgery and prepare electronic discharge summaries. This is widely used: every day over 33,000 clinicians log on and open 471,000 charts, order 194,000 tests and book 26,000 appointments electronically.
- Comprehensive digitisation of medical images and results, and the associated imaging processes, through the State-wide rollout of a Picture Archiving Communication System and Radiology Information System (PACS/RIS). This rollout was completed in mid-2014. It has removed the need for film to be printed, while enabling images to be accessed and shared much faster and more effectively.
- Broad access beyond the hospitals to clinical documents and medical imaging studies through the State-wide HealtheNet system and Enterprise Imaging Repository (EIR). This means that irrespective of which public health facility a patient visits, their treating clinicians have ready access to the patient's current and previous radiology images and reports and other key clinical documents. This provides clinicians with a more comprehensive picture of the patient's condition and medical history, as well as assisting them to make a faster and more accurate diagnosis and treatment plan, leading to better patient outcomes.

This again provides a strong base to build from, notwithstanding further work is required and happening. NSW Health has committed significant investment to a range of strategies, actions and programs to improve digital connectivity for a smart, networked health system, as outlined in the *eHealth Strategy for NSW Health: 2016-2026*. The vision is to have a digitally enabled and integrated health system delivering a patient-centred health experience and promoting quality health outcomes.

Genome sequencing has been identified in the eHealth Strategy as one of the drivers for digital change and an opportunity to improve health outcomes and deliver more personalised care. As new information sources such as genomic data are identified and integrated into the NSW Health data holdings, there will be an increased demand on improved data acquisition, storage and data linking solutions.

In the genomics field, collaborative bio-informatics, genomic medical research and training to support personalised translational medicine in NSW are already having a major impact for patients across the State. The eHealth Strategy seeks to extend the coverage of these capabilities across the entire NSW Health system through partnerships and innovation with key stakeholders. New capabilities for quality data and analytics will support broader policy directions and priorities of NSW Health.

More information can be found in the *eHealth Strategy for NSW Health: 2016-2026* and the *NSW Health Analytics Framework*.

Developing cloud based technology – NSW Health Pathology

eHealth, in partnership with NSW Health Pathology, is investigating a cloud-based technology to manage the collection, analysis and secure sharing of genomics data. It is hoped this will enable better, faster access to centralised diagnostic data and allow improved clinical decisions, regardless of the patient's location.

3.5 Collaborations and partnerships

Collaborative partnerships have played an important role in supporting Genomic innovation in NSW.

In recent years the NSW government has invested significantly to support NSW based researchers to access the latest technology and support further research. Partnerships have been established with key internal and external stakeholders to achieve this goal.

Of note is the $24 million invested in the Sydney Genomics Collaborative, which brings NSW researchers and clinicians together to strengthen genomic research into inherited diseases and disorders with a genetic component, including cancer. The Collaborative utilises a high capacity genome sequencing system operated by the Garvan Institute of Medical Research, which enables the study of whole-genome sequences at the scale of large populations. Grant funding has supported researchers to undertake whole-genome sequencing to improve understanding of the genetic causes of disease, examples of which are included in this document.

In 2015, the NHMRC recognised Sydney Health Partners (SHP) as one of four Advanced Health Research and Translation Centres (AHRTCs) across Australia. It comprises several LHDs, including Northern Sydney, Sydney and Western Sydney, the Sydney Children's Hospitals Network, the University of Sydney, as well as other research institutes including: Children's Medical Research Institute, Kolling, Centenary, Anzac, and Westmead Institute of Medical Research. Genomics is one of the cross-cutting themes, and this has facilitated communication between clinical and laboratory leaders, researchers and academics working in the genomics area. SHP is looking to develop an ethical and governance framework to facilitate research into rare genetic diseases. This is expected to yield insights of wider relevance for clinical genomics.

The NSW Government is also supporting ground-breaking innovation in cancer research. $6 million has been allocated over five years to the Children's Medical Research Institute (CMRI) and the Garvan Institute of Medical Research as a part of the Cancer Moonshot initiative. While this initiative was established by the National Cancer Institute in the United States to accelerate cancer research, NSW is leading the international collaborative through its innovative work on the cancer proteome. Proteomics is developing at a rapid pace and has the potential to significantly change disease diagnosis and treatment as outlined in the following vignette.

Proteomics (ProCan)
– Children's Medical Research Institute (CMRI)

The **ACRF International Centre for the Proteome of Human Cancer (ProCan)**, which is based at the CMRI, aims to replace traditional cancer pathology testing with a single test that can measure thousands of proteins simultaneously and give an accurate diagnosis from a very small tumour sample within 24-36 hours. This same test would also allow oncologists to determine the most effective cancer treatments for each individual patient and is a major step forward for cancer diagnosis and treatment. Further details on this collaboration can be found at **Appendix E** (page 50).

I'm hoping that these next 20 years will show what we did 20 years ago in sequencing the first human genome, was the beginning of the health revolution that will have more positive impact in people's lives than any other health event in history.

Craig Venter

4 THE VISION FOR NSW HEALTH GENOMICS

The vision for NSW Health genomics

By 2025, NSW Health will be recognised as a leader in the development and use of appropriate genomic technologies in healthcare and public health for the benefit of the NSW population. NSW will be seen as the preferred partner for industry in (gen)omics research, education and training, with effective translation into clinical practice and public health initiatives. This will attract talent and investment to NSW to help realise the promise of genomics.

The level of interest and activity in genomics continues to increase, as the associated medical science and technologies mature, and public expectations are raised through emerging success stories. Such developments create an opportunity to integrate clinical genomics into mainstream care. At the same time the field is changing rapidly and many stakeholders, including clinicians, consumers, patients, the community and funders, feel underprepared and overwhelmed by genomic developments. A shared vision across NSW Health stakeholders to guide the development and application of such services across the State is required.

Such a vision needs to be sufficiently broad, yet robust, to accommodate further discoveries and developments: the science of genomics will continue to unfold in new and unpredictable ways. Such advances must be carefully incorporated into clinical care if the promise of precision medicine is to be realised and confidence in the health system maintained. This requires careful planning and collaboration across the various stakeholders. A shared vision is integral to achieving this.

Implicit in this vision is a belief that genomics will continue to progressively permeate clinical care, providing new diagnostic, prognostic and treatment avenues for different conditions, such that the benefits of genomics are progressively extended from the few (e.g. patients with rare genetic disorders or certain cancers) to the many. Over time, genomic analysis and monitoring will become part of the standard of care for many conditions. Ultimately, a significant proportion of the population will have their genome sequenced, subject to their consent. This information will be incorporated into their medical records and clinical management plans. It will then be available to help them get well and stay well, in partnership with their carers and health providers.

The NSW Health genomics vision also encompasses the following elements:

- Through strong industry and academic partnerships, NSW will both contribute to the global genomics knowledge base and excel in translating research into improved patient care and health outcomes. This hinges on developing an effective interface between research and the clinic, and vice versa, to enable the seamless co-creation and transfer of knowledge;
- Where indicated genomic information will be accessible state-wide on an equitable basis, with cost-effective and quality-assured processes in place for requesting and conducting tests. Combined with specialist expertise and advice to aid interpretation and clinical decision-making, the development of close relationships with general practitioners and other carers as part of an integrated network will promote safe, ethical and appropriate use of the technology;
- Closing the gap in Aboriginal health outcomes is a priority for NSW Health. The absence of specific genomic reference information means that Aboriginal people may not enjoy the same diagnostic benefits as non-Aboriginal people. NSW Health will work with other government agencies and bodies, particularly the Commonwealth, to help close the clinical genomics gap by 2025;
- Health professionals in NSW will confidently use genomic information within their roles, supported by enhanced and responsive education and training in genetics and genomics;
- Clear and unambiguous consent procedures will provide assurance to patients and families and enable them to make informed decisions in partnership with their treating clinicians, including the handling of incidental findings[20];
- Robust safeguards will be enacted so that personal genetic and genomic data is handled at all times in a way that builds and sustains public confidence in the NSW health system. This includes adherence to the relevant Commonwealth and State guidelines, policies and laws such as the *NSW Genetic Health Guidelines* and the *NSW Health Privacy Manual for Health Information*[21]; and
- The NSW community will play an active and informed role in the development of genomic services across the State. This will be achieved through effective and ongoing public engagement to promote understanding of the use of genomic information in healthcare. Consumers and patients will be informed and supported to make appropriate health and wellness choices for their own benefit, for the good of their families and the wider Australian community.

[20] A national consent working group has been established under the auspices of the Australian Genomics Health Alliance to generate a national approach to consent for genomic testing. For a simple explanation of dynamic consent, go to: http://www.geneticalliance.org.uk/news-events/news/dynamic-consent-what-s-that/

[21] http://www.health.nsw.gov.au/policies/manuals/Documents/privacy-manual-for-health-information.pdf

4.1 Realising the vision

A significant change journey is required, as no-one can accurately predict how the various (gen)omics technologies and the associated medical advances will develop.

This vision is ambitious but achievable, given the strong base that NSW has to build upon, as outlined in Chapter 3. However, it is difficult to anticipate how consumers will respond: will the majority actively seek out DNA testing or respond more cautiously as testing options proliferate? How they respond will significantly influence the speed and scale with which health systems are forced to respond as technology advances.

Careful choices must be made in the face of such uncertainty. "Rushing in" risks over-committing prematurely to what may become the wrong path, while "standing back" means ceding the potential to help shape the development of clinical genomics and establish leading capabilities in NSW.

Following extensive consultation, NSW Health will **take an adaptive stance to clinical genomics**[22]. This means investing judiciously in those areas that are most likely to yield results (i.e. taking action in certain areas), while developing the readiness to respond quickly and effectively to advances in the field. Such a strategy requires the development of new governance capabilities at a state-wide level to leverage off existing capabilities whilst monitoring wider (gen)omic developments to guide appropriate planning and investment decision-making.

Figure 3 **Realising the Vision**

[22] For further explanation, see https://hbr.org/1997/11/strategy-under-uncertainty

Three key stages have been identified to realise the NSW Health genomics vision over the coming decade:

1. Strengthening the foundations (0-2 years)

The starting point for this journey is to build on the strong foundations already in place in NSW in terms of clinical genomics. Excellent examples can already be found where genomic technologies are making a real difference to patient care and public health, as outlined in Chapter 4.

Understanding the value of these new genomic technologies over existing clinical care options will help to build the case for the wider application and funding of genomic medicine. Increasing community support and clinical readiness for such advances is also necessary.

The need to understand the ethical, legal and social issues (ELSI), as well as an exploration of the psychological impact of testing will be required. This will ensure that any expansion of testing is done in a way that is both representative of good ethical practice and supportive of consumer decision-making.

In the short term, NSW Health will foster existing collaborations between current genomics experts, working together to ensure the genomics network is co-ordinated and connected. A strong foundation will allow for a unified approach to realise the benefits of genomics, to take full advantage of new opportunities, and to develop a strong and integrated network that is proactive in extending evidence-based genomics services across the State.

2. Enhance disease management and prevention (2-7 years)

The second phase centres on expanding the application of such technologies to improve patient care across a much wider range of diseases and disorders, while ensuring equity of access across the State. This should be primarily clinically-led rather than technology-driven with NSW Health support focused on areas where:

- Genomics can provide a definitive diagnosis not easily obtained by other means;
- The disease or disease group is prevalent in the population;
- There is a demonstrable positive impact from a genomic test for the patient, the community and/or the healthcare service;
- Genomics supports predictive medicine where susceptibility to disease is actionable; e.g. early intervention can prevent the onset of disease or genomics informs treatment response and risk estimates;
- There is existing expertise in either clinical services or genomic diagnostics, hence the ability to become a leader in the provision of high quality services.

Such an expansion hinges on developing new medical practices, workforce, information technology and data governance capabilities while facilitating the adoption of such advanced methods across the various clinical specialties. With the solid foundation described in Chapter 3, NSW Health will be well positioned to deliver enhanced disease management and prevention for its population.

3. Towards precision medicine (beyond 7 years)

The third phase lifts the focus beyond individual patient care to harnessing the potential of genomic technologies to transform healthcare. This requires a paradigm shift from disease management to prevention and wellness.

While each phase builds upon the previous phase, this will not be a linear path due to the uncertainties involved. A flexible approach will be required to enable genomic medicine to be incorporated into routine clinical care, and routine care to be transformed.

Despite major advances over the past decade, it is still broadly unclear whether this promise is achievable. The predictive value of genomics is still emerging, with the risk that mainstreaming could lead to imprecise predictions. This in turn could result in over-diagnosis and potential harm to the individual and their family in the absence of appropriate governance.

Nonetheless, our understanding of what is possible and practical in terms of precision medicine is constantly evolving. However, the goal of precision medicine will not be achieved by waiting until we fully understand the implication of what genomic technology can offer. Therefore significant steps must be commenced if we are to be active in our goal of achieving our strategic vision for genomics in NSW.

5 | DELIVERING THE VISION

Achieving the NSW Health genomics vision will require coordinated action across several dimensions. This chapter details key recommendations for achieving this.

NSW Health is committed to national harmonisation of policy and regulation in this area. This reflects both the universal nature of many of the issues, such as ethical and regulatory considerations and sharing of genomic information across geographic boundaries. NSW Health will continue to work with the Commonwealth Government, jurisdictions, and relevant stakeholders, to align the NSW direction with the National Health Genomics Policy Framework.

The full promise of clinical genomics hinges on the broad adoption and appropriate use of the technology in mainstream care. NSW Health has an essential role in enabling, integrating and amplifying innovation so that the benefits of genomic technology can become more widely and equitably available. This starts with leadership and governance: creating the context for quality and safety, as well as a platform for State-wide service innovation and improvement, including the requisite infrastructure and skills.

As previously indicated, the future of clinical genomics cannot be determined with certainty and hence an adaptive strategic stance is required. This is predicated on the ability to recognise and respond quickly to genomic developments. Mechanisms are required to monitor the environment in order to respond appropriately as circumstances change. Leadership and governance have an essential role to play here.

5.1 Leadership and governance

Delivering the vision requires effective leadership and governance to ensure a coordinated approach to the longer-term development of clinical genomics in NSW. This includes the development of services in a way that is ethically sound, informed by evidence and supportive of patient engagement. A new Governance committee will be established for NSW, bringing together key leaders and stakeholders from across the State. The role of this body will be to oversee the implementation of the NSW Health Genomics Strategy.

No single individual or organisation can deliver the vision outlined in this document. Realising the vision hinges on the various parties that span medical research and clinical care in NSW working together, including LHDs and specialty health networks, healthcare professionals, researchers, consumers and experts in the field of health economics, health law, ethics, health education.

The Committee will facilitate and support collaboration and partnerships to ensure that key NSW Health investment in genomic technology drives towards a common goal, is coordinated, and avoids unnecessary fragmentation and duplication of resources.

To address the recommendations outlined in this chapter, the Committee will oversee the work of a range of sub-committees.

Recommendation 1:

Establish a Governance Committee to guide the strategic direction for clinical genomics in NSW and provide leadership at a State level, including appointing a suitable subject matter expert to co-chair this Committee in conjunction with an appropriate NSW Health executive.

5.2 Focussed application: clinical need, validity and utility

Rapid advances in (gen)omic technology and medical research have the potential to advance the diagnosis and treatment for a range of conditions. However, a number of steps are required before they can be applied in general clinical care.

A rigorous assessment of both clinical validity and utility is required for the effective commissioning and introduction of any new technology or service into mainstream care. Accordingly, the need to establish clinical validity and utility is not unique to genomics; instead, it is a case of applying the same rigorous standards used in other areas of medicine to a new field.

Clinical genomics is already demonstrating real, significant and sustainable patient benefits in a range of areas including gene therapy, as illustrated by the following example.

Gene therapy – Royal Prince Alfred Hospital

People with beta-thalassaemia major, a severe sub-type of the disease, require lifelong regular blood transfusions and suffer serious complications from the consequent build-up of iron in their body, including heart and liver damage. This is treated with iron chelation therapy, which has unpleasant side effects. Until now, the only possible cure for beta-thalassaemia major has been donor bone marrow transplantation, which is generally recommended for children with matched sibling donors, less than 25 per cent of people with this condition.

A Phase 1/2 international clinical trial of gene therapy for beta-thalassaemia major is offering new hope to these patients. At the laboratories of the Department of Cell & Molecular Therapies at Royal Prince Alfred Hospital, haematopoietic stem cells from patients' own blood are collected and then genetically reprogrammed under strict centralised procedures to produce functional haemoglobin, using a viral vector containing an engineered gene. After myeloablation, these cells are infused into the patient as an autologous transplant, without the risks associated with receiving donor cells.

For the small number of patients treated so far, blood transfusions are no longer needed or are reduced by half, depending on their specific genetic thalassaemia subtype.

Expediting and expanding a small number of clinical genomic services where clinical validity and utility has been established would be a significant step forward. However, this is not enough on its own given the pace and nature of developments in clinical genomics, and the challenges this presents for existing evaluation mechanisms. These mechanisms are inherently and rightly conservative to ensure new developments are safe, clinically beneficial and cost effective before they are made available through the NSW health system.

This should include measures to achieve appropriate balance and equity of access in terms of use of (gen)omic technologies. This can be done by promoting applications that address a range of healthcare issues from those that may affect large parts of the community to others targeting rare conditions. This needs to be aligned with on-going research to evaluate the clinical validity and application of the genomic testing, noting the complexities across specialties.

Recommendation 2:
Enhance, simplify and expedite the mechanisms for assessing the clinical need, validity and utility of new developments in health genomics and prioritise their potential for translation into the NSW public health system.

5.3 Service delivery: commissioning and utilising genomic technology

The vision for the use of genomics in the NSW health system promotes cost-effective and clear processes for requesting and conducting tests, increasing access to specialist genomic services through established networks, and increasing access to appropriate genetic counselling support.

As the largest commissioner and provider of healthcare in Australia, NSW Health has an essential role to play in developing coordinated and collaborative service delivery models.

To achieve this NSW will apply a number of design principles to develop these services. These include:

- **Build on what works today** – innovative models of care harnessing genomic technology are emerging both locally and internationally. We should learn from these services and models[23] as we shape and develop future State-wide service delivery models;
- **Consumer-centred design** – engaging consumers and their representatives in the design process so that services provide a positive service experience in line with consumers' needs and preferences, enhanced health outcomes and care as close to home as possible;
- **Integrate genomic medicine into mainstream care** – where appropriate, streamlining adoption by incorporating genomics into existing clinical pathways and service models;
- **Design for collaboration and efficiency** – promoting and requiring shared resources across traditional boundaries to avoid unnecessary fragmentation and duplication of resources;
- **Recognise "one size doesn't fit all"** – there are many different applications of genomics and different clinical pathways and models will be required to suit differing diseases, conditions and local contexts. For example, the genomic analysis of tumours does not require routine assessment by genetic counsellors except in the minority of cases where germline mutations are identified; and
- **Design for the future** – new service models must adapt as genomics develops, the number and range of tests and therapies increase and new service delivery options emerge (e.g. near-patient testing (Point of Care Testing) in primary care and outpatient settings). Future-proofing will also mean taking advantage of digital technologies (e.g. electronic patient records, telehealth, mobile devices and applications) where possible.

Consideration will be required to address the particular needs of patients and consumers in rural and remote areas and specific ethnic, social and cultural groups. The genetics services established in the Hunter New England Local Health District provide an example of how the needs of rural and remote communities can be met.

[23] For example, rural/regional outreach genetic counsellors have a unique perspective on working in such areas; this should be incorporated into new service designs.

Rural and Regional Models of Care – Hunter New England Local Health District

The General Genetics Service is part of Hunter Genetics and provides clinical genetics services within Hunter New England and some Outreach clinical genetics services to the northern parts of New South Wales. The outpatient service is based at Waratah. Outreach clinics are conducted at Taree, Tamworth, Port Macquarie, Coffs Harbour, Lismore and Kingscliff. In the absence of service level agreements, the provision of Outreach clinical genetics services is dependent on specialist staffing levels at Hunter Genetics. Service provision also includes multidisciplinary clinics covering Maternal Fetal Medicine, Baby Hearing clinic and, Paediatric Neurogenetic Clinic. Metabolic clinics are managed by Westmead Metabolic team at Hunter Genetics. Huntington disease psychiatric clinic is managed by the Psychiatry Department. The caseload in General Genetics Service is largely made up of referrals from clinicians including Paediatricians, Neurologists, General Practitioners and Ophthalmologists.

Every clinic is assigned a Clinical Geneticist, a Genetic Counsellor and administrative support. Face to face contact with patients is available during outreach clinics and the option of telehealth is also used regularly.

Multi-disciplinary clinical review meetings are held centrally on a weekly basis, with outreach staff having the option to dial in to contribute to case discussions. Once a year the Human Genetics Society of Australasia (HGSA) holds a scientific meeting where outreach, centrally located staff and overseas professionals can meet for networking and professional development opportunities.

The Service orders tests directly from the pathology provider and prioritises ordering based on the type of test available and the budget required. Priority is given to test results that may have a potential to impact on family planning decisions. Hunter Genetics can access the most advanced technology for analysis through domestic and overseas laboratories. Domestic laboratories are utilised where possible to support local capacity building.

Opportunities to explore a range of options to enhance access to high quality care will need to be explored to maximise service availability and meet local needs. This includes the appropriate leveraging of digital technologies, while considering privacy and confidentiality requirements (e.g. electronic referrals, telehealth, and the provision of information and support via consumer portals and mobile devices).

Recommendation 3:

Develop new service delivery models linked to clinical pathways that incorporate genomic and digital advances to provide safe and equitable access across NSW.

5.4 Genomic data and infrastructure: handling "big data"

A key feature of genomics is the dependence on advanced information and communication technology (ICT) as much as medical science.

The convergence of digital and biotechnologies enables the vast quantities of data generated through DNA sequencing to be handled significantly faster, cheaper and more effectively than was possible even a decade ago.

This, combined with wider advances in digital health (such as the introduction of electronic patient records, including electronic ordering of tests and results, and advanced analytics), is central to enabling genomics to be integrated into mainstream healthcare.

Integrating genomics as part of the wider health system is reliant upon designing genomic data protocols and infrastructure that leverage on, and align with, existing approaches and resources. The following approach is recommended in terms of genomic data and infrastructure:

- Ensure greater consistency in terms of how data is captured (including patient consent protocols), shared, stored and protected in line with evolving community expectations as well as legal and regulatory requirements[24];
- Support effective clinical decision-making in terms of test ordering and the delivery and interpretation of results, including access to relevant experts and advice (potentially using telehealth and other collaborative tools) to support high quality patient care;
- Develop the supporting data infrastructure required to improve accessibility and analysis. This involves bringing together the disparate data sets that have developed around clinical research groups focused on particular diseases or communities as well as the clinical or phenotypic data that is increasingly stored in electronic patient records;
- Enhance the tools and computed solutions available to clinical researchers, clinical genomic scientists and bioinformaticians to interpret the data generated through next generation sequencing to support effective diagnosis;
- Embrace more effective and efficient approaches to data sharing and storage as the demand for exome and whole genome sequencing grows (e.g. protocols for the sharing of large files as well as storage utilising public or private cloud);
- Provide appropriate workflow management tools, including reporting, to coordinate activities across the various parties involved (e.g. patient, general practitioner, hospitals, public and private testing labs, genetic counselling services) and monitor performance against service standards;
- Operate, support and enhance the enabling infrastructure, recognising the need to keep pace with technological developments and the associated expectations of staff working in this domain; and
- Provide consumers and their families with better access to information and resources utilising digital channels and tools (e.g. patient portals).

[24] To fully leverage the potential of the genomic data collected, ICT infrastructure needs to be set up in a way that facilitates the sharing of data. Delivering such infrastructure is beyond the remit and capacity of NSW Health – hence will require wider cooperation between governments and industry if it is to be achieved. This has also been raised at a national level within the National Health Genomics Policy Framework.

Some of these elements are more appropriately addressed at a national level, such as the development and adoption of information management standards and protocols; however, others fall within the remit of NSW Health (e.g. provision of enabling infrastructure to integrate hospitals with test centres).

It is also important to note the potential for high quality ICT infrastructure to attract specialised talent and facilitate medical advances. NSW needs to explore opportunities to support this. This includes due consideration of the factors required to promote effective data sharing and usage across different parties, recognising the behavioural shift implicit in moving from a research paradigm into mainstream clinical care and introducing new work practices[25].

The challenges associated with developing such supporting infrastructure and standards are significant. We are starting from a base where existing clinical datasets are incomplete, non-standardised and fragmented (e.g. located within the individual Local Health Districts or disease-specific registries). Bringing these data sets together will be a major undertaking aside from the privacy and security challenges associated with linking and sharing such sensitive information. Nonetheless, this work must be undertaken if the promise of genomics is to be fully realised.

Recommendation 4:

Work with relevant parties to define the information standards, protocols and enabling infrastructure required to integrate clinical genomics into mainstream care.

5.5 Preparing the workforce for genomics

The rise of genomic medicine presents a major workforce development challenge for healthcare professions and organisations, including NSW Health. Clinical genetics has historically been a relatively small specialist service within the NSW Health system. Making genetics and genomics an integral part of mainstream clinical practice, a key tenet of the NSW vision, will change this profoundly.

It will become necessary for NSW Health to ensure more of the workforce is aware and literate in the use of genomics in public healthcare. A broader group of clinicians will be required who understand genomics and how it can be applied in their day-to-day practice. This will be particularly important for referring and treating physicians who have an essential role to play in ensuring appropriate use of genomic testing. Clinicians will need to understand the array of tests available, the information they generate, the risks associated with the results, and the services and support options available for patients and their families so that potential outcomes can be managed appropriately.

As clinical genomics becomes mainstream, such testing and ongoing care may increasingly be offered by health professionals without a genetics specialty, such as general practitioners and other primary healthcare providers. This highlights the pending workforce challenge in responding to the rise in demand for genomic services.

A workforce needs assessment is the first step towards understanding how to address these challenges, some of which are already apparent. For example, stakeholders report the apparent lack of funded training positions in Australia which may be creating a bottleneck for those seeking training.

In addition, NSW Health Workforce Branch has recently explored the issues facing the genetic counselling workforce in NSW. These are summarised on the following page.

[25] Healthcare is replete with examples where technology has disappointed due to insufficient attention being given to human factors – such as, a failure to adequately consider the complexities of practice or what is required to make them acceptable to those who must use them. Mitigating this hinges on carefully considering the local, practical issues in the design, configuration and deployment of healthcare technologies – hence a socio-technical approach.

The changing landscape of the genetic counselling workforce

The results of the NSW Health consultations with genetic counsellors identified several emerging challenges. Most of these challenges relate to the growing field of genomic testing, increased demand for genetic services and the related workforce issues. These challenges include:

- The transition from genetic counsellor to "genomic counsellor"
- The current (and anticipated) mismatch between demand for and supply of genetic counselling services
- Challenges associated with ensuring consistent service provision and adequate governance of an evolving workforce.

Workforce planning and service delivery re-design will assist in ensuring that these challenges are overcome, and genetic counsellors can continue to deliver high quality services to NSW patients.

The report consultations identified the genetic counsellor workforce to be an adaptable group that provide a valued and important service across the NSW health system.

More information is available at the following link: ***The changing landscape of the genetic counselling workforce final report.***

Similarly, in order to establish and deliver high quality genomic services there is increasing demand for a number of other specialised clinicians; for example, clinical geneticists, genetic pathologists, clinical genomic scientists and bioinformaticians.

A number of overlapping challenges exist in Australia which may make it hard to build and retain these specialist workforces. Challenges include:

- Limited numbers of qualified clinicians (e.g. clinical geneticist, genetic pathologists);
- Limited training positions (e.g. genetic pathologists, genetic counsellors);
- Roles are often not clearly defined or well understood, making career pathways indistinct (e.g. clinical geneticists, clinical scientists);
- Some of the professions that currently provide the vast majority of genomic data and interpretation in Australia are, unlike a number of their international counterparts, un-registered professions and there is a perception that this may be influencing workforce development initiatives (e.g. genetic counsellors, clinical scientists);

The role of bioinformaticians may be pivotal to establishing and developing new systems to manage the data from genome sequencing, and up-skill the laboratory genomics workforce; including scientists and genetic pathologists.

More broadly, there is a need to increase genetic and genomic literacy across all existing clinical subspecialties and levels, to support the translation of genomic technology into service delivery and patient care. This ranges from medical students to junior and senior hospital doctors, nurses, midwives, general practitioners and specialists in the community. To achieve this a national workforce development approach is needed which will require close cooperation with the Commonwealth, relevant medical and nursing colleges and educational institutions. NSW Health is committed to supporting such an approach.

Similarly, expert genomic knowledge will be required by the health professionals involved in dealing with infectious disease outbreaks and risks; these include medical microbiologists, infectious disease clinicians, public health and infection control professionals – among others[26].

Recommendation 5:

Work with relevant NSW stakeholders and national bodies to identify future workforce requirements, including awareness and genomic literacy within NSW Health, and develop a plan to address these needs.

[26] Strategic partnerships, like the one between UTS (the ithree institute) and the NSW Department of Primary Industries, are promoting the One Health approach to infectious disease through Australian Genomic Epidemiological Microbiology (Ausgem). This includes training higher degree researchers, postdoctoral scientist and early-midcareer scientist in the application of genomics and bioinformatics, as well as other "omics" sciences.

5.6 Community engagement: maintaining public trust and confidence

Public support will be critical to realising the NSW Health genomics vision.

Realising the NSW Health genomics vision rests on increasing public awareness and understanding of genetics and genomics, as well as appropriate engagement in key decisions affecting individuals, families and communities.

This will be challenging as public awareness around genetics requires further development and the range and breadth of issues presented by genomics have the potential to be controversial. The type of information generated through genomic testing is likely to be more complex when compared to results patients have previously received (e.g. risk prediction, implications for relatives as well as self).

The following study being conducted by the University of Sydney is examining how economic, psycho-social and ethical aspects of receiving risk information may impact on patients and their health choices.

The "Managing Your Risk" Study – University of Sydney

Melanoma is highly preventable by modifying personal sun habits. More than 80% of melanomas in NSW could be prevented through reduced sun exposure. With improved knowledge of how genetics influences the risk of melanoma, questions are arising as to whether and if so how risk-stratified population prevention and screening may be feasible and desirable. The NHMRC-funded Managing Your Risk Study (2017-2020) is being led by the Sydney School of Public Health at the University of Sydney. It involves a national randomised controlled trial to see whether providing information on personal genomic risk of melanoma modifies preventive health behaviours in the general population (such as increased sun protection, or skin examinations) compared with standard prevention advice. Nearly 1,000 people from the general population will be recruited.

As a component of the trial, the study will also evaluate the economic, psycho-social and ethical aspects of receiving this risk information, to help understand its broader impact. This will include evaluating: value for money, the consent process, how well participants understood the information they were provided, the psychological impact of the information, if and how participants communicated with family members, friends and health professionals about their genomic risk, whether there was perceived genetic determinism, the medicalisation of normal genomic variation, over diagnosis and the impact on individual responsibility for health.

If the study suggests "proof of concept" of the testing, it will help inform the responsible introduction of genomic testing for melanoma prevention and early detection. It also presents a translational model that could then apply to other diseases.

The study will also contribute to the debate regarding whether receiving disease risk information based on common genomic variants has a motivating effect on behaviours.

Given these complexities, an adaptive, integrated approach to community engagement is needed involving the range of organisations and professionals likely to be involved in delivering health genomic services. Such an approach should include:

- Basic literacy building in terms of genetics and genomics. There is a need for community education regarding the appropriate use of genomics in healthcare including the benefits and limitations. This includes highlighting the risks associated with discovering incidental clinically relevant findings as well as the choices and avenues available to consumers in terms of genomic services (e.g. consent models). Community education will become increasingly important as the availability, and active promotion of, direct to consumer testing grows;
- Public engagement approaches that are tailored to the needs and preferences of different groups and communities (e.g. screening or risk assessment for certain racial and ethnic groups). To facilitate high levels of participation, this needs to be done in a way that builds and sustains community confidence and trust;
- Steps to safeguard and strengthen the public's trust in the safety of their medical data (including genetic and genomic data) and how it will be used. This includes measures to ensure consumers cannot be discriminated against on the basis of their genetic makeup;
- Direct consumer involvement in determining how they receive clinical genomic services (e.g. service co-design to promote shared decision-making, with patients informed and able to participate in key decisions with an understanding of the implications for themselves and their families);
- A balanced approach to testing, whereby choosing not to have a test is deemed a valid/acceptable option for some individuals, and this is built into consent and clinical services models;
- Encouragement for consumers to allow their genetic information to be aggregated and used for research purposes, hence the wider common good subject to appropriate safeguards and controls;
- On-going government involvement and support to ensure consumers have access to accurate, evidence-based, up-to-date, impartial information on genetics and genomics to enable them to make informed choices in terms of the use of such services. Information should be actively promoted to help shape and inform community attitudes rather than passively published on a website; and
- Collaboration and consistency of message across the range of parties involved in informing consumers and delivering genomic services in NSW. General Practitioners are particularly important here, given their important role in guiding patients with the provision of appropriate care.

Realising the NSW Health genomics vision hinges on moving forward in a way that builds and sustains public confidence and trust at all times, both in the general community and within specific groups, to ensure that they are not stigmatised. Effective community engagement is central to achieving this.

Recommendation 6:

Work with key stakeholders, including general practitioners and Primary Health Networks, to engage the community regarding clinical genomics to build and sustain public confidence. This includes working with consumers as equal partners to develop services that reflect their needs and preferences in line with ethical, legal and professional standards.

6 MOVING FORWARD

The NSW Health Genomics Strategy has been developed to bring greater focus and alignment to the efforts of various stakeholders working in and around genomics. This is premised on a belief that more can be achieved for the benefit of the people of NSW by working collectively rather than individually.

A strategy alone will not deliver the vision, it must be translated into actions and implemented. This chapter outlines the proposed next steps for achieving this, including:

1. **Establish governance** – assign overall accountability for owning, executing and adapting the Strategy (as circumstances require). Establish mechanisms to facilitate effective communication and coordination between stakeholders.
2. **Develop the NSW Health genomics implementation plan** – define the projects and activities required to achieve the strategic objectives; mobilise the effort working in partnership with stakeholders.
3. **Create a system of accountability** – monitor and evaluate progress against the agreed objectives, providing regular updates to stakeholders.

6.1 Governance

As noted in Recommendation 1, a new governance body, the NSW Health Genomics Steering Committee, will be established to advance the recommendations outlined in Chapter 5. The Committee will play a pivotal role in promoting collaboration across the various stakeholders to develop clinical genomics in NSW into a mature, well-functioning system of clinical care informed by research.

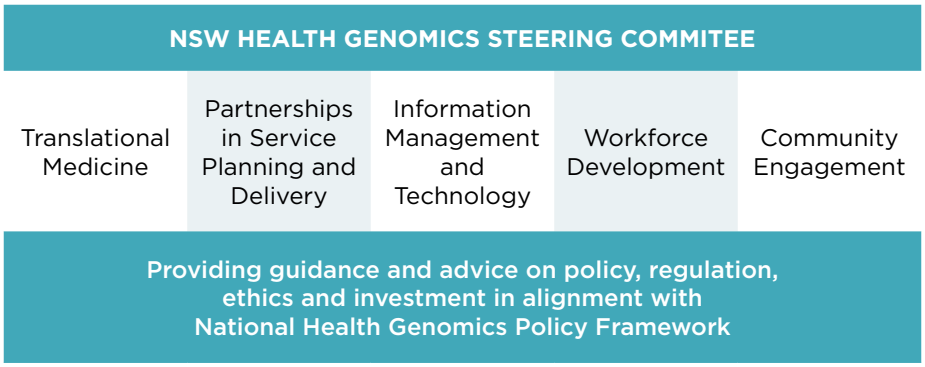
This includes developing an overall implementation plan to guide action on the recommendations in this Strategy. The Committee will also be responsible for working with relevant parties (including other Australian governments, national genomic alliances and consumer groups) to put in place an appropriate bioethical framework for NSW that addresses the ethical, legal and social implications (ELSI) associated with incorporating genomic information into mainstream healthcare.

The Committee will be supported by five sub-committees, each focusing on a specific area within the Strategy. These are:

- **Translational medicine** – the translation of research from clinical studies into everyday clinical practice and health decision making (Recommendation 2)[27];
- **Partnerships in Service Planning and Delivery** – development of State-wide networks to deliver coordinated high-quality clinical services to maximise access whilst avoiding fragmentation and unnecessary duplication of resources (Recommendation 3);
- **Information Management and Technology** – the development of supporting information management protocols, infrastructure and tools (Recommendation 4);
- **Workforce Development** – the development of a suitably skilled workforce to deliver high quality services across NSW (Recommendation 5);
- **Community Engagement** – building public awareness and understanding, hence public confidence and trust in the new services (Recommendation 6).

The governance structure is shown below:

Figure 4 **NSW Genomics Strategy Governance Structure**



The structure will be established progressively with representation from across the various organisations and geographies involved in clinical genomics to guide the implementation of the NSW Health genomics strategy. The Governance structure will be flexible and evolve over time as further advances in genomic technology and service provision become apparent.

[27] The Institute of Medicine's Clinical Research Roundtable described 2 "translational blocks" in the clinical research enterprise: T1 and T2 (JAMA:2008). The first roadblock (T1) is primarily concerned with the laboratory (bench to bedside), while the latter (T2) is more concerned with bringing the results of T1 research to the public (bedside to policy and practice). For clarity, the focus of the sub-committee is on the latter (T2): translating new treatments and interventions into system-wide change.

6.2 Implementation planning

Strategy must be turned into action if it is to lead to results. Accordingly, an important next step is the development of an implementation plan bringing together activities across the sub-committees. This work has already started: in developing the Strategy, a number of actions were suggested by workshop participants with various timescales in mind across three phases as discussed in Chapter 4.

NSW Health will develop an implementation plan to reflect and guide the work of the sub-committees noted in Figure 4. A diagrammatic representation of the implementation plan is provided in Figure 5.

NSW Health recognises the opportunity and challenges presented by (gen)omic technologies. Based on the collective vision, capabilities and passion of our people and institutions, we are ready to move forward and embrace the future in this area.

Working together with the right structures and a common goal, great things will be achieved for the benefit of the people of NSW.

Figure 5 **Implementation**

- Launch Strategy
- Develop the implementation plan
- Establish Governance Committee
- Establish sub-committees:
  - Translational Medicine
  - Partnerships in Service Planning and Delivery
  - Information Management and Technology
  - Workforce Development
  - Community Engagement
- Identify work-plans and priorities for each sub-committee
- Undertake NSW genomic/genetic service stocktake

7 | GLOSSARY

Key Term	Definition
Bioinformatician	Person who develops data algorithms and specialised software to analyse biological data, such as DNA or RNA sequences.
Bioinformatics	The use of algorithms and software to analyse biological data.
Clinical geneticist	Physicians who have undergone speciality training in genetics after general professional training (such as paediatrics and oncology) and see referred patients for diagnosis, management, genetic testing and genetic counselling.
Clinical genetics	The medical specialty which provides a diagnostic service and "genetic counselling" for individuals or families with, or at risk of, conditions which may have a genetic basis.
Clinical genomic scientist	Person with a Fellowship of the HGSA (Molecular Genetics or the RCPA FSc (FFSc Medical Genomics or Biochemical Genetics) who interprets and reports genomic data to referring clinicians.
Clinical genomics	Is an emerging medical discipline that involves using genomic information about an individual as part of their clinical care (e.g. for diagnostic or therapeutic decision-making) and the health outcomes and policy implications of that clinical use (also used interchangeably with genomic medicine, precision medicine, personalised medicine, stratified medicine).
Clinical utility	The usefulness of the genomic test to the patient (i.e. to what extent does it influence the effectiveness of the proposed intervention or clinical decision making and result in improved clinical outcome).
Clinical validity	How well the test for the genetic variant being analysed predicts the presence or absence of the phenotype of the clinical disease or predisposition.
DNA	Deoxyribonucleic acid, a self-replicating material which is present in nearly all living organisms as the main constituent of chromosomes. It is the carrier of genetic information.
Exome	Part of the genome formed by exons, the sequences which, when transcribed remain within the mature RNA after introns are removed by RNA splicing.
Gene	The basic physical and functional unit of heredity. Genes, which are made up of DNA, act as instructions to make molecules called proteins.
Genetics	The study of genes, genetic variation, and heredity in living organisms.
Genetic counsellor	Healthcare professionals who have undergone speciality training to help individuals, couples and families understand and adapt to the medical, psychological, familial and reproductive implications of the genetic contribution to specific health conditions.
Genetic pathologist	Pathologists who have undergone speciality training in genetics and genomics who provide specialist input to genomic tests including test selection, results and interpretation to aid in the diagnosis, management and treatment of patients with a genetic basis for their disease.
Genetic test	Type of medical test that identifies changes in chromosomes, genes, or proteins.
Gene therapy (or editing) of germline cells	Is when DNA is manipulated (inserted or deleted) from reproductive cells, eggs or sperm, in the body. Changes can then passed be down from generation to generation (e.g. preventing the inheritance of a disease trait). Germline therapy is prohibited in Australia under legislation.
Gene therapy (or editing) of somatic cells	Is when the DNA of any human cells, except germline cells, are manipulated (inserted or deleted) to treat disease. These changes are not passed down from generation to generation.
Genome	The complete set of genetic information in an organism.
Genomics	The application of genome-based knowledge through the study of genes and other genetic information, their functions and inter-relationships for the benefit of human health.
Genomic data	Refers to data produced from DNA sequencing of a genome. It can be compared with a reference genome.
Genomic knowledge	Includes information about the interpretation of genomic data and the implications of these findings, as well as relevant non-genomic clinical information.

Key Term	Definition
Genomic medicine	Is an emerging medical discipline that involves using genomic information about an individual as part of their clinical care (e.g., for diagnostic or therapeutic decision-making) and the health outcomes and policy implications of that clinical use (also used interchangeably with clinical genomics, precision medicine, personalised medicine, stratified medicine).
Genomic services	Sequencing of tens, hundreds or thousands of genes or the whole genome, and analysis available for research, screening or diagnostic purposes.
Genomic testing	Involves the analysis of multiple genes from a cell or tissue simultaneously using sophisticated computer-based algorithms.
Genotype	The part (DNA sequence) of the genetic makeup of a cell, and therefore of an organism or individual, which determines a specific characteristic (phenotype) of that cell/organism/individual.
Microbiome	The totality of microorganisms and their collective genetic material present in or on the human body or in another environment
Metabolomics	The study of metabolomes (the set of metabolites present within a cell or tissue) and their functions
Next-generation sequencing (NGS)	NGS also known as Massively Parallel Sequencing, is the catch-all term used to describe modern sequencing technologies which enable WGS and many other applications in genomics.
'omics	Suffix that refers to the analysis of all the molecules of one type in a cell or tissue. For example: genomics (investigation of all DNA molecules in a cell), proteomics (all proteins), transcriptomics (all RNA molecules), metabolomics (all metabolites). *Note: for the purpose of this paper, the study of exome, the part of DNA responsible for producing proteins, is considered part of the 'omics family.*
Pathogen genomics	The utilisation of genomic and metagenomics data gathered from high through-put technologies (e.g. sequencing or DNA microarrays), to understand microbe diversity and interaction as well as host-microbe interactions involved in disease states.
Personalised medicine	Individualised treatment for patients through stratification by subclass of disease or the likelihood of responding to a particular therapy, intervention, or disease management strategy.
Pharmacogenomics	The study of how the actions of, and reactions to, medicines vary with the patient's genes using large datasets.
Phenotype	Is the composite of an organism's observable characteristics or traits, such as its morphology, development, biochemical or physiological properties and behaviours.
Population health	Health discipline focusing on understanding health and disease in community, and on improving health and well-being through priority health approaches addressing the disparities in health status between social groups.
Precision medicine	Individualised treatment for patients through stratification by subclass of disease or the likelihood of responding to a particular therapy, intervention, or disease management strategy. The use of the term Precision Medicine is preferred over Personalised Medicine in a number of jurisdictions e.g. USA (see also clinical genomics, genomic medicine, personalised medicine, stratified medicine).
Proteomics	The study of proteomes (sets of proteins within a cell or tissues) and their functions.
Stratified medicine	Stratifying cohorts of patients by subclass of disease or the likelihood of responding to a particular therapy, intervention, or disease management strategy. The term "stratified medicine" reflects the effects of medicines at population level, while the term "personalised or precision medicine" refers to individualised treatment based on genetic information. (Also see clinical genomics, genomic medicine, personalised medicine, precision medicine).
Tissue typing	The assessment of the immunological compatibility of tissue from separate sources, particularly prior to organ transplantation.
Transcriptomics	The study of transcriptomes (the sum total of all the messenger RNA molecules expressed from the genes of an organism) and their functions.
Virome	The genomes of all the viruses that inhabit a particular organism or environment.
Whole exome sequencing	A laboratory technique for sequencing all the known protein-coding regions of DNA in an organism's genome (known as the exome).
Whole genome sequencing	A laboratory process to determine the complete DNA sequence of an organism's genome.

8 | APPENDICES

Appendix A

Precision oncology
– South Eastern Sydney Local Health District

In 2013 a 73 year old woman sought medical advice for a hoarse voice. Investigation found several tumours in her chest, which after surgical resection were diagnosed as being follicular dendritic cell sarcoma (FDCS), a rare cancer with a highly variable clinical course. Despite having surgery, a new tumour mass was subsequently found. Conventional treatment was provided but was not effective.

Genomic testing found the possibility of a germline BRCA2 mutation. This genetic mutation is more commonly associated with breast and ovarian cancer but also found in other cancers. As a result, risk reducing surgery and family counselling were offered to the patient and her family, and a family history of breast cancer emerged.

The patient was treated with specific chemotherapy targeted to the BRCA2 mutation. Reduced cancer activity was found after the fourth cycle of treatment and her condition remained stable during 5 months of targeted chemotherapy. This approach suggests that precision oncology provides both greater therapeutic effectiveness and tolerability for the patient.

Appendix B

Rare genetic disease
– Northern Sydney Local Health District

In 2007 the Sydney Morning Herald published an article titled “Fight against the unknown”, regarding the illness and death of a young woman from Cowra. The article outlined the difficulties for the patient and her family over more than a decade of investigations that did not result in a diagnosis, which often left her feeling unsupported and misunderstood.

Finally, following referral to the Department of Neurogenetics at Royal North Shore Hospital, DNA testing confirmed that she had mitochondrial myopathy, neuropathy and gastrointestinal encephalopathy (MNGIE) syndrome, which allowed her to accept the terminal nature of her condition. Tragically, this came just a fortnight before her death at the age of 24.

MNGIE syndrome is a genetic disease due to a mutation affecting the enzyme thymidine phosphorylase, causing the nucleosides thymidine and deoxyuridine to accumulate in the body. This in turn impairs the function of mitochondria, an intracellular structure that enables cells to convert nutrients into usable energy. The tissues most severely affected are nerves, muscles and the gastrointestinal tract, causing relentless symptoms including progressive loss of sensation, muscle weakness, abdominal pain, vomiting and weight loss.

While MNGIE and other mitochondrial diseases are difficult to diagnose given their rarity and relatively non-specific symptoms, a definitive diagnosis is important. If diagnosed early enough, MNGIE can now be treated with bone marrow or liver transplant to replace the defective enzyme. For some mitochondrial diseases, secondary preventive measures such as dietary modification can slow or halt their progression. Research to develop gene therapy to “reprogram” the patient’s cells is also underway.

Appendix C

Genetics in cardiac disease
- Sydney Local Health District

Over 40 inherited cardiac diseases have been identified, most with an autosomal dominant pattern of inheritance but wide variation in onset and severity of symptoms. The most devastating manifestation of this is sudden cardiac death (SCD), particularly in young, previously healthy people. No clear cause of death is found in up to one third of young SCD aged 1 to 40 years and primary arrhythmogenic disorders (not associated with structural cardiac abnormalities) are thought to be the underlying cause.

To illustrate this, a mother contacted the Centenary Institute's Genetic Heart Disease clinic at Royal Prince Alfred Hospital, having been referred for assessment following the sudden death of her 15 year old son while playing sport. During the consult, his clinical history, the circumstances of his death and options for genetic testing were discussed in detail. Clinical screening evaluation of the parents and 2 young siblings of the deceased found no abnormalities.

Family members were still grieving, especially the mother, who witnessed her son's collapse and unsuccessful attempts to resuscitate him. Both parents were also concerned about the possible risk to their remaining children and other relatives. The need to understand and act on complex genetic information at such a time requires skilled pre- and post- test counselling from a cardiac genetic counsellor, who is also a constant contact for the family as ongoing care is provided with input from an expert multidisciplinary team including cardiologists, electrophysiologists, nurses and psychologists.

The family agreed to posthumous DNA testing of a post-mortem blood sample ("molecular autopsy"), which eventually revealed a pathogenic mutation in the DSP gene and a variant of uncertain significance in the MYH7 gene, which both encode cardiac proteins. Classification of the variants involved comprehensive curation efforts by the Molecular Cardiology Program and discussion at the group's monthly multidisciplinary pathogenicity meetings. They were advised that the DSP mutation likely related to the sudden death, while the significance of the MYH7 variant was uncertain. Following guidelines, cascade genetic testing was offered for the DSP mutation and the mother and older sibling were found to be positive. They were counselled to limit exercise to avoid disease expression and continue to receive annual cardiac evaluation.

Establishing genetic causality is a challenge and careful clinical evaluation of family members and post-mortem genetic testing can reveal a clinical phenotype in up to 40% of SCD cases. A positive gene result can identify asymptomatic gene carriers at the earliest preclinical stages, while a negative gene result will provide reassurance and eliminate years of unnecessary clinical surveillance.

Periodic reclassification of uncertain variants is also part of the service model, to reflect the ever-changing understanding of genetic variants. As illustrated in this case, increasingly complex genetic results pose significant challenges for families. Management in centres with high-level specialised multidisciplinary models of care are critically important and will provide the best possible care for families with inherited cardiac diseases.

Appendix D

Disease control and prevention – Western Sydney Local Health District

Foodborne disease: Despite public health efforts, rates of foodborne salmonellosis (gastroenteritis) in Australia have climbed steadily from 38/100,000 in 2004 to 76/100,000 in 2016, with a record-breaking 18,170 cases last year (National Notifiable Diseases Surveillance System). As this probably represents only about 9% of the actual disease burden, the estimated direct and indirect costs are in excess of $37 million per annum.

Genome sequencing has played an increasingly important role in the investigation and management of foodborne salmonellosis, such as the multi-jurisdictional outbreak of rockmelon-associated Salmonella Hvittingfoss. The NSW Pathogen Genomics Partnership (PGP), was established in 2015 between the Centre for Infectious Diseases and Microbiology at Westmead Hospital, NSW Health Pathology and the University of Sydney Marie Bashir Institute for Infectious Diseases and Biosecurity. The PGP has implemented prospective whole genome sequencing, which "fingerprints" Salmonella strains with higher resolution than alternative subtyping techniques. NSW Health led the investigation and control of this national outbreak and the PGP has been providing genome sequencing support for South Australia, Australian Capital Territory, Western Australia and Queensland.

Conventional surveillance by NSW Health epidemiologists recently found an increase in Salmonella agona infection, significantly above historical background trends. Further investigation suggested links to sushi from a shopping centre in western Sydney. Whole genome sequencing allowed rapid analysis of Salmonella agona isolates diagnosed in NSW to separate background (most likely overseas-acquired) cases from outbreak cases. This incriminated the sushi as the source and also demonstrated that the first cases occurred earlier than previously thought. This capacity for high-resolution public health surveillance and early warning will support disease control measures for ongoing outbreaks of locally transmitted disease in NSW.

Drug resistant organisms: Methicillin-Resistant Staphylococcus aureus (MRSA) is a serious community and hospital-acquired pathogen, with highly successful clones that cause severe disease and are difficult to contain. Investigation by the PGP using rapid sequencing-based typing identified MRSA Sequence Type 22 as the causative agent of an outbreak in a neonatal intensive care unit in Sydney. This also suggested pathways of spread and allowed hospital clinicians to implement targeted infection control measures to successfully control the outbreak.

Tuberculosis in vulnerable populations: NGS at the NSW Mycobacterium Reference Laboratory (NSW Health Pathology West) has radically improved the accuracy and speed of diagnosis for this major public health threat. During an outbreak of pulmonary tuberculosis among indigenous communities in NSW, more precise tracking enabled the assessment of the most probable transmission pathways and risk factors.

Appendix E

Proteomics
– Children's Medical Research Institute, Westmead

For more than four decades, cancer clinicians have been making treatment decisions on the basis of tumour histopathology and the detection and quantitation of a small number of specific proteins, mostly using immunohistochemistry (IHC). A very well-known example is detection of estrogen receptor protein in breast cancer samples to guide the decision whether to use antiestrogen treatment. Most cancer treatments work via their effects on proteins, so the ability to analyse all proteins (i.e., the "proteome") in any cancer sample would be a major step towards enabling clinicians to choose the most effective treatments for each individual cancer patient.

Until very recently, it was not possible to reliably analyse large numbers of proteins simultaneously in small tumour samples. Therefore, many research groups have been using DNA and/or RNA sequencing of cancers essentially as a surrogate for protein measurements, but it is very difficult to use this information to accurately predict actual protein levels. In 2015, a combination of technologies (referred to as PCT-SWATH-MS) developed in Zurich, Switzerland, made it possible for the first time to analyse many thousands of different proteins rapidly in tiny tumour samples (1mg or less). In December 2015, researchers at Children's Medical Research Institute (Westmead, NSW) were awarded the Australian Cancer Research Foundation (ACRF)'s 30th anniversary grant of $10 million to build a laboratory, called the ACRF International Centre for the Proteome of Human Cancer ("ProCan"), which would make high throughput proteomic analysis possible. Officially opened in September 2016, ProCan is one of only two such facilities internationally, and the only one focussed on cancer.

Over the next 5-7 years, the ProCan human cancer proteome project will analyse the proteomes of 70,000 cancers (representing all types of cancer) for which the outcome of treatment is known. Samples which also have DNA sequencing (genomic) data and other 'omic data will be prioritised. Machine learning/artificial intelligence approaches will be used to identify patterns in the proteomic and other 'omic data that correlate best with outcome of treatment. This will mean that, when a cancer patient is newly diagnosed, their cancer can be analysed within 24-36 hours, and the treatment most likely to be effective for that individual cancer can be chosen (and, just as importantly, ineffective treatments can be avoided).

It may be possible to replace most or all existing IHC-based cancer diagnostics by proteomic analysis. More importantly, the cost savings to the health system of using existing treatments more effectively are anticipated to be very substantial. The extensive cancer proteomic database created by this project will be made publicly available, with appropriate privacy protections. It is expected that the data will lead to enhanced understanding of the molecular mechanisms in cancer, and reveal suitable molecular targets for development of novel therapies.

In addition to funding of the ProCan facility by ACRF and CMRI, operational support is being provided through philanthropy, the University of Sydney, and a $3.75 million Translational Program Grant from Cancer Institute NSW to investigate how the speed, accuracy and thoroughness of cancer diagnosis and treatment decision-making can be improved. The NSW Government is also supporting this project through the Cancer Moonshot Proteogenomics grant of $6.02 million awarded jointly to CMRI and Garvan Institute to study proteogenomics of sarcomas and childhood cancers.

It is expected that the expertise being developed in cancer proteomics will also be applied to other diseases. Many clinical situations where tissue samples (e.g., blood, cerebrospinal fluid, organ biopsy) are obtained for the purposes of diagnosis and treatment decision-making may benefit from rapid, simultaneous measurements of large numbers of proteins.

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