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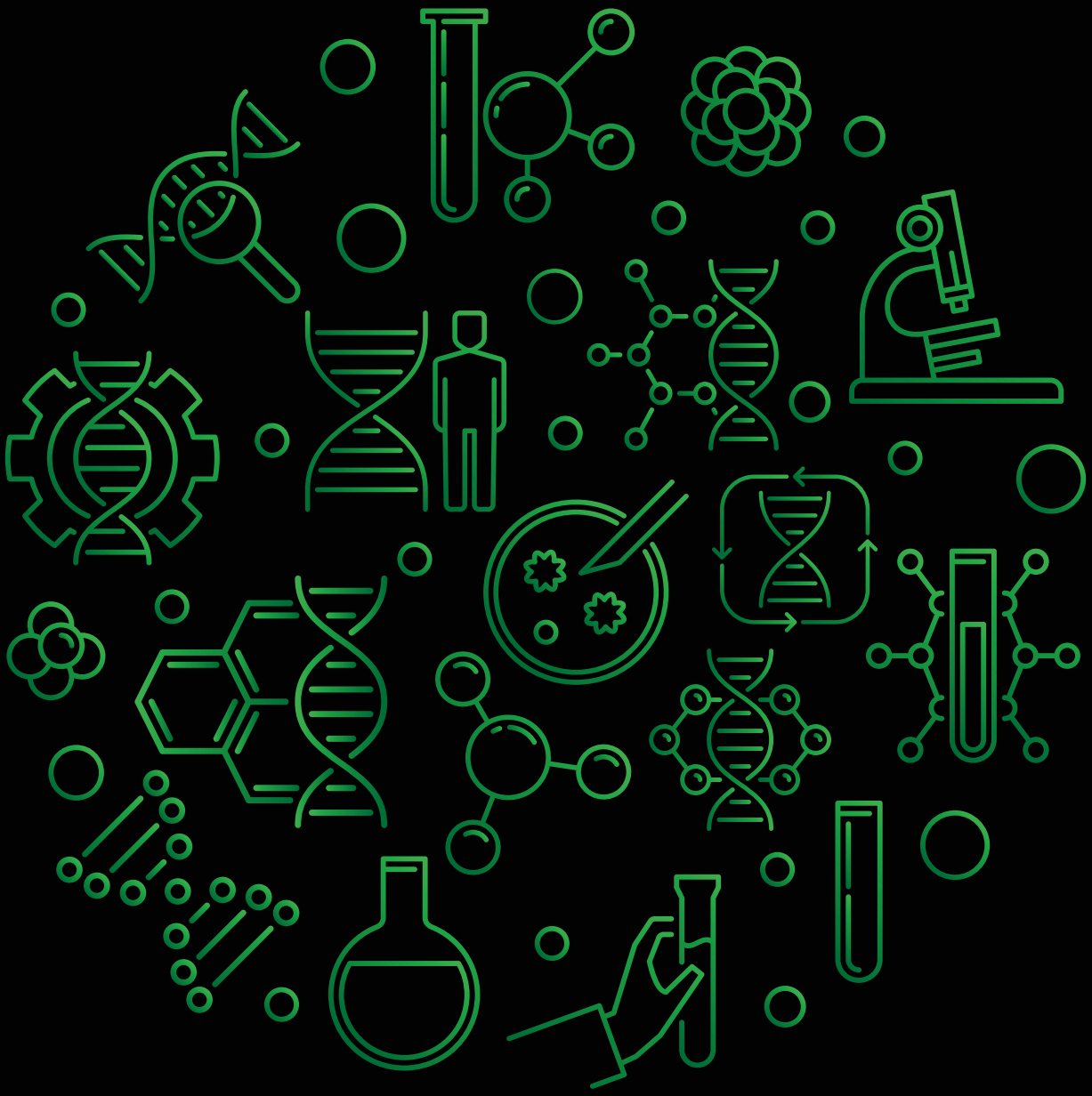


Valuing the impact of genomics on healthcare in Australia

Industry Genomics Network Alliance (InGeNA)

December 2021

Deloitte Access Economics

Contents

Glossary

Acronym	Full name
AIDH	Australasian Institute of Digital Health
BRCA	BReast CAncer gene
CLN2	Ceroid lipofuscinosis type 2
CoE	Centre of excellence
COAG	Council of Australian Governments
CPGx	Combinatorial gene testing
CPIC	Clinical Pharmacogenetics Implementation Consortium
DNA	Deoxyribonucleic acid
EEG	Electroencephalogram
ERT	Enzyme replacement therapy
FH	Family history
GAA	Glucosidase alpha acid
HIV	Human immunodeficiency virus
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IVF	In vitro fertilization
MBS	Medical Benefits Scheme
MCRPC	Metastatic castration-resistant prostate cancer
MDD	Major depressive disorder
MRI	Magnetic resonance imaging
MSAC	Medical Services Advisory Committee
NBS	Newborn screening
NHS	National Health Service
PARP	Poly (ADP-ribose) polymerase
PBS	Pharmaceutical Benefits Scheme
PCR	Polymerase chain reaction
PGD	Preimplantation genetic diagnosis
PGx	Pharmacogenetics
rhGGA	recombinant human acid alpha-glucosidase
QALY	Quality Adjusted Life Year
RRM	Risk reducing mastectomy
RRSO	Risk reducing salpingo oophorectomy
RT	Reverse transcription
TPP1	Tripeptidyl peptidase 1
UK	United Kingdom
USA	United States of America
WGS	Whole genome sequencing

Foreword

In Australia's healthcare future, a new frontier of precision health is emerging, underpinned by the science of genomics.

Soon, testing, diagnosis, care and treatment could be tailored for patients and consumers based on their unique profile as a human being.

Genomics is already engaged across many facets of healthcare as it currently enables access to treatment in areas like cancer and rare diseases.

However, while genomics may one day be omnipresent, Australia - like most nations - has a long way to go to translate the opportunities it presents society. Right now, the field of genomics is advancing quicker than healthcare translation can keep pace.

The Industry Genomics Network Alliance (InGeNA) was formed in late 2020 by around 20 forward thinking companies who wanted to advance the possibilities of genomics by bringing an unified industry voice to the genomics value chain.

Working in collaboration with health consumer bodies, research, government and service providers, InGeNA has embarked on a mission to harness the collective skills and expertise of industry to integrate genomics into healthcare.

This report was commissioned to begin laying the foundations for an evidence basis that outlines the potential value of genomics in various healthcare settings.

The case studies it contains illustrate some of the ways InGeNA believes genomics will be useful in diagnosis and treatment, adding an unquantifiable value to the lives of thousands of individuals.

The report would not have been possible without the support and guidance of the consumer and patient representatives and healthcare stakeholders who participated in the development of case studies and who are embedded across all facets of the InGeNA program.

Thank you to the members of the InGeNA committee, whose vision brought the network to life and who continue to be ambassadors for the role of genomics in our future health system.

The work of InGeNA to date, including this valuable report, was facilitated by foundational funding from its committee and delivered under the auspices of the Australasian Institute of Digital Health (AIDH).

InGeNA has received funding through the MTPConnect Project Fund Program – a dollar-for-dollar matched program investing to improve the productivity, competitiveness and innovative capacity of Australia's medical technology, biotechnology and pharmaceutical sector. MTPConnect is supported by the Australian Government Industry Growth Centres Initiative – learn more at mtpconnect.org.au

InGeNA Chair

David Bunker

InGeNA

Industry Genomics Network Alliance

Executive summary

Background

Genomics, the study of genes, is making it possible to predict, diagnose, and treat diseases more precisely and personally than ever. Advances in genomic testing technologies are increasing the capacity to accurately test for risk of cancer, diagnose rare conditions, and optimise treatment choices by providing clinicians with information on an individual's likely response to treatment. These are just some examples of how genomics, can, and will, revolutionise clinical practice across a diversity of health settings. This report demonstrates the potential transformative impact of genomics on the Australian health system, by profiling its benefits for patients, families/carers, health services and the national economy.

The benefits of genomic medicine are broad and diverse. Personal economic benefits accrue from genomically informed maintenance and restoration of health and consequent earning capacity for both patients and their families/carers. Higher precision in risk identification can result in preventive treatments which reduce the incidence of disease and lower costs to the health system. Greater precision in treatment selection reduces health system costs by avoiding adverse reactions and unnecessary treatments. Genomic medicine will also have a major impact on the national economy, not only by reducing productivity losses and decreasing costs of treating disease, but also by improving the selection of patients for clinical trials and the time to market for new medicines.

Deloitte Access Economics' research provides a snapshot of the potential value of genomics on healthcare in Australia by profiling a suite of case study applications across the screening, diagnosis, and treatment stages of the care continuum.

Within each case study, a cost-effectiveness analysis is performed to quantify the extent to which the additional upfront costs of genomic testing (compared to current practice) are offset by longer-term benefits such as improved health outcomes, cost-savings to the health system, and productivity gains to society.

Providing evidence on the impact of genomic testing relative to current practice is important given that access to these potentially lifesaving technologies in Australia varies, with some already being embedded into national, publicly funded health systems while others are offered only in some jurisdictions, only in the private sector or directly to consumers.

The case studies profiled in this report are:


Expanded genetic carrier screening for couples


Additional genetic testing in newborns for Pompe disease


Genetic testing for BReast CAncer genes (BRCA) for all patients with breast cancer and relatives of affected individuals


Genetic testing to confirm a diagnosis of one form of childhood dementia, neuronal ceroid lipofuscinosis 2 (CLN2), when symptoms first present


Pharmacogenomic (PGx) testing to guide choice of drug treatment for patients with Major Depressive Disorder

Summary of benefits

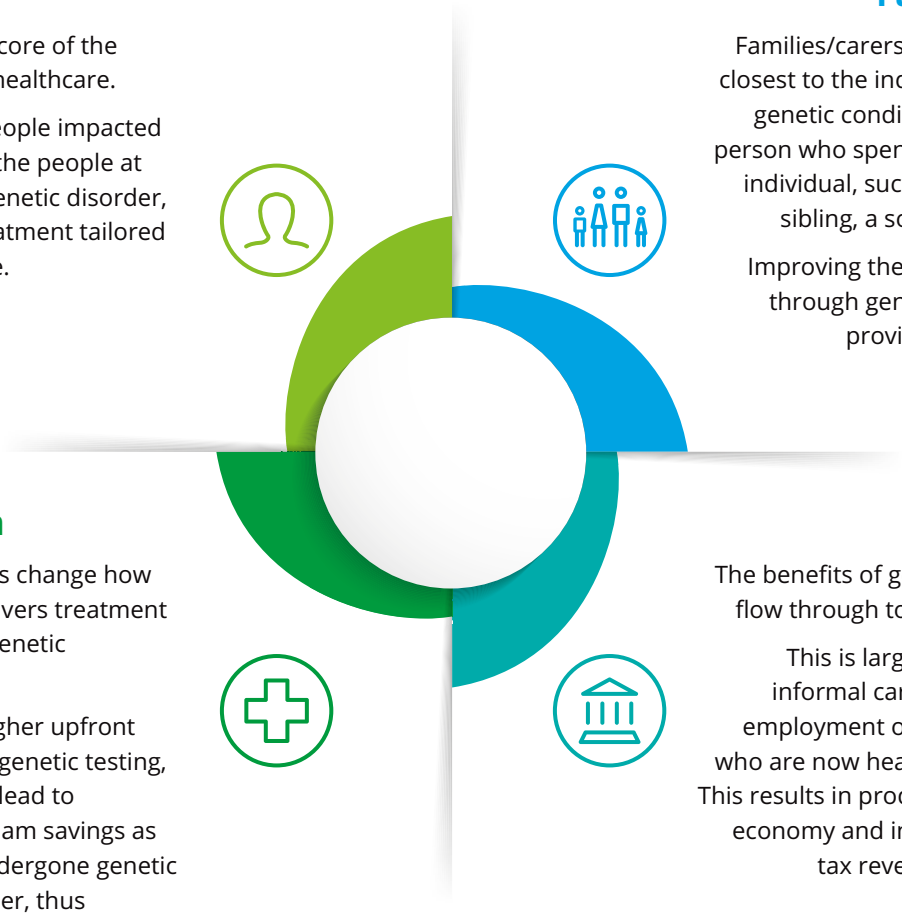
Diagnostic applications of genomics in healthcare have the potential to realise significant clinical, economic and social benefits for all areas of society (as shown in Figure i). Benefits that accrue to individuals, their families/carers, the health system and society are highlighted below using insights from each of the five case studies profiled. Note that all costs reported are discounted to the year 2021.

Figure i: Framework for discussion of benefits

Individuals

Individuals are at the core of the value of genomics in healthcare.

They represent the people impacted by genetic disorders, the people at risk of developing a genetic disorder, or people seeking treatment tailored to their genetic profile.



Families/Carers

Families/carers represent the people closest to the individual impacted by a genetic condition. They include any person who spends time caring for the individual, such as a parent, spouse, sibling, a son/daughter or friend.

Improving the lives of the individual through genetic interventions can provide significant value to their families/carers.

Health system

Genomic interventions change how the health system delivers treatment to individuals with a genetic condition.

Typically, there are higher upfront costs associated with genetic testing, however, these often lead to longer-term downstream savings as patients who have undergone genetic testing remain healthier, thus requiring less treatment.

Society

The benefits of genomic interventions flow through to the broader society.

This is largely achieved through informal carers returning to paid employment or through individuals who are now healthy enough to work. This results in productivity gains for the economy and in turn leads to higher tax revenue for government.

Individuals

Genomics can help in decision making and planning.

- Carrier screening provides prospective couples with the additional information needed to make informed decisions about their reproductive options based on the likelihood of having a child with a severely debilitating or life-threatening genetic condition. The modelling estimates that population carrier screening would identify 1.2% of prospective couples as 'at-risk'.
- Genetic testing for BRCA gene mutations can identify mutation carriers before they develop breast or ovarian cancer. This gives the individual important information as to their risk of cancer, allowing them to undertake risk-reducing procedures. The modelling estimated that by offering genetic testing to all people diagnosed with invasive breast cancer in 2021 and relatives of affected individuals, an additional 1,145 relatives with a BRCA mutation would be identified, as compared with family history (FH) testing alone. Providing risk reducing interventions to these people is estimated to prevent 218 cases of breast or ovarian cancer, and 75 deaths from cancer.

Figure ii: Patient impact stories

"Knowing my risks has allowed me to make significant life choices and take action related to my physical and mental health, including having risk reducing surgery and those related to fertility preservation. Knowledge is power and it gives me options that others in my family were not lucky enough to have"

– BRCA carrier

"The BRCA test is a powerful tool, with the potential to alter a person's genetic destiny. I am alive because I knew my risk and changed my future. I am one of the lucky ones. I am part of a generation of women who get to save our lives. All of us are linked to women who did not get that chance"

– BRCA carrier

Genomics can improve health outcomes and treatment pathways.

Genetic testing in newborns for rare diseases such as Pompe disease and CLN2 (a form of childhood dementia) improves the time to diagnosis and ensures children can begin effective treatment earlier. This delays disease progression and improves quality of life and life expectancy.

- The literature indicates that standard testing coupled with genomic testing for children diagnosed with CLN2 could result in a two-year improvement on the typical time to diagnosis. Because of the improved time to diagnosis, it was modelled that up to 65% of children diagnosed with genetic testing would be diagnosed in the earliest stage of disease progression (health stage 1 and 2). Comparatively, only 16% of children were diagnosed at this stage under standard testing. Over a lifetime, this equated to an additional 11 Quality Adjusted Life Years (QALYs) per child diagnosed with CLN2.
- Similarly, children with Pompe disease can be diagnosed months earlier with genetic testing at birth, an intervention which was modelled to identify 100% of cases before the onset of severe symptoms. This compares to diagnosis using standard care, where the majority of cases will progress to severe symptoms, characterised by ventilator dependency and a high risk of mortality. Over a ten-year period, this difference equated to an additional 2.5 years of life per child diagnosed with infantile Pompe disease.
- Genomic testing also offers benefits for rare conditions with no regulatory approved treatment. An earlier diagnosis of such a condition could result in improved access to clinical trials, with the opportunity to receive a new and novel treatment that could stabilise symptoms and improve quality of life.

Figure iii: Patient impact stories

"Childhood dementia is every parent's worst nightmare. We've had to watch our beautiful seven-year-old daughter lose the ability to run, to walk, to dance. She's lost the ability to speak. She's going blind, she's finding it harder and harder to recognise family and friends."

Earlier diagnosis would have minimised this level of symptom deterioration.

– Carer of child with childhood dementia

"Childhood dementia strips children of the ability to engage, communicate and then strips them of their life – this is just evil."

Earlier diagnosis would have minimised this level of symptom deteriation.

– Carer of child with childhood dementia

Genomics can improve Quality Use of Medicines.

- Pharmacogenomic (PGx) testing can be used to personalise medication treatment to improve a person's likelihood of responding to medication and reduce the chance of adverse responses to medication. With Pgx guided drug treatment for patients with depression, 48% of patients were modelled to be alive and in remission after five years, compared to 32% of patients receiving treatment based on standard drug selection.
- In a hypothetical cohort of 75,000 patients with depression, combinatorial PGx guided drug selection was estimated to prevent 11 suicides and improve the number of people in remission by 12,000 at five-year follow-up.

Families/Carers

Genomics can reduce the carer time provided by families/carers.

Genetic testing improves the quality of life of the individual and thereby, reduces their dependence on informal care. This gives time back to families, allowing carers to return to work, reducing the psychological and mental stress associated with caring, providing carers with an opportunity to build new relationships in the community and/or to pursue further education.

- Children with severe symptoms of Pompe disease require around the clock care. The modelling estimates that if a child was treated earlier, the productivity benefit for families/carers attributable to reduction in informal carer time would be approximately $396,000, per child diagnosed, over a ten-year time horizon.
- It is estimated that informal carers provide an average of 59 hours of care per month to breast and ovarian cancer patients in the first year of diagnosis. By avoiding the eventual incidence of cancer in an additional 218 people, expanded use of genetic testing in breast cancer patients, avoids the hours of informal care required for each of these people.

Genomics provides families/carers with the 'value of knowing'.

Genetic testing allows families to make informed choices based on the genetic diagnosis of the individual.

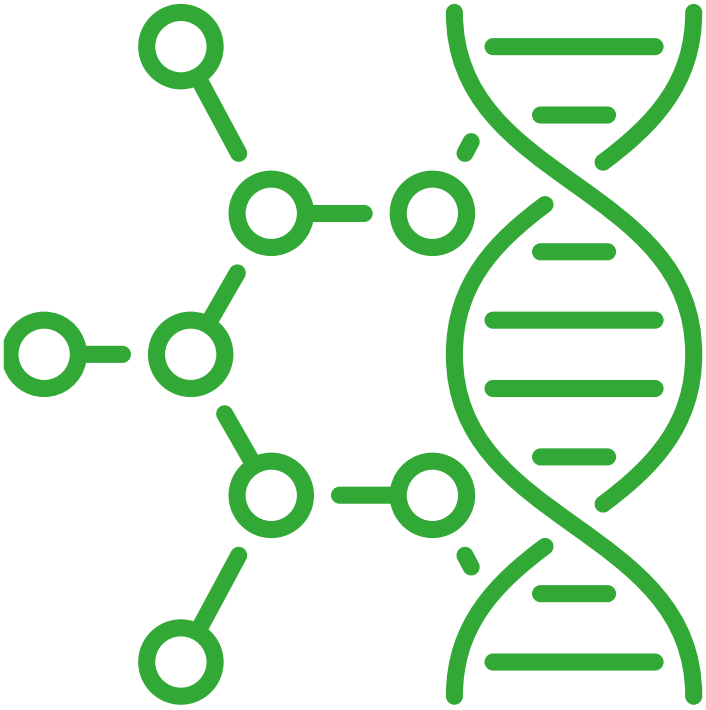
- Some newborns will be diagnosed with late onset Pompe disease, a genetic condition where symptoms may not present until later in life. This gives families the knowledge and support needed to make informed decisions for their child. It can also be used to inform future family planning decisions.
- By improving time to diagnosis and time to effective treatment, genomic testing to confirm diagnosis of conditions such as Pompe disease and CLN2 at birth or during early childhood, reduces time spent in the diagnostic odyssey. This has an important impact on reducing psychological stress and anxiety for families/carers.

Health system

Genomics can reduce burden on the health care system.

The modelling estimates that PGx testing, testing for BRCA gene mutations and carrier screening can significantly reduce downstream health system costs relative to current approaches. This is because in each case, the intervention resulted in healthier individuals. For example, there were more people in remission following PGx guided drug selection and less cases of cancer following expanded testing for BRCA gene mutations.

- Over a five-year period, the modelling estimated that in a hypothetical cohort of 75,000 people with depression, PGx guided drug selection relative to standard drug selection saves the health system a total of $132 million in treatment costs (e.g. reduced hospital stays, clinical appointments, drug costs etc.), over a five-year period. This equated to a saving of $1,750 per person tested.
- By offering genetic testing to all people diagnosed with breast cancer in 2021 and relatives of affected individuals, the model estimated that over a lifetime horizon, the intervention relative to FH testing alone saves the health system a total of $12.8 million in cancer care costs (e.g. reduced hospital stays, treatment costs, palliative care costs etc.) This equated to a saving of $503 per person tested, or $11,650 per mutation detected.
- By offering carrier screening to prospective couples, the modelling estimated that the health system savings over a lifetime horizon were more than the costs of offering testing, which made the intervention 'cost-saving' from a health system perspective.[1]
- The modelling estimated that the interventions associated with Pompe disease and CLN2 increase health system costs. However, these increased costs are due to prolonging of life, which would be expected. Further, the modelling for Pompe disease and CLN2 capture only the impact of testing for a single gene, whereas it is acknowledged that genetic testing is far more cost-effective if testing is conducted for multiple genes at once.



[1] If an intervention is cost saving, the intervention increases the number of QALYs gained (or Disability Adjusted Life Years [DALYs] averted), while also saving money.

Society

Genomics has an economic impact on society, improving productivity and tax revenues.

- Individuals who are able to remain in remission after receiving PGx guided treatment for depression are more likely to be more productive at work. This is measured by the number of days a person takes off work (absenteeism) and a person's lost productive time while at work (presenteeism). It was estimated that, over a five-year period, PGx guided treatment for depression could improve productivity by $2,230 per person tested relative to standard drug selection. For a hypothetical cohort of 75,000 people with depression, this equated to approximately $167 million in productivity savings.
- As noted above, the modelling estimates that if a child with Pompe disease was treated earlier, the productivity benefit for families/carers attributable to reduction in informal carer time would be approximately $396,000, per child diagnosed, over a ten-year time horizon. These increased earnings result in higher tax revenue for government, which in turn benefits the rest of society.

Takeaways

The analysis presented in this report provides a strong clinical and economic case for further investment and focus on embedding genomics within the Australian health system.

In all case studies profiled, the genomic application was able to improve the number of lives saved and quality of life for the individuals tested, relative to current practice.

Of the three case studies profiled that were not related to a rare disease (carrier screening, BRCA screening in all breast cancer patients and relatives of affected individuals, and PGx guided depression treatment), the genomics application was considered either cost saving or highly cost-effective when compared against common willingness to pay benchmarks, demonstrating strong value for money.[2] Given these conditions are highly prevalent within the Australian population, if scaled, these applications could have a significant positive impact on the productivity of the national economy.

While the cost-effectiveness ratios for the two rare disease case studies (Pompe disease and CLN2) were above traditional willingness to pay thresholds, this is because the genomic technology was able to prolong life – and thereby, time receiving treatment. However, in both cases, the intervention demonstrated strong clinical value by increasing the time to diagnosis, time to effective treatment, and preventing symptom onset/progression. This clinical value translates to benefits for families/carers by reducing informal care hours, as well as reducing time spent in the diagnostic odyssey. This 'value of knowing' has an important impact on reducing psychological stress and anxiety for families/carers, a benefit not captured in the modelling.

A national and coordinated approach to enhancing workforce, data systems, finance mechanisms, and public awareness is required to accelerate and achieve the full potential of genomic medicine in Australia.

The complexity of the genomics ecosystem will require a national and coordinated approach to genomic data and medicine for the successful integration, maintenance and delivery of genomics within the health system. This approach should include a focus on:

Workforce. The continued innovation in human genetics and genomics requires expanding our current workforce to keep up with the demand of genomic technology and advocacy for national legislation to support the implementation of genomic research into clinical care.

Education. Strong investment in education and awareness campaigns with consumers and healthcare practitioners will build trust and understanding of the benefits of genomics to support widespread integration. Healthcare practitioners also require tools and guidelines to support best-practice and standardised implementation.

Finance and policy. Innovative pathways to achieving equity of access to genomic technology for all Australians is required. Health Technology Assessment (HTA) processes need to evolve to better account for the unique complexities and benefits (that fall outside of traditional health outcomes) associated with genomics. This is particularly important in the context of rare disease where metrics such as time to diagnosis and time to effective treatment may be more appropriate than traditional value for money metrics.

Research and data. Investment in research targeted at translating genomic research into routine clinical practice is key to integration within existing systems and pathways. To enable this type of research, data linkage and sharing across sectorial stakeholders is paramount, including genomic and bioinformatics databases, electronic medical records, and administrative health datasets.

[2] Common willingness to pay thresholds are $50,000 per additional quality adjusted life year gained.

A ZOOM DISCUSSION HOSTED BY DELOITTE & InGeNA

THE IMPACT OF GENOMICS ON HEALTHCARE IN AUSTRALIA

CHANGES IN GENOMICS: TODAY AND IN THE FUTURE

SCREENING

- SCREENING FOR COMMON AND COMPLEX DISORDERS
- REPRODUCTIVE SCREENING
- SCREENING MORE BROADLY, FOR MULTIPLE CONDITIONS AT ONCE
- COST DROPPING $
- IDENTIFYING 'AT RISK' INDIVIDUALS IN LARGE POPULATIONS
- TARGETED SCREENING IN FAMILIES

DIAGNOSIS

- RAPID IDENTIFICATION OF CONDITIONS
- TESTING NOT ALWAYS ACCESSIBLE
- LIMITED FUNDING SOMETIMES HIGH OOP COSTS
- RAPID DIAGNOSIS!

TREATMENT

- HAS BEEN FOCUSED ON RARE + GENETIC DISEASES
- SUPPORTING PATIENT CARE ACROSS JOURNEY
  - GENETICS COUNSELLORS
  - PROFESSIONALS
  - INDUSTRY PARTNERS
- MENTAL HEALTH CONDITIONS STILL AN EMERGING AREA
- IMPROVING COST TO BENEFIT RATIO

GENOMICS, AT THE HEART OF DECISION-MAKING

GENOMICS WILL IMPACT ALL PARTS OF OUR LIVES!

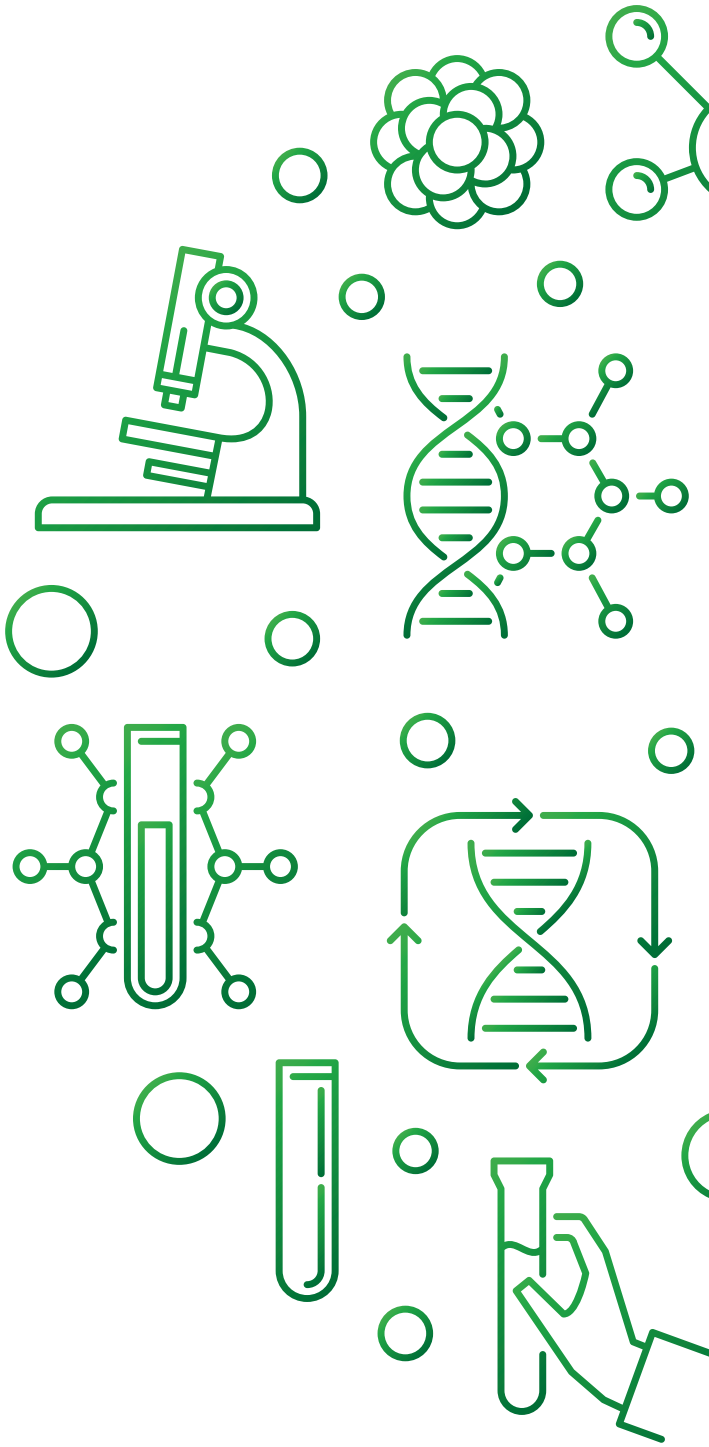
BENEFITS OF GENOMICS

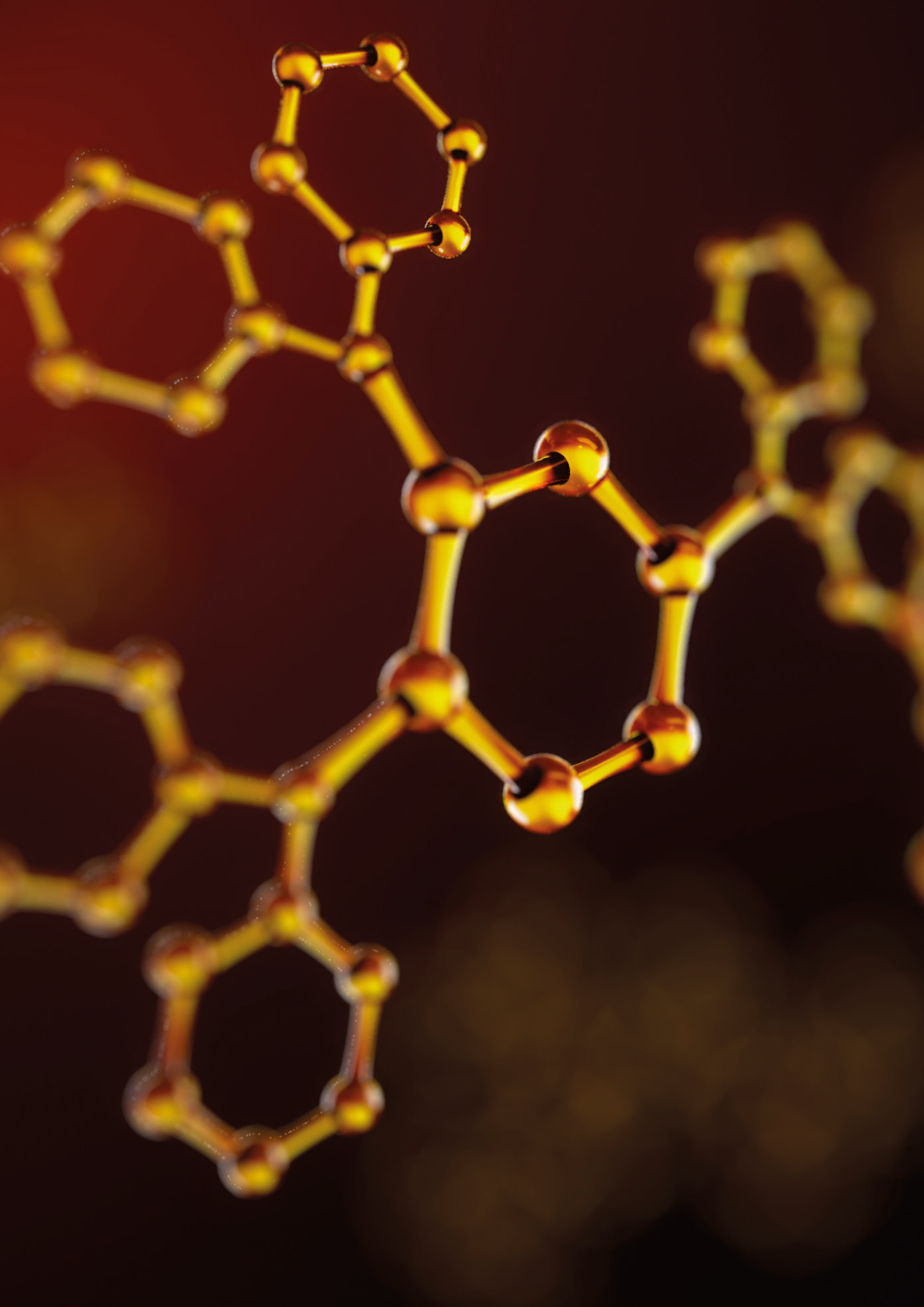
- FAMILIES + PATIENTS
  - BETTER DECISION MAKING
  - IMPROVED HEALTH
- THE HEALTH SYSTEM
  - NEW, INNOVATIVE TREATMENTS FROM CLINICAL TRIALS!
  - HEALTH COSTS DECREASING
  - LOWER RESOURCE UTILISATION
- SOCIETY
  - KNOWLEDGE SHARING + INNOVATION
  - R+D COMMERCIALISATION RETURN $
  - STRONGER WORKFORCE
  - OVERALL SIZE OF ECONOMY IS BIGGER!
- GOVERNMENT
  - IMPROVED BUDGET POSITION
- PATHOGEN TRACKING (COVID-19)
  - CONTACT TRACING
  - STRAIN I.D.
  - VACCINE DEVELOPMENT

GENOMIC TESTING COSTS ARE GREATLY OUTWEIGHED BY DOWNSTREAM SAVINGS...

ACTIONS & BARRIERS

- DATA
  - WAYS TO MANAGE, ACCESS + SECURE GENETIC DATA
    - ✓ CONSISTENT
    - ✓ FUTURE-PROOF
- GENOMICS LITERACY
  - EDUCATION TO INCREASE CONSUMER CONFIDENCE AND RAISE GENOMICS LITERACY
  - BROADER ACCESS TO TESTING
  - ADDITIONAL SUPPORT RESOURCES
- SERVICE
  - DEVELOP EVIDENCE-BASED GUIDELINES
  - MULTI-DISCIPLINARY APPROACH TO CARE
  - COLLABORATION AT ALL LEVELS
- FINANCE
  - IMPROVE FUNDING OF GENOMICS
  - GENERATE THE EVIDENCE THAT SHOWS THE BENEFITS OF GENOMICS
  - INCENTIVISE FURTHER INVESTMENT IN GENOMICS
- WORKFORCE
  - EDUCATION AND TRAINING ACROSS ALL DISCIPLINES
  - ESTABLISH CENTRES OF EXCELLENCE FOR GENOMICS
- POLICY
  - STANDARDISATION OF OUR APPROACHES TO REPORTING TO CREATE CONSISTENCY OF CARE
    - ✓ PUBLIC + PRIVATE
    - ✓ STATE + NATIONAL





1. Introduction

This report highlights the diagnostic value of genomics on healthcare in Australia, with a view to raising awareness of the potential applications of genomics and its impact on patient, health system and broader societal outcomes.

1.1 Purpose and scope of this report

This report investigates the value of genomics within the Australian healthcare system. To highlight the potential impact of genomics, the report draws on the latest evidence both within Australia and internationally coupled with insights gleaned through consultation with key industry stakeholders.

The research is underpinned by a suite of case studies which profile a range of potential diagnostic applications of genomics across the screening, diagnosis and treatment stages of the care continuum. Within each case study, a cost-effectiveness analysis is performed to assess the extent to which the additional upfront costs of genomic testing (compared to current practice) are offset by longer-term benefits such as improved health outcomes, cost-savings to the health system, and productivity gains to society. This case study approach was used to enable assessment of the incremental value of an application in improving economic and social outcomes in the context of a specific condition.

The scope of this report is limited to quantifying benefits where evidence was readily available through the public domain or could be informed through expert opinion. Where this was not possible, benefits are described qualitatively.

The Industry Genomics Network Alliance (InGeNA) commissioned Deloitte Access Economics to prepare this report. The findings presented serve to aid discussions that raise awareness of the potential diagnostic applications of genomics in healthcare, and their potential impact on patient, health system and broader societal outcomes. This report should not be used for the purposes of informing health technology assessments.

About the Industry Genomics Network Alliance

InGeNA was formed between industry organisations and partners to bring a shared perspective on critically important areas underpinning the future of genomics and its use in precision health and medicine. The Alliance ensures a shared vision for Australia's leadership in the adoption of genomics in healthcare and contribution to the developing field of genomics. The Alliance emphasises the value of collaboration with other bodies to optimise the health benefits for all Australians.

InGeNA is hosted by the Australasian Institute of Digital Health (AIDH), Australia's leading organisation in informatics and digital health. AIDH was awarded funding by MTP Connect's Industry Growth Project Fund Program to establish InGeNA.

1.2 Structure of this report

The remainder of the report is structured as follows:

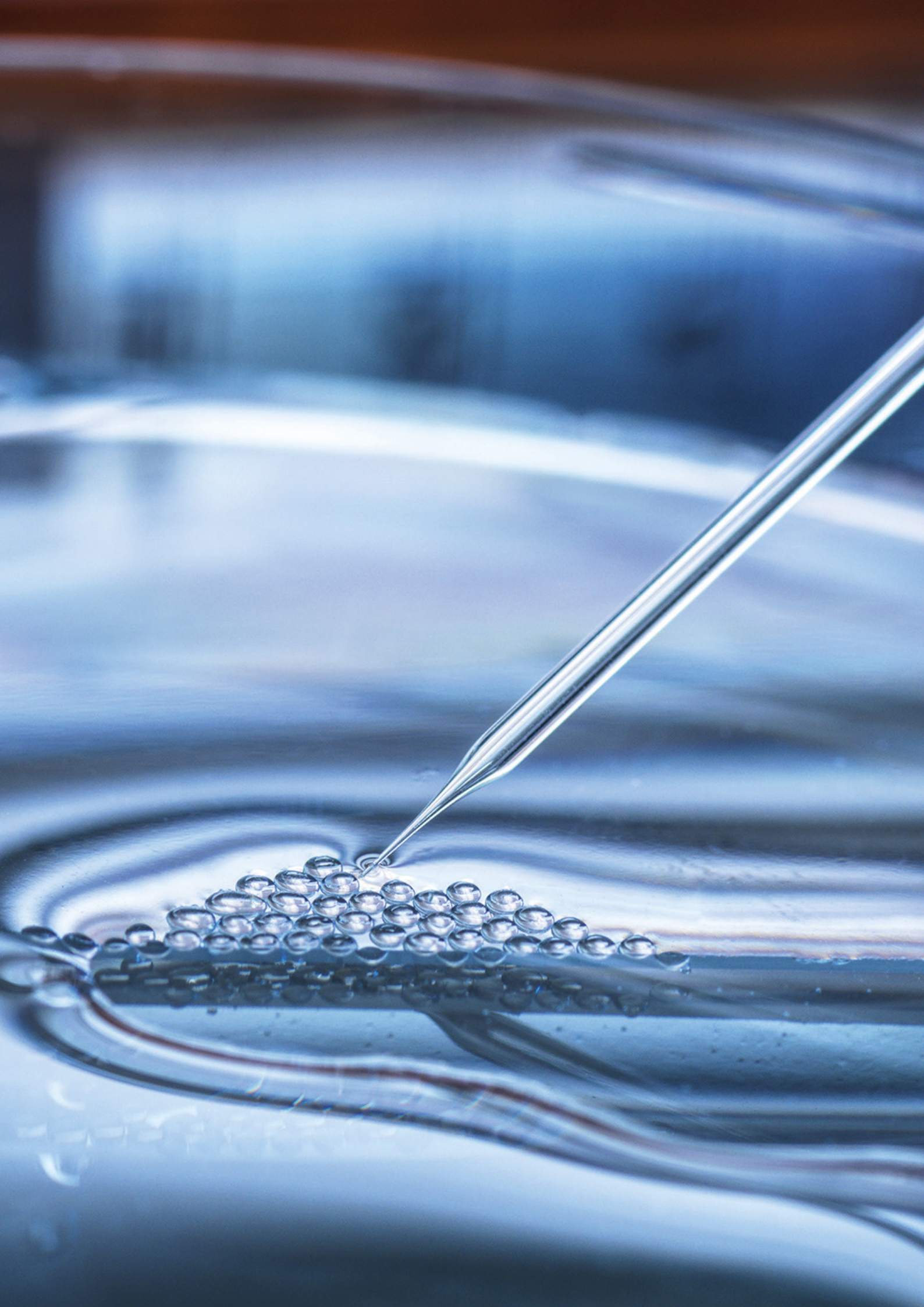
Chapter 2 – The genomics landscape in Australia: Summarises the genomic policy context in Australia and the current and emerging applications of genomics across the care continuum.

Chapter 3 – Value of genomics in healthcare: Highlights the benefits of genomics across different stakeholder groups. Five case studies are used to demonstrate the cost-effectiveness of different diagnostic genomic applications across the screening, diagnosis and treatment stages of the care continuum.

Chapter 4 – Implementation and considerations: Outlines the framework required to achieve the full potential and benefits of genomics in Australia and the actions needed to realise this potential through a suite of high-level recommendations.

Appendix A – Cost-effectiveness methodology: Provides a detailed description of the methodology used to develop the case studies.

Appendix B – Case study model details and inputs: Describes the detailed model frameworks and inputs used in the cost-effectiveness analyses.



2. The genomics landscape in Australia

This chapter provides an overview of the genomics landscape in Australia, and the current and future applications of genomics in improving the health for all Australians.

2.1 The current policy landscape for genomics within the Australian healthcare context

Over the past few decades, scientists and clinicians have made strides in advancing knowledge of the human genome and its role in health and disease. Successful translation of this research will transform clinical medicine by making it possible to predict, diagnose, and treat diseases more precisely and personally than ever. In recognising this, the Australian government, academic institutions, clinicians, and industry leaders have sought to engage in coordinated action to embed genomic knowledge into clinical practice. An overview of the current health genomic policy context in Australia is provided below.

The policy context in Australia

The National Health Genomics Policy Framework (the Framework) was established by the Australian government in 2016, with the goal of accelerating genomic activity in the Australian healthcare system. The Framework outlines five key strategic priorities areas for action by the sector – person-centred approaches, workforce, financing, services, and data. The Framework also emphasises the need to ensure genomic knowledge is applied ethically, legally and socially. In 2017, the Framework was approved by the Council of Australian Governments (COAG) Health Council.[1]

The COAG Health Council subsequently approved an associated Implementation Plan in 2018 that outlines the key actions and timelines to deliver on the Framework over the next three years. The Implementation Plan includes 28 actions aligned with the five strategic priority areas and details the key responsibilities of the federal and state/territory governments that will enable Australia to achieve the goals outlined in the Framework.[2]

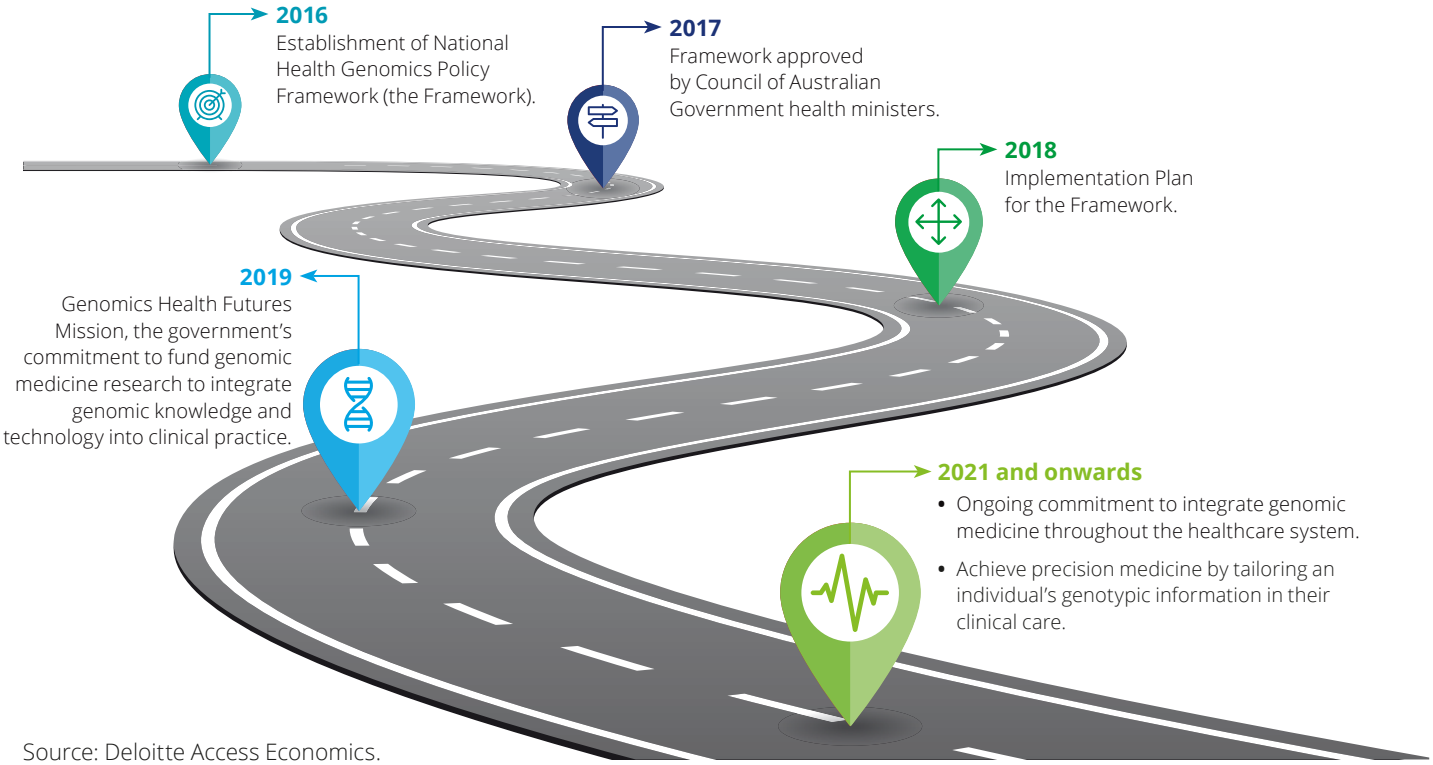
In delivering on its responsibility as part of the Implementation Plan, the Australian Government announced the Genomics Health Futures Mission (Health Futures Mission) in 2019. The Health Futures Mission is a government fund with a commitment to invest $500 million over 10 years in genomic research. Early funding priorities include but are not limited to: reproductive carrier screening for rare genetic conditions; cancer proteomic, genomic and related multi-omic big data analysis to improve diagnosis and treatment; and bioinformatics capability.

While the Framework and Implementation Plan prioritise key areas for initial consideration and action, they do not address all issues related to genomics and health. Within the community, there is limited understanding and awareness of the benefits of genomics, which is a key barrier to its adoption.

InGeNA was established in 2020 by AIDH with funding from MTPConnect's Industry Growth Centre Project Fund Program. InGeNA aims to unlock the potential of Australia's precision medicine sector to improve health outcomes for all Australians and to build a stronger and more diverse industry that can contribute internationally. This report is one of InGeNA's first initiatives, and was commissioned with the goal of increasing community understanding of the potential benefits of genomics within a clinical context. Separately, InGeNA is working to increase access to genomic technologies by advocating for new Health Technology Assessment (HTA) pathways that better account for the unique complexities and benefits associated with genomic interventions.

A schematic of the key policy milestones related to health genomics in Australia is shown in Figure 2.1.

Figure 2.1: Schematic of key genomic policy milestones in Australia

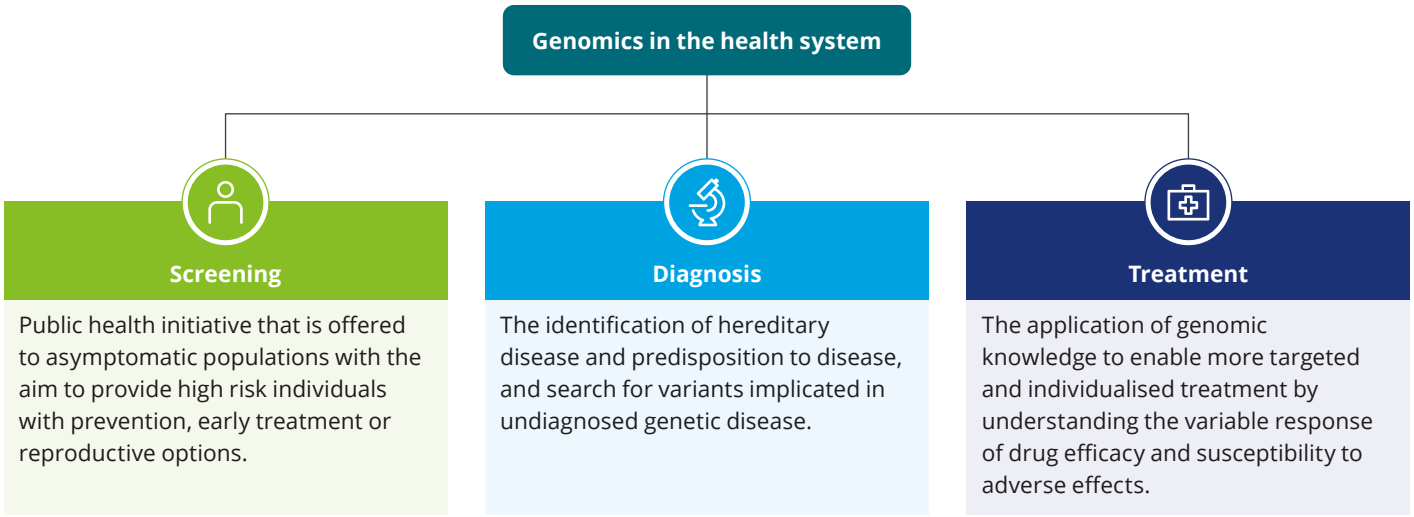


Source: Deloitte Access Economics.

2.2 Applications of genomics

The application of genomic knowledge and technology in healthcare is broadly categorised across the following two stages of the care continuum: the screening and diagnosis phase, and the treatment phase, as outlined in Figure 2.2. Screening and diagnosis are categorised together, as they are often complimentary within the care continuum, where screening of high-risk asymptomatic populations can lead to the identification of individuals with a condition, given their predisposition to that condition and previous family history.

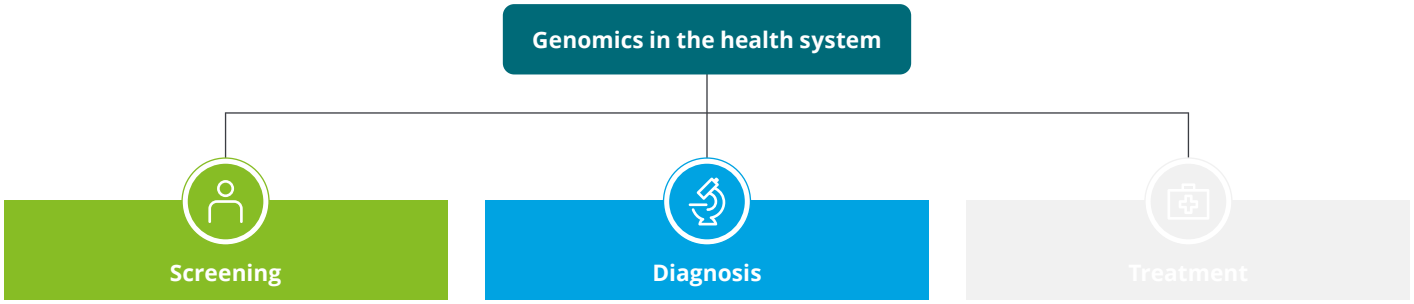
Figure 2.2: Overview of genomics applications across the care continuum



Source: Deloitte Access Economics.

Australia continues to build its capabilities to embed genomics as part of routine clinical practice. Genomic applications in healthcare have increased over the past few decades, particularly as part of genetic testing in newborns. However, future applications of genomics have the potential to transform clinical medicine across all medical specialists, health conditions and care pathways.

The current and future applications of genomics, across the screening and diagnosis, and treatment phases of the care continuum are discussed in Section 2.2.1 and Section 2.2.2, respectively.



2.2.1 Screening and diagnosis

Genomic screening is a public health initiative that is offered to asymptomatic populations with the aim to provide high risk individuals with preventative, early treatment or reproductive options. Genomic technologies are also used to diagnose conditions more accurately and efficiently than more traditional diagnostic technologies.

Current applications

In Australia, the most diverse and accessible form of genetic testing is the Guthrie test, which is offered to all newborns to screen for hereditary and rare monogenic conditions including phenylketonuria, hypothyroidism and cystic fibrosis.[3] There are an additional 300 screening tests available across all age groups across a range of conditions. From an equity of access perspective, it is important note that although these genetic tests are available in both the public and private settings, typically only individuals with familial history of a condition can access these tests through the public health system.

The use of genomic technologies to screen for high-risk populations plays an important role in the identification of hereditary disease, predisposition to disease and search for variants implicated in undiagnosed genetic diseases. A confirmed diagnosis of a condition such as childhood syndromes can empower patients and their families and caregivers to make appropriate decisions about treatment and care plans. Further, timely diagnosis ensures the patient has the best opportunity to achieve a positive health outcome and to reduce the time and financial effort spent in the diagnostic odyssey.

Outside of screening, in Australia, several conditions including lung cancer, Alport syndrome and other rare conditions use genomic material to confirm a diagnosis. Without genomic technology, it may take years to diagnose these conditions with more traditional tools and tests.

Future applications

The future application of genomics in the screening and diagnosis stage of care continuum will allow for greater screening of rare diseases and unknown conditions. It holds the possibility to screen for hundreds of conditions (e.g. cancers, heart disease and mental health conditions) across hundreds of genes at one time. This will occur as the industry evolves, in its shift away from custom gene panel testing to those which yield greater clinical utility such as whole genome sequencing (WGS), and as researchers and clinicians better understand how to interpret, and act on, genomic information (i.e. clinically actionable mutations).

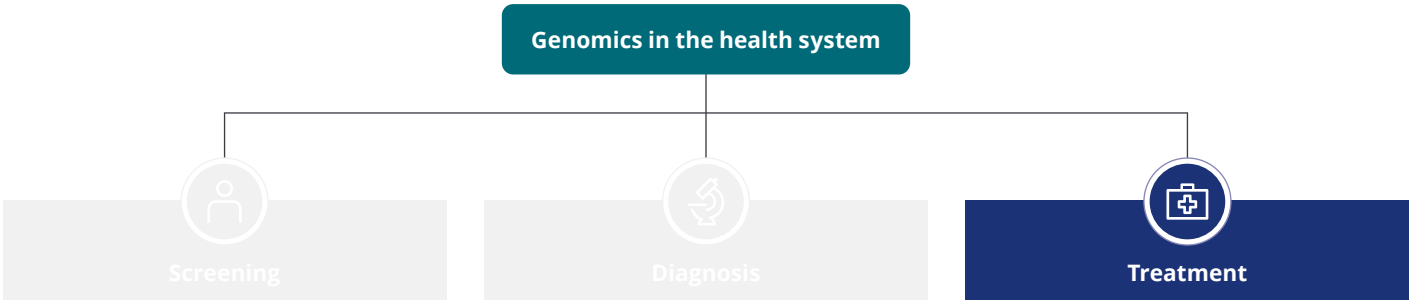
The United Kingdom's (UK) 100,000 Genomes Project is an example of this shift and what Australia's future could look like. The project combined genomic sequencing data with medical records to improve the lives of those living with rare conditions and cancers (additional detail on the Project is described in Box 1).[4] This future state of genomics could also potentially see the cohesive integration of newborn screening (NBS) with other types of screening programs to achieve maximum clinical and patient utility while being cost-effective (by reducing the need for multiple individual tests) to the healthcare system.

Work in this area is already underway by the Sydney Genomics Collaborative's Genomic Cancer Medicine Program. The Program uses genomic information in novel ways to understand the genetic contribution to cancer risk (including childhood cancers) and identify new therapeutic opportunities for individual patients. The results from this study will contribute to the understanding of inherited genetic alterations that cause cancer and may lead to improved cancer screening and surveillance programs, increased options for reducing cancer risk, and more personalised cancer treatments with better outcomes.

Box 1. Learning from the UK

Genomics England in the UK has sequenced 100,000 genomes from patients with over 100 rare diseases in seven common cancers, including their family members. The 100,000 Genome Project was initiated to establish the use of WGS in the National Health Service (NHS), the UK's single-payer national healthcare system, and drive change within NHS care delivery. The project has contributed to the transformation of local systems at participating centres, including tissue handling, collection of data, processing of results, and clinical practice.

The data collected from the 100,000 Genome Project was successful in confirming the diagnosis of patients with rare diseases.[5] These patients were able to receive more appropriate, effective and personalised treatment – improving quality of life both them and their families/carers. The contributions of patients to the 100,000 Genome Project will go towards advancing genomic research and creating a future that will enable the NHS to offer genomic services more widely to any patient who might benefit.



2.2.2 Treatment

Genomic knowledge is used to individualise treatment by understanding an individual's variable response to treatment efficacy and safety.[6] The most common application of genomics at the treatment stage of the care continuum is PGx. PGx is the study of how people respond to drug therapy based upon their genetic makeup or genes. The aim of PGx is to tailor drug treatment to the specific genomic makeup of an individual to ensure patients receive the most effective treatment earlier in the treatment pathway. It is noted that differences in genetic ancestry may introduce genetic variations which alter the efficacy of some drug therapies.[7] This highlights the importance of PGx within Australia's culturally diverse population.

Current applications

The field of PGx in Australia is new and emerging, particularly when compared with overseas countries. The main source of funding for pharmacogenetic tests in Australia at present is the patient, with very few tests available on the Medical Benefits Scheme (MBS). The tests that are available are mostly limited to identifying people at-risk of having severe side effects. One example of a test that is available through the MBS is the human leukocyte antigen HLA-B*5701 gene test. People with this variant may develop a severe skin reaction to abacavir therapy which is used to treat human immunodeficiency virus (HIV).

In Australia, people can also access PGx tests privately. These PGx tests that are available on the private market aim to provide clinicians with information on drug-gene interactions that can inform test-guided prescribing in areas as broad as mental health, neutrology, cytotoxic therapy, breast cancer and pain management.

Future applications

A key application of PGx that is likely to become further embedded within the Australian healthcare system in the coming years is PGx guided drug treatment in mental health. In 2019, the Australian government committed to funding $7 million for research into the use of PGx to improve mental health treatment outcomes and help reduce suicide in patients living with mental health.[8] Through the Medical Research Future Fund, the funding will support research that aims to improve or develop new PGx tests that better personalise how medications are prescribed for patients with mental health challenges, with the goal of improving recovery from conditions such as severe depression and anxiety.

The clinical adoption of PGx is still relatively limited in Australia. Internationally, the Clinical Pharmacogenetics Implementation Consortium (CPIC) have identified five genes involved in the response to 30 medications for which the clinical utility of testing has the highest level of evidence.[iii] Many of these drugs are listed on the Pharmaceutical Benefits Scheme (PBS) and are, therefore, likely to be strong candidates for PGx-guided prescribing in Australia in the medium term.

Outside of PGx applications, there are broader future potential applications of treatment on the basis of an individual's genetic profile. In cancer, identifying genetic alterations may direct health care practitioners towards specific targeted therapies or to avoid treatments that have poorer outcomes.

[iii] The CPIC provide frameworks for evaluating medication–gene associations and expert guidance about prescribing for patients with given variant.

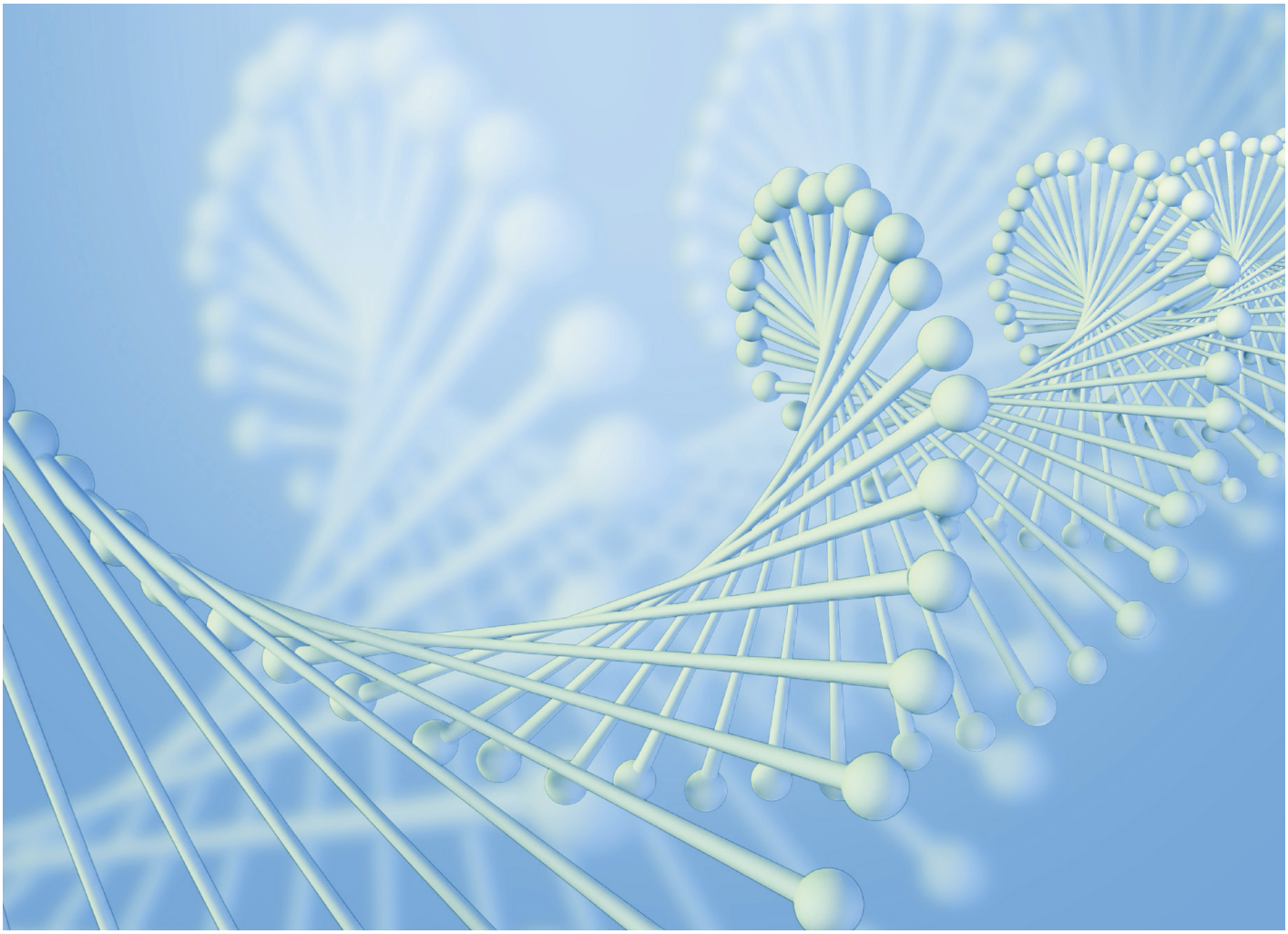
2.2.3 Other applications of genomics

The applications of genomics in healthcare extend beyond those that those that are diagnostic in nature. Other examples are outlined in Table 2.1.

Table 2.1: Examples of genomic applications beyond diagnostics

Application	Description
Drug discovery	Genomic information can be used to advance the development of new biopharmaceuticals to treat diseases by using genetic biomarkers to provide molecular targets for drugs that are engineered to bind to targets.
Optimising the efficiency of clinical trials	Genetic and genomic information can be used to target recruitment of participants into clinical trials preselected through the presence of genetic biomarkers. This is particularly important for rare diseases, as this has the potential to advance more drugs successfully to market as they are more likely to demonstrate efficacy and improved tolerability.
Gene editing	The knowledge of gene variants associated with disease can provide targets for potential modification of a patient's genes themselves. This modification has the capability to treat and potentially cure the target disease through gene editing and gene therapy, such as Huntington's disease.[9]
Managing disease outbreaks	Genomics approaches and technologies played a circular role in the responses to the coronavirus disease 2019 (COVID-19) pandemic, including its role in genomic sequencing, diagnostic testing, contact tracing and development of vaccinations. A detailed discussion of the application, impact and benefit of genomics during the COVID-19 pandemic can be found in Box 2.

Source: Deloitte Access Economics.



Box 2. Genomics in the COVID-19 pandemic

In January 2020, the World Health Organisation declared COVID-19 a Public Health Emergency of International Concern. By March 2020, COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a global pandemic. Genomics continues to play a significant part in the effort to reduce the spread and impact of COVID-19, from the analysis of genomic variants to the study of genetic mutations of the COVID-19 genome to inform vaccine development.

The genomic makeup of the SARS-CoV2 virus

Similar to other viruses, SARS-CoV-2, the virus responsible for the COVID-19 pandemic, undergoes genetic mutations which change the genetic sequence of the virus. Using genomic sequencing, scientists were able to distinguish the different genes which makeup the SARS-CoV-2 genome. One important gene of the SARS-CoV-2 genome includes the genetic instructions to build the spike protein, which allows the virus to attach to human cells during the infectious period. Knowledge about spike mutations provides scientists with the knowledge about how infectious the virus is, how severe the infection may become and how well current vaccines protect against it.

Identification of new variants

The application of genomic sequencing has led to the identification of new variants of the SARS-CoV-2, including the B.1.1.7 that emerged in the UK, B.1.351 that emerged in South Africa and B.1.617 that emerged in India. All three variants are more contagious than previous SARS-CoV-2 variants. Understanding the difference in genetic mutations was used to identify a single source of infection and contain outbreaks.

Diagnosis of COVID-19

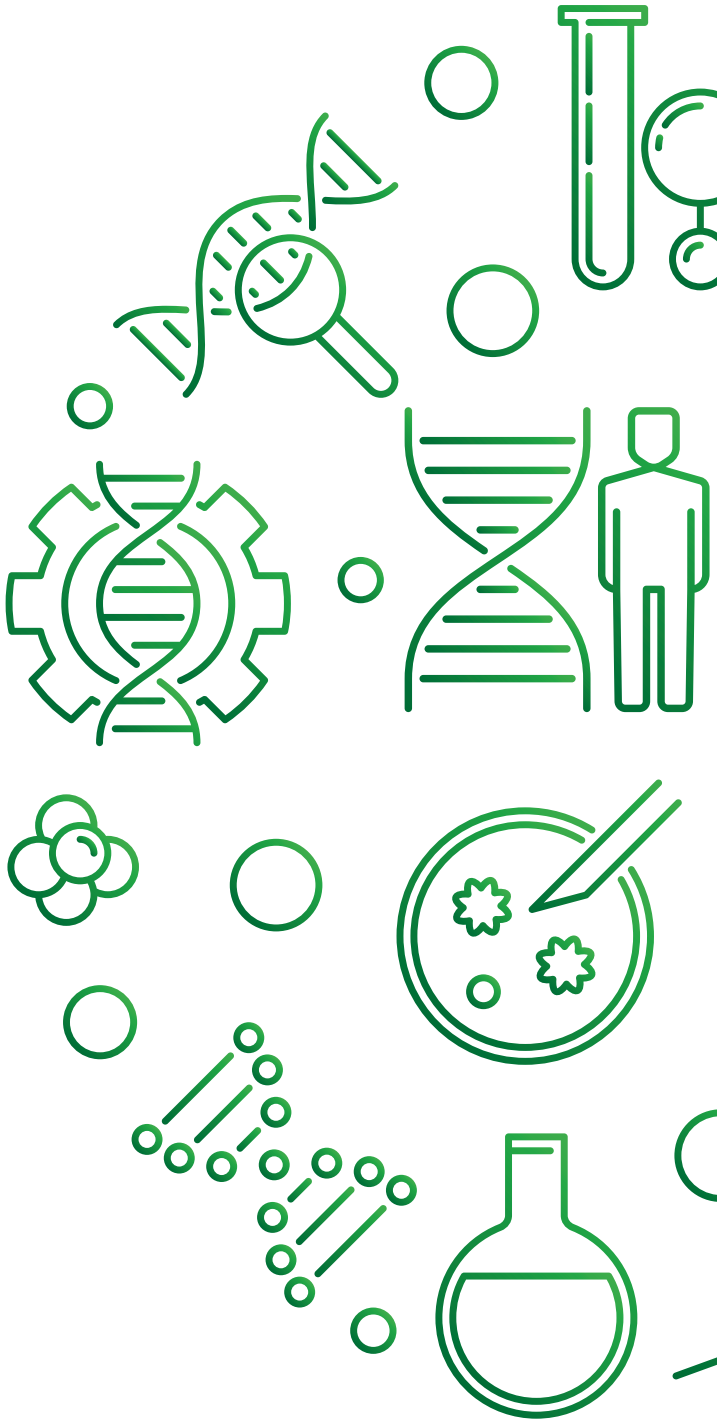
Early characterisation and sharing of the viral WGS has enabled the development of the gold standard test used to diagnose COVID-19. Real time reverse transcription (RT) polymerase chain reaction (PCR) testing uses a sample from a nasopharyngeal swab of the mouth and throat to measure the amount of the virus' genomic material.

Two other diagnostic tests exist for COVID-19 in Australia including rapid antigen test and serology antibody test. A rapid antigen test can be used to detect the presence of viral protein from SARS-CoV-2 in a symptomatic patient. The test is best performed within the early stages of acute infection when viral load is at its highest levels but is considered less sensitivity than a PCR test. The second test, a serology antibody test, is intended to detect antibodies to SARS-CoV-2 when a patient has previously been infected with SARS-CoV-2. Its applicability to diagnose a patient currently infectious with the SARS-CoV-2 virus is therefore limited. The genomic sequence of the SARS-CoV-2 and its application in PCR tests therefore remain the gold standard for diagnosis of COVID-19.

Vaccination and therapeutic drug development

The development of vaccines against the SARS-CoV-2 virus would not be possible without genomic technology. In Australia, two vaccines are available, the Pfizer and and AstraZeneca vaccine. Both vaccines use the genetic code of the SARS-CoV-2 virus to produce the spike protein, which acts as the antigen for which the body's immune system recognises as a foreign 'invader', prompting a protective immune response.

In the context of therapeutic drug design and discovery, the study of the virus' genomic and protein structure empowered scientists with the knowledge to develop more effective vaccine and drug targets. Vaccine developers and other scientists use this genetic information to test whether the new variants change and how well current vaccines work.



3. Value of genomics in healthcare

This chapter provides an overview of the value of genomics to the Australian healthcare system and society more broadly by profiling five diagnostic genomics use cases across the care continuum.

This chapter discusses the benefits of genomics across the different phases of the care continuum for patients and their families/carers, the health system, government, and society. The discussion is supplemented with five case studies that quantify the benefits of genomics (relative to other technologies) at a use-case level by profiling discrete diagnostic applications of genomics.

The chapter is structured by the two key phases of the care continuum where genomics is typically applied:

- screening and diagnosis (Section 2.2.1)
- treatment (Section 2.2.2).

Within each section, the benefits of genomics are described qualitatively at a macro level, before introducing quantitative estimates of impact at a micro level as part of the case studies. Each case study presents the results from a cost-effectiveness analysis that compares the incremental net costs and benefits of using a genomics test to screen, diagnose or treat a particular health condition, against the next best intervention (i.e. current clinical best practice without genomics). The case studies profiled are outlined in Table 3.2.

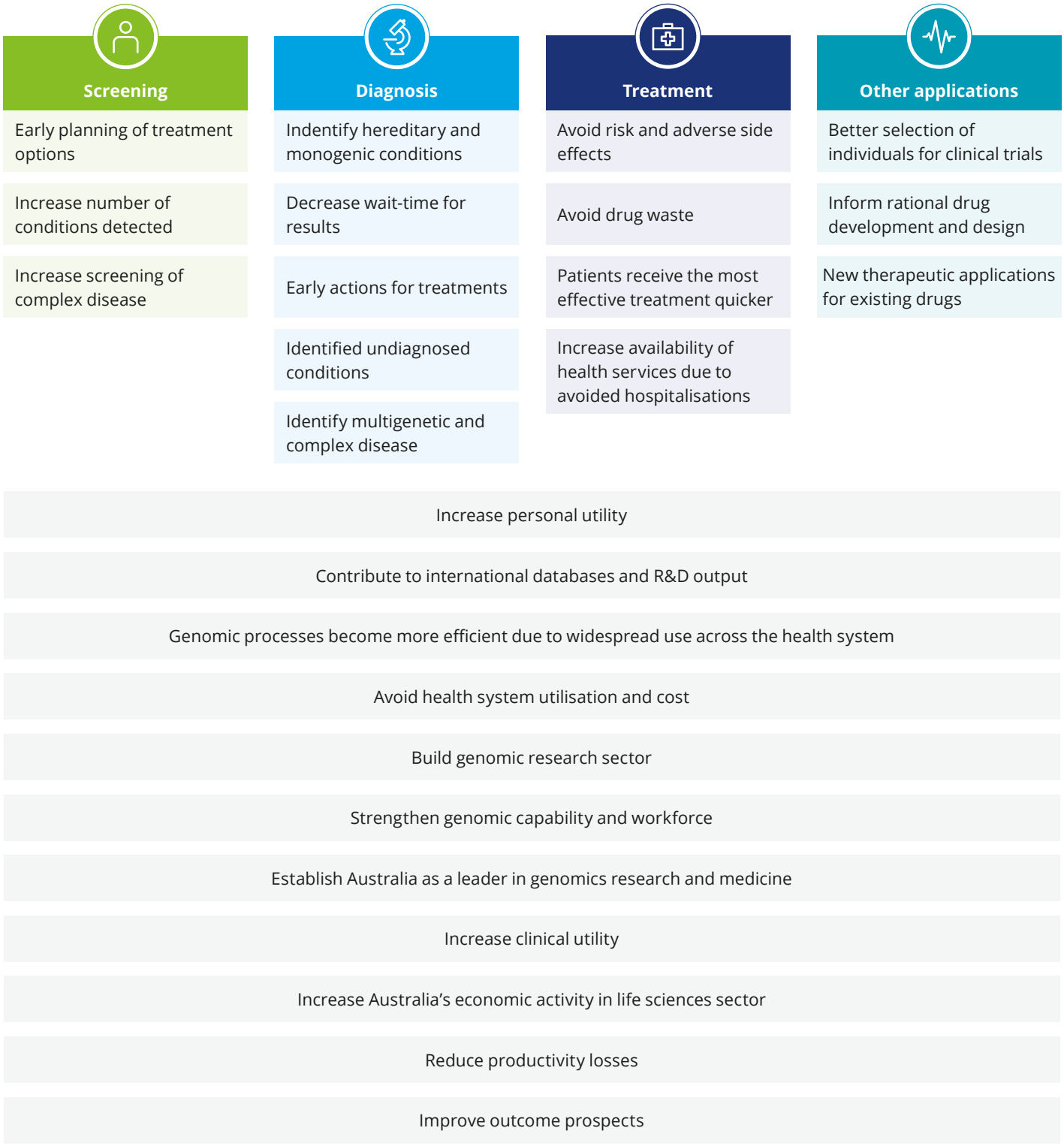
The benefits associated with genomic applications in healthcare are broad and diverse, as outlined in Figure 3.1. These benefits are quantified, where possible, in each of the case studies. Where a benefit was not quantified, it is referred to qualitatively.

Table 3.2: Overview of case studies profiled

Application	Reference
Screening and diagnosis	
Expanded genetic carrier screening for couples	Section 3.2.1
Additional genetic testing in newborns for Pompe disease	Section 3.2.2
Genetic testing for BRCA mutation for all patients with breast cancer and relatives of affected individuals	Section 3.2.3
Genetic testing to confirm a diagnosis of one form of childhood dementia, (CLN2) when symptoms first present	Section 3.2.4
Treatment	
PGx testing to guide choice of drug treatment for patients with Major Depressive Disorder	Section 3.3.1
Genomic testing to inform tailored treatment for individuals with somatic BRCA mutations	Section 3.3.2

Note: Six applications are shown across the five case studies as BRCA testing has benefits in both the 'screening and diagnosis' and 'treatment' phases of the care continuum.

Figure 3.1: Overview of the potential benefits of genomics



Source: Deloitte Access Economics.

Box 3. Interpreting cost-effectiveness analysis

A cost-effectiveness analysis (CEA) is performed to assess the value for money of a particular intervention. A CEA compares an intervention to another intervention (or the status quo) by estimating the incremental net costs required to gain a unit of a health outcome, such as a Quality Adjusted Life year (QALY) or a Disability Adjusted Life Year (DALY).

QALYs is a generic measure of disease burden, including both the quality and the quantity of life lived. It is used in economic evaluation to assess the value of medical interventions. One QALY equates to one year in perfect health. QALY scores range from 1 to 0.

A CEA provides evidence to answer the question – do the extra health benefits outweigh the extra costs?

Results are typically reported as an incremental cost effectiveness ratio (ICER), which is interpreted as the net incremental cost per QALY gained (or DALY averted) associated with the intervention. In the context of this report, when the CEA is evaluated from a health system perspective, the 'net incremental cost' element captures the additional upfront costs associated with genetic testing relative to a comparator, less the long-term cost-savings in the form of healthcare resource utilisation. If the CEA is conducted from a societal perspective, the cost element is broadened to capture additional monetised benefits such as productivity costs.

If an intervention is cost saving, the intervention increases the number of QALYs gained (or DALYs averted), while also saving money. As most new treatments are thought to be more effective and more costly, most interventions have an ICER with a cost per QALY gained (or DALY averted). A Willingness-To-Pay (WTP) benchmark of ~$50,000 per QALY gained (or DALY averted) is commonly used to assess if an intervention is deemed value for money.

3.2 Benefits in screening and diagnosis

The benefits of genomic medicine and technology offer advancements in the screening and diagnosis of conditions, in both asymptomatic and symptomatic populations. Widespread integration of genomic technology at the screening and diagnosis stage will increase the early detection of a number of homogenic, multigenic and complex conditions.

For individuals, this includes benefits such as increased clinical utility from more effective treatment options, reduced time in the diagnostic odyssey, and increased personal utility due to the 'value of knowing', which can influence lifestyle decisions. These each contribute to improved outcome prospects, such as survival and quality of life.

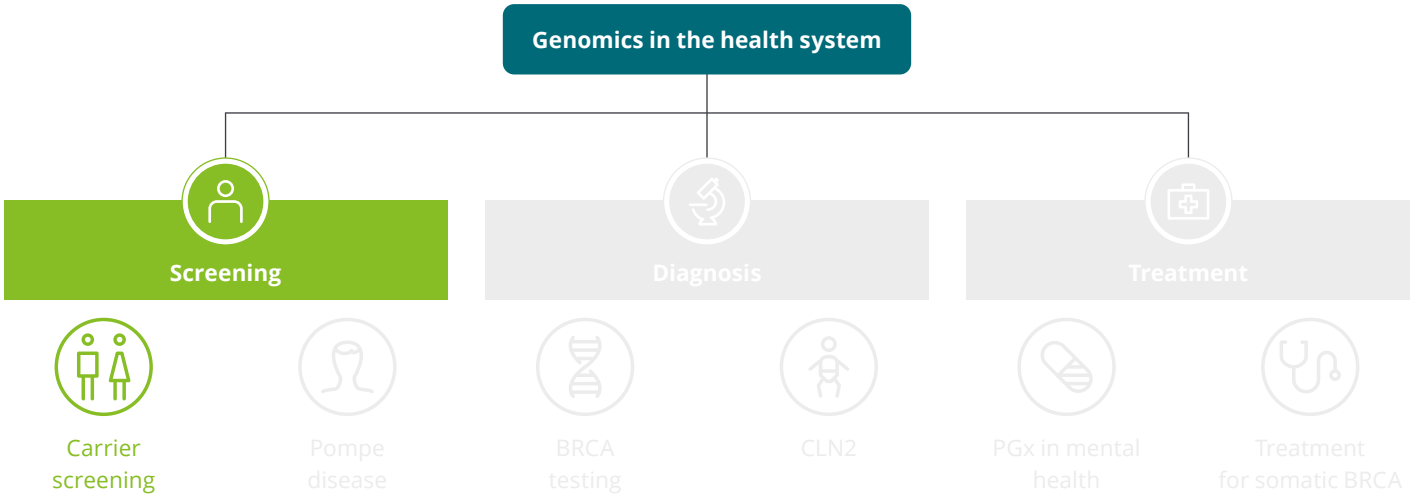
For families/carers, includes many of the same benefits accruing to individuals. In addition, health outcomes for a patient may reduce the total hours of informal care required each week. This in turn allows families/carers to reintegrate within the workforce.

For the health system, widespread integration of genomics will result in immediate benefits such as more efficient screening and diagnostic processes, reduced wait time for results, and a reduction in the misclassification of conditions. Longer term benefits include reduced costs associated with a reduction in utilisation of healthcare services (due to healthier patients who are less reliant on the health system).

For the genomics industry, benefits include building Australia's capability as a leader of genomic medicine, both on the international stage and within Australia, by creating a network of health professionals capable of providing precision care tailored to each person's needs. In addition, genomic databases can be used to accelerate Australia's research and development output.

For society, healthier patients improve workforce participation (by both patients and their families/carers), which results in productivity benefits for society as a whole.

These benefits are profiled at a more granular level in the following sections which use case studies to explore the incremental costs and benefits of genomic testing relative to standard practice in the screening or diagnosis of specific conditions.



3.2.1 Carrier screening

Genetic carrier screening, a genetic test that determines if a person is a carrier for a serious genetic condition, has been used to demonstrate the value of genomics at the screening stage of the care continuum. Traditional carrier screening focuses on testing people for single genes to determine if they are a carrier of a specific genetic condition. In the past, this screening was conducted based on known family history for a condition which warrants testing or on a person's ethnicity. Many genetic conditions are autosomal recessive – a child inherits one faulty gene from each parent. A carrier of a genetic condition is a person with one healthy copy of the gene and one faulty copy. As the conditions are recessive, carriers are asymptomatic as only one copy of the gene is faulty and having one healthy copy of the gene is sufficient to not be affected. If both parents are a carrier of a condition, a child will have a 25 per cent (1 in 4) chance of inheriting the condition – equal to the probability they inherit the faulty gene from both parents.[10]

Carrier screening is available for the most prevalent genetic conditions. An estimated 1 in 25 Australians carry a gene fault for cystic fibrosis.[11] Similarly, around 1 in 40 Australians are carriers of a gene fault for spinal muscular atrophy.[12] Most of these Australians are unaware that they are carriers of these gene faults. The cost of carrier screening for these individual conditions is around $200, the cost of which is not currently covered through the MBS.

Unlike traditional carrier screening which tests for a single gene, expanded carrier screening tests for many genes. As a result, expanded carrier screening detects many more carriers and carrier couples than traditional screening.

Current examples of expanded carrier screening in Australia include *Mackenzie's Mission*, a research project which will provide reproductive genetic carrier screening to around 8,000 Australian couples who are either planning to have children or are in early pregnancy.[13] The project is testing around 1,300 genes associated with about 750 autosomal recessive and X-linked genetic conditions. Researchers in the program are aiming to evaluate the outcomes of the screening, the psychosocial impacts reported by couples, the ethical issues that arise from carrier screening, and the health economic impacts of the test. The cost of the screening test is estimated to be between $600 and $900.[14, iv]

Methodology

This case study estimates the potential benefits of expanded carrier screening, using next-generation sequencing to screen for 176 conditions. To quantify the benefits, a cost-effectiveness analysis was performed drawing on a previous economic evaluation undertaken in the United States of America (USA).[13] The most prevalent genetic conditions included in the cost-effectiveness analysis model were cystic fibrosis, fragile x-Syndrome, Fabry disease, Smith-Lemli-Opitz syndrome, spinal muscular atrophy and congenital adrenal hyperplasia. There were more than 5.2 million women aged 15 to 44 in Australia in June 2020.[15] Carrier screening presents an opportunity for these women and their partners to be informed about their reproductive options, enabling them to make choices according to their own values.

The purpose of the CEA model was to determine if preconception carrier screening is a cost-effective approach to detecting carriers of genetic conditions relative to no screening. The model assumed a hypothetical cohort of 300,000 couples having carrier screening to determine if the couple is 'at risk' of their child having a severely debilitating or life-limiting genetic condition. Given the nature of autosomal recessive and X linked conditions, an at risk couple generally has a 25 per cent chance of giving birth to a child with a genetic condition.

[iv] Sensitivity analysis was conducted to account for any additional costs related to the interpretation of screening test results that may not be included in this initial cost of the test. The sensitivity results are provided in Table 3.3.

Alongside the carrier screening, it was assumed that at risk couples would receive genetic counselling to help the couple make an informed decision. This may include deciding to proceed with conception, pursuing alternative means of conception such as in vitro fertilization (IVF), or choosing not to have a child. Notably, this case study did not consider the cost or effect of preimplantation genetic testing (PGT), which is testing performed on early embryos created through assisted reproductive technology. The aim of PGT is to only transfer embryos free of the genetic condition carried by the parents.[16] The Australian Government has recently announced $95.9 million for new tests on the MBS for PGT.[17]

The base case modelling assumed a likelihood for a couple to choose each of these options based on previous research.[18] Comparatively, the no screening arm assumes that each couple in the hypothetical cohort proceeds with conception without any genetic testing or genetic counselling.

The modelling estimated the number of children born in each scenario disaggregated by the number of children born with and without these genetic conditions, and those born through reproductive interventions. It was assumed that children born through reproductive interventions would have a 100 per cent chance of being healthy. The effectiveness of the intervention was dependent on the number of healthy births achieved through reproductive interventions, without which the child would have had a severely debilitating or life limiting genetic condition.

In the base case, it was assumed that 30 per cent of at risk couples would undertake a reproductive intervention. The impact on the health system was quantified by measuring the change in health system costs, and the change in quality of life was estimated by comparing the expected lifetime wellbeing of the children with and without a genetic condition.

Additional details on the model structure and inputs used are provided in Appendix B.

Results and discussion

In the base case, the model estimated that carrier screening of the hypothetical cohort of 300,000 couples would detect 3,605 couples at risk of an affected birth. It was assumed that 30 per cent of these couples would choose to proceed with an alternative birth given the greater risks posed by conventional pregnancy. It was estimated that 451 couples who intervened with an alternative pregnancy would have otherwise had a child with a genetic condition.
This decision resulted in significant savings to the health system (enough to offset the cost of testing in all couples) and an improvement in quality of life.[v] The lifetime cost of a child with a genetic condition was expected to be $1.5 million, solely from the perspective of the health system. Furthermore, these children were expected to lose an average of 26 QALYs because of their condition.

Table 3.3: Base case and one-way sensitivity analysis for cost-effectiveness of carrier relative to no screening, 300,000 couples hypothetical cohort, health system perspective

Scenario	Genetic conditions averted	QALYs gained	Cost per QALY gained ($)
Base case, lifetime time horizon	451	2,610	Cost saving
Base case, 1-year time horizon	451	2,610	112,061
Base case, 3-year time horizon	451	2,610	88,331
5% reproductive intervention	180	1,044	43,079
1.5x cost of screening	451	2,610	Cost saving
5% reproductive intervention, 1.5x cost of screening	180	1,044	194,478
5% reproductive intervention, 2.0x cost of screening	180	1,044	345,877

Source: Deloitte Access Economics calculations.

[v] Improvement in quality of life was measured by comparing the expected QALYs of a child born without a genetic condition, compared to a child born with a genetic condition.

As shown in Table 3.3, under an alternative assumption that every at-risk couple decided to pursue an alternative means of pregnancy, carrier screening was estimated to avert 901 affected births. However, this decision is ultimately a choice for the couple, unique to their circumstances. As such, the impact to the health system and to quality of life may vary based on population decision making. However, the value in terms of information provided to the couple, which allows them to make an informed decision, remains consistent. It is recognised that an assumption of 100 per cent intervention may be unrealistic, as couples may have personal beliefs or other ethical reasons not to proceed with IVF, while other couples may be unable to afford the significant out of pocket costs.[18] However, even under an assumption of low rates of reproductive intervention, carrier screening was still found to be cost effective under traditional willingness to pay thresholds. The only cases where carrier screening was not deemed cost-effective was under assumed low rates of reproductive intervention combined with increased testing costs.

The results in Table 3.3 indicate that carrier screening may be cost saving to the health system over a lifetime horizon. This finding is supported by results from international literature.[vi,19,20] Carrier screening is also highly scalable. While this case study has focussed on 176 conditions, carrier screening can be expanded further to test for many more conditions, which would lead to further savings to individuals and the health system.

Further, there are other societal benefits which have not been quantified. For example, people born with cystic fibrosis are significantly more likely to experience productivity losses and more likely to require an informal carer. Productivity losses stem from a lower likelihood entering and remaining in the workforce, and through impacts such as absenteeism[vii] and presenteeism.[viii] The productivity cost of cystic fibrosis was most recently estimated to be approximately $25,000 per person per year.[21] These impacts extend to the parents and to the broader family of the child. In a qualitative analysis of Australian carer perspectives for children with spinal muscular atrophy, carers reported significant financial and caregiving burdens, limitations to career progression and difficulty accessing funding, equipment, support and resources.[22] Caring for children with severe genetic conditions also led to substantial emotional and social impacts.

Expanded carrier screening has the potential to be cost saving when evaluated from a health system perspective, with additional benefits derived from improvements to productivity and a reduced burden on caregivers. Screening has the potential to provide thousands of at risk couples with greater knowledge and understanding of the risks of conception, allowing them to make informed decisions moving forward based on their individual circumstances.

A summary of the key clinical, economic and social benefits of expanded carrier screening relative to no screening is provided in Table 3.4

[vi] Cost saving indicates that the cost of the intervention was less than the savings that the intervention would produce for the health system.

[vii] Absenteeism captures the additional time a person takes off of work due to their condition.

[viii] Presenteeism accounts for lower productivity while at work due to the person's condition.

Table 3.4: Summary of the clinical, economic and social benefits of expanded carrier screening relative to no screening for Australian couples

Benefit	Outcome
Clinical benefits	
Improved identification of couples affected	The model estimated that expanded carrier screening would find that 1.2% of Australian couples were at risk of having an affected birth. In a hypothetical cohort of 300,000 couples, this represents 3,605 couples who give birth each year. It was estimated that 451 of these couples (i.e. 0.15% of the original cohort) intervened with an alternative pregnancy. These couples would have otherwise had a child with a genetic condition.
Other economic and social benefits, by stakeholder beneficiary	
Individuals	One of the key benefits of diagnostic applications of genomics in healthcare is the 'value of knowing' for individuals. In this case, screening has the potential to provide thousands of at risk couples with greater knowledge and understanding of the risks of conception. This allows these couples to make the best decision applied to their unique circumstances, whether that be to proceed with conception, proceed with an alternative birth or to choose not to have children. In addition, the model estimated that each child born without a genetic condition was expected to gain 26 QALYs over their lifetime, as compared to if they were born with a genetic condition.
Health system	The model estimated that the lifetime health system expenditure costs (e.g. hospital stays, clinical appointments, treatment costs etc.) for a person with a genetic condition was estimated to be more than $1.5 million, discounted to the year 2021. In a hypothetical cohort of 300,000 couples, carrier screening thus has the potential to reduce health system expenditure by more than $680 million over a lifetime horizon, discounted to the year 2021. After subtracting the reduction in health system expenditure costs from the additional costs of testing, the savings to the health system are $350 million, making the intervention cost-saving. This equates to a saving of $1,200 per couple screened.
Families/carers and societ	There are other societal benefits which have not been quantified. For example, people born with a genetic condition are more likely to experience productivity losses and more likely to require an informal carer. Productivity losses stem from a lower likelihood entering and remaining in the workforce, and through impacts such as absenteeism an presenteeism. For example, the productivity cost of cystic fibrosis was most recently estimated to be approximately $25,000 per person per year.[23] These impacts extend to the parents and to the broader family of the child. In a qualitative analysis of Australian carer perspectives for children with spinal muscular atrophy, carers reported significant financial and caregiving burdens, limitations to career progression and difficulty accessing funding, equipment, support and resources.[24]

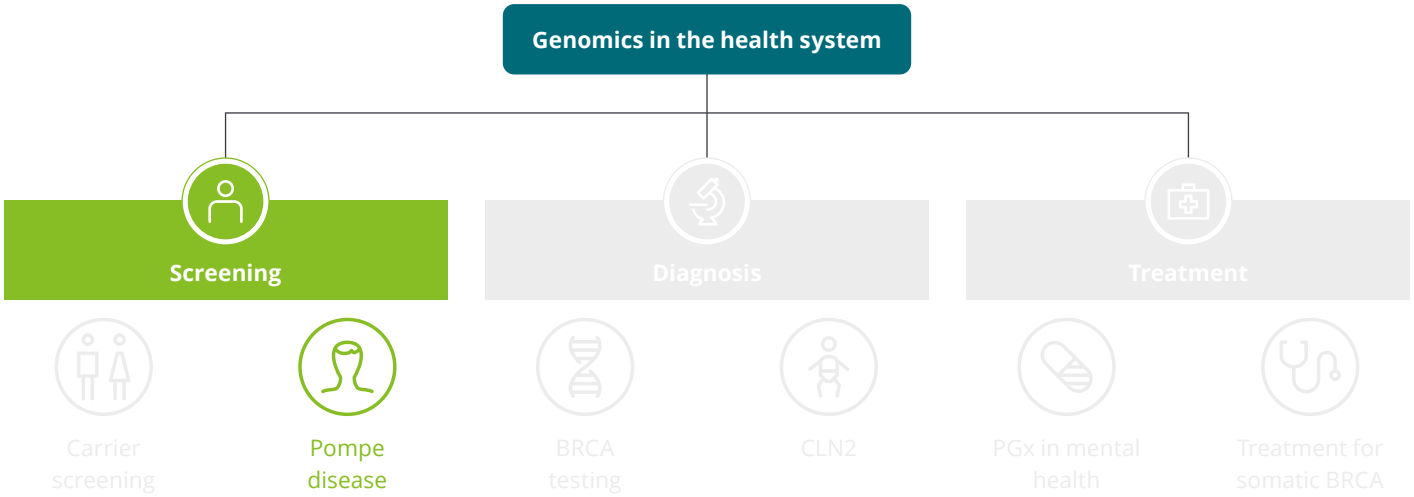
Source: Deloitte Access Economics calculations.

Box 4. Expanded genetic carrier screening for couples – key takeaways

This case study evaluated the cost-effectiveness of expanded carrier screening relative to no screening from a health system perspective, over a lifetime horizon.

In the base case, carrier screening was cost saving to the health system, meaning that the upfront cost of the test was less than the longer-term cost-savings realised through reduced healthcare expenditure for children with severely debilitating genetic conditions. Out of a cohort of 300,000 couples, the intervention was modelled to avoid 451 genetic conditions.

Carrier screening has the potential to provide prospective couples with the information needed to make informed decisions about their reproductive options based on the likelihood of having a child with a severely debilitating or life-threatening genetic condition. Further initiatives such as implementation of the findings from the carrier screening research program *Mackenzie's Mission* should be supported to begin realising this value within Australia.



3.2.2 Pompe disease

Another example application of genomics at the screening phase of the care continuum is screening of Pompe disease in newborns. Pompe disease is a genetic disorder that leads to problems with breaking down glycogen. Pompe disease is caused by mutations in the glucosidase alpha acid (GAA) gene, which leads to low levels of the acid alpha-glucisidase enzyme.[25] GAA is one of several enzymes that breaks down cellular glycogen within lysosomes. The accumulation of glycogen is harmful to the human body, leading to irreversible damage to the heart, skeletal muscle and the lungs.

The course of the disease can vary widely based on the specific mutation to the GAA gene. People with a mutation on both GAA alleles that prevent the production of functioning GAA have a uniformly severe phenotype referred to as the classic infantile form. This form of Pompe disease leads to progressive weakness and cardiomyopathy. If untreated, the life expectancy of classic infantile Pompe disease is less than two years.[26]

Without genomics, the diagnosis of Pompe disease is based on a clinical evaluation including detailed patient and family history, and a variety of biochemical tests measuring GAA activity. Diagnosis of Pompe disease is often delayed due to its rarity, overlap in signs and symptoms with other neuromuscular disorders, variable diagnostic approaches and a lack of awareness of the clinical manifestations.[27] Presenting symptoms for infantile Pompe disease include hypotonia, feeding difficulties, muscle weakness, delayed motor milestones, respiratory distress, congestive heart failure, enlarged tongue and shortness of breath at rest.[28] One study capturing the diagnostic gap (the time from onset of signs and symptoms of Pompe disease to the time of diagnosis of Pompe disease) found a median diagnostic gap of 1.4 months in cases of infantile onset Pompe disease. This was after onset of symptoms occurred on average at two months. This is a significant delay considering the rapidness of disease progression for infantile onset Pompe disease. Left untreated, median survival time has been reported to be 8.7 months, with only nine per cent of infants living beyond two years.[26]

Enzyme Replacement Therapy (ERT) is an approved treatment for all patients with Pompe disease. ERT involves the intravenous administration of recombinant human acid alpha-glucosidase (rhGAA). ERT is not a cure of Pompe disease, however it vastly improves the life expectancy of individuals with infantile-onset Pompe disease. Early treatment with ERT may further improve the life expectancy and quality of life for individuals with infantile onset Pompe disease. One study of patients diagnosed with Pompe disease using NBS with genetic testing (with a median age at diagnosis of 16 days), and subsequently treated early with ERT, found significantly better survival, mechanical ventilator free survival and life quality compared to clinically diagnosed patients with a median age at diagnosis of several months.[29]

Late-onset Pompe disease occurs when an individual with a GAA mutation does not develop significant weakness during infancy. Most individuals with late-onset Pompe disease present with symptoms in adulthood. While NBS can identify individuals who may develop late onset Pompe disease, these people may remain asymptomatic for decades. Diagnosis of late onset Pompe disease leads to 'patients in waiting' – people who are currently healthy but have knowledge of their pre-symptomatic disease. This can have negative consequences for the individual and their family, including ongoing clinical surveillance and testing which may not yield any results.[30] While knowledge of the possibility of late-onset Pompe disease would presumably lead to earlier diagnosis, the outcomes of earlier treatment remain uncertain. As such the modelling approach has not assessed the benefits of diagnosis for late onset Pompe disease.

Methodology

The purpose of this case study was to determine if NBS with genetic testing (referred to collectively as NBS) is a cost-effective means to diagnose cases of infantile onset Pompe disease. The modelling used a ten year time horizon and was evaluated from a societal perspective. The NBS arm of the model assumed that all Australian newborns (approximately 300,000 in one year) were screened for Pompe disease at birth. The cost of this screening was assumed to be $10.[31] Infants who received a positive screening underwent further genetic testing to confirm the diagnosis of Pompe disease. Without NBS, infants were not screened for Pompe disease, and it was assumed that diagnosis of Pompe disease would be delayed.

Based on the estimated prevalence of Pompe disease, NBS was estimated to identify 11 cases of Pompe disease, of which approximately three cases were infantile onset Pompe disease.[32] With NBS, these cases of infantile onset Pompe disease would be diagnosed before the onset of severe symptoms. It was modelled that 30 per cent of these cases would have no symptoms with the remaining 70 per cent experiencing mild symptoms. Without NBS, it was assumed that the diagnosis gap would result in worse symptoms upon diagnosis for infants with Pompe disease. Specifically, it was assumed that approximately 32 per cent of infants whose symptoms included cardiomyopathy would experience severe symptoms of Pompe disease by the time they were diagnosed. This severe health state was characterised by ventilator dependence.

A Markov model constructed to analyse patient progression over a ten year time horizon. All patients were assumed to receive ERT over this period. However, the likelihood of transitioning to more severe health states (or death) was tied to the patient's starting state. Cases of infantile onset Pompe disease which were diagnosed before the onset of symptoms had a high probability of remaining without symptoms over the entire time horizon. Conversely, infants in a severe health state upon diagnosis had high mortality rates. Transition probabilities were based on a previous study of NBS impacts on infantile onset Pompe disease.[31]

Additional details on the model structure and inputs used are provided in Appendix B.

Results and discussion

Under a ten-year time-horizon, in total, children in the NBS arm were estimated to lose 4.1 QALYs due to Pompe disease. Notably this was driven by reduced quality of life, with no deaths occurring during the period. Under the clinical identification arm, children were expected to lose 11.9 QALYs, with slightly more than one death (attributable to Pompe disease) expected. Newborn screening with genetic testing was thus estimated to save an additional 8 years of life, or 2.5 years of life per child with infantile Pompe disease. These results are shown in Table 3.5.

Table 3.5: Base case and one-way sensitivity analysis for cost-effectiveness of NBS with genetic testing in all newborns relative to clinical identification, societal perspective

	NBS total cost ($ million)	Clinical identification cost ($ million)	QALYs gained	Cost per QALY gained ($)
Base case	10.3	7.6	7.8	342,288
Low ERT costs (-50%)	7.4	5.4	7.8	254,355
High ERT costs (+50%)	13.2	9.8	7.8	430,221
Improved starting state (40% of cases with no symptoms, NBS arm)	10.1	7.6	8.4	295,813

Source: Deloitte Access Economics calculations.

The incremental cost-effectiveness estimate of using NBS with genetic testing to diagnose cases of infantile onset Pompe disease relative to standard diagnostic approaches was above traditional WTP thresholds, when evaluated from a societal perspective. This finding is reflected in other international literature.[31] However, the intervention still demonstrates significant value to the individuals affected in the form of life-years saved. NBS also provides additional benefits to the families/carers of affected individuals. This includes significantly fewer hours of informal and formal care required for individuals with mild symptoms compared to severe symptoms. The literature indicates that severe infantile-onset Pompe disease was estimated to require 24 hour care, split across both formal and informal carers.[31] This presents a significant cost to the individuals carers, likely preventing them from being able to work. The modelling estimates that the productivity benefit for each family/carer attributable to reduction in informal carer time resulting from the use of NBS with genetic testing relative to standard diagnosis, is approximately $396,000, over a ten-year time horizon.

The model was limited to a ten-year time horizon due to the limited data availability on longer term outcomes for people with infantile-onset Pompe disease. As such the cost effectiveness of this case study is understated – for example years of lost life were assumed only to accrue within the ten year time horizon. Broadening this to a lifetime time horizon based on the life expectancy of children with infantile onset Pompe disease treated with ERT would yield significant additional benefits from avoided mortality. Further, as treatment for Pompe disease becomes more effective over time, the value attributed to early diagnosis will continue to increase.

There is also value attributable to genetic counselling for patients diagnosed with Pompe disease and their family. Genetic counselling can be a source of much needed information about the disease, helping families make informed medical and personal decisions.[33] This is particularly important for the cases of late-onset Pompe disease. The case study estimated that there would be approximately eight cases of late onset Pompe disease identified through NBS. For these individuals, there is no immediate health impact to the individual, and no indication for the initiation of ERT. However, genetic counselling should be provided to these individuals and their family to explain the long term implications and practical considerations attached to this diagnosis.[33]

A summary of the key clinical, economic and social benefits of NBS with genetic testing for Pompe disease relative to standard clinical diagnosis is provided in Table 3.6.

Table 3.6: Summary of the clinical, economic and social benefits of NBS with genetic testing for Pompe disease relative to standard clinical diagnosis

Benefit	Outcome
Clinical benefits	
Improved time to diagnosis	The model estimated that if all newborns were screened using NBS with genetic testing, approximately 11 cases of Pompe disease would be identified at birth in each year. Of these cases, three would have infantile-onset Pompe disease and would commence treatment with ERT immediately. The intervention improves the time to diagnosis in each of these cases by a couple of months, which is significant in the context of infantile-onset Pompe disease, where disease progression is rapid.
Reduction in symptom onset and progression	By reducing the time to diagnosis of infantile onset Pompe disease and facilitating earlier treatment with ERT, NBS with genetic testing results in fewer cases developing severe symptoms. Over a ten-year time horizon, cases of infantile onset Pompe disease identified through the intervention are expected to remain without symptoms, or with only mild Pompe disease symptoms. This compares to diagnosis using standard care, where the majority of cases will progress to severe symptoms, characterised by ventilator dependency and a high risk of mortality. In delaying symptom onset, NBS with genetic testing significantly reduces the probability of mortality. The model estimated that over a ten-year time horizon, NBS with genetic testing would avert one death (i.e. reducing the mortality rate from one third of cases to zero cases), relative to standard clinical diagnosis.
Other economic and social benefits, by stakeholder beneficiary	
Individuals	For individuals with infantile onset Pompe disease, NBS with genetic testing facilitates improved quality of life and life expectancy. Over a ten-year time horizon, NBS with genetic testing relative to standard clinical diagnosis was estimated to save: • a total of 7.8 QALYs, across all cases of infantile onset Pompe disease diagnosed in a given year, or • 2.5 QALYs per child diagnosed with infantile Pompe disease.
Health system	Using NBS with genetic testing to diagnose infantile onset Pompe disease increases costs incurred by the health system because the intervention is able to prolong life – and thereby, time receiving ERT, a relatively costly treatment. Given that there is no cure for infantile onset Pompe disease, increases in health system costs is expected when patient life expectancy increases.
Families/carers and societ	By reducing the likelihood that a case of infantile onset Pompe disease will progress to severe symptoms, NBS with genetic testing reduces informal carer time, and thereby the opportunity cost of workforce participation for families/carers. Returning to the workforce facilitates productivity gains for society as a whole. The model estimated that, over a ten-year time horizon, the intervention relative to standard clinical diagnosis, resulted in a productivity benefit attributable to reduction in informal carer time worth $396,000 per case of infantile onset Pompe disease diagnosed, discounted to the year 2021. These increased earnings result in higher tax revenue for government, which in turn benefits the rest of society.

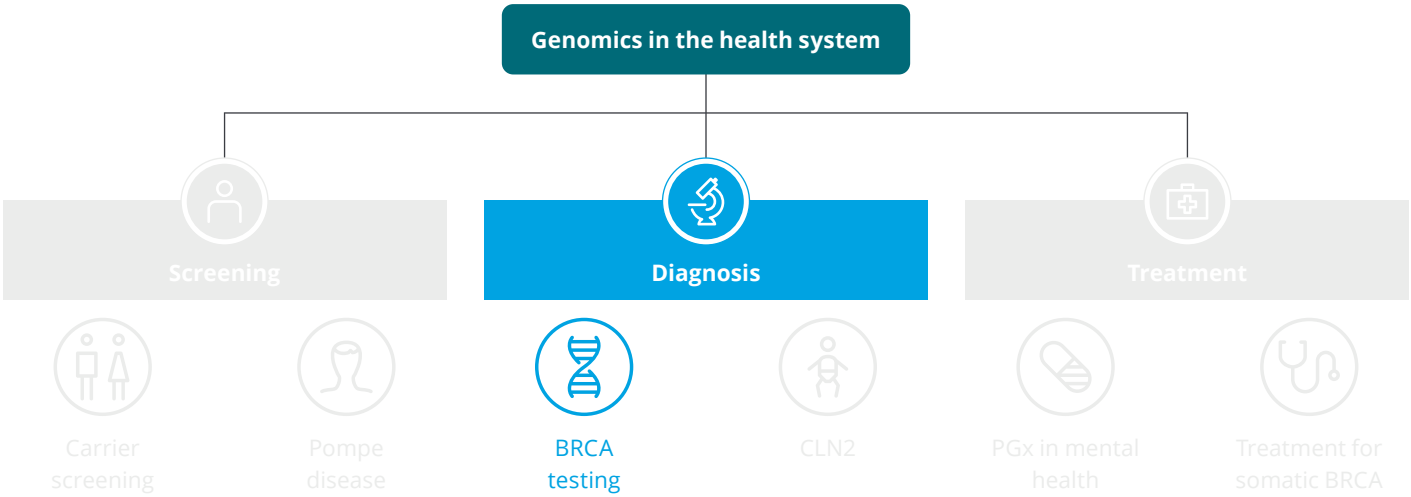
Source: Deloitte Access Economics calculations.

Box 5. Additional genetic testing in newborns for Pompe disease – key takeaways

This case study evaluated the cost-effectiveness of newborn screening and genetic confirmation testing for infantile onset Pompe disease relative to clinical diagnosis, over a ten-year time horizon, from a societal perspective.

The cost-effectiveness ratio associated with providing newborn screening with genetic testing for Pompe disease relative to standard clinical diagnosis is above traditional willingness to pay thresholds. However, this form of screening improves time to diagnosis and effective treatment, delays symptom onset/progression, and has the potential to be a life saving intervention for the handful of children born with infantile onset Pompe disease each year.

The cost-effectiveness ratio for newborn screening for Pompe disease is likely to improve over time, as treatment becomes more effective in improving the long term quality of life for children diagnosed, and as newborn screening evolves to screen for multiple conditions at the one time.



3.2.3 Breast Cancer gene 1 and 2

A third example of a genomics application at the screening stage of the care continuum is the detection of BRCA mutations. Some people have an elevated lifetime risk of developing breast cancer based on mutations to the BRCA1 and BRCA2. BRCA1 and BRCA2 are known as tumour suppressor genes, they produce tumour suppressing proteins that control cell growth.[34] Mutations to either of these genes leads to a significantly higher lifetime risk of breast cancer and ovarian cancer.[35] The BRCA mutations are also associated with increased risks of pancreatic and prostate cancer.[35] The average lifetime risk of breast cancer for women is approximately 12 per cent, which increases to around 70 per cent when a BRCA mutation is present.[37] While breast cancer is far less common in men (fewer than one per cent of all breast cancers occur in men), men with mutations to BRCA2 may have an eight times greater risk of developing breast cancer by the time they are 80 years old.[38] A positive test identifies a carrier of a mutation to BRCA1 or BRCA2, this information can be used to inform treatment pathways to reduce the risk of the person developing breast cancer. This testing is currently offered in Australia where the estimated probability of finding a mutation is greater than 10 per cent (i.e. family history).[39]

It is projected that just over 20,000 cases of breast cancer will be diagnosed in 2021.[40] Approximately five per cent of people diagnosed this year will have either a BRCA1 or BRCA2 germline mutation.[41] Germline mutations are hereditary – passed on through family. Detection of germline BRCA1 and BRCA2 mutations gives an indication that close relatives to the person may also be carriers of the mutation. Knowledge of BRCA carrier status can substantially improve population health outcomes through the use of risk reducing procedures. Despite this, up to 97 per cent of BRCA carriers in the general population remain unidentified.[42]

Methodology

This case study estimated the number of additional BRCA carriers that could be identified through genetic testing of all people with an invasive breast cancer diagnosis. This was compared to genetic testing based only on family history (comparator here on referred to as 'FH'). Where a clinically significant BRCA mutation is found, cascade testing was then provided to relatives to identify BRCA carriers without cancer. The cost-effectiveness was evaluated over a lifetime horizon, from a health system perspective.

Cascade testing refers to the provision of genetic testing to individuals at risk for inheriting a genetic variant previously identified in a biologic relative. The process is repeated as more carriers are identified within the family. It was assumed that cascade testing would identify approximately 1.4 additional unaffected carriers.[ix] This means that for every BRCA carrier with breast cancer, it was assumed that cascade testing would identify an average of 1.4 relatives with a BRCA mutation and no current cancer. Identified carriers without breast cancer were offered interventions including risk reducing mastectomy (RRM) or risk reducing salpingo oophorectomy (RRSO). The modelling assumed a significant population uptake of one or both of these interventions which reduced the likelihood of the person developing breast or ovarian cancer in the future.[41] Other risk reducing medications such as Tamoxifen were not included in the analysis due to relatively low rates of uptake in the Australian population.[43]

Additional details on the model structure and inputs used are provided in Appendix B.

[ix] Where an unaffected carrier is a person without cancer who has a mutation to either BRCA mutation.

Results and discussion

The modelling estimated that by offering genetic testing to all people diagnosed with breast cancer in 2021, an additional 1,145 unaffected relatives with a BRCA mutation would be identified, as compared with FH testing alone. This was estimated to result in 159 avoided cases of breast cancer, 59 avoided cases of ovarian cancer, and 75 avoided deaths due to cancer, over a lifetime horizon.

The intervention was significantly more costly than standard practice, with genomic testing provided to more than 20,000 people with breast cancer and a further 5,000 relatives. The estimated cost of screening was $30.5 million more than would be expected through FH testing alone.

Approximately three out of four additional unaffected carriers identified by the intervention were assumed to undertake RRM, RRSO or both risk reducing procedures. It was assumed that none of these procedures would have taken place without the additional screening. While the cost of these interventions was estimated to total $8.9 million, there were significant longer-term savings to the health system through reduced cancer care costs. The reduction in cancer care costs attributable to expanded genetic testing was estimated to fall from $26.9 million to $14.0 million, as a result of lower cancer incidence and improved cancer survival. Table 3.7 summarises the results of this case study.

Table 3.7: Base case and one-way sensitivity analysis for cost effectiveness of genetic testing for BRCA mutation in all patients with breast cancer in 2021 and relatives of affected individuals relative to testing based on FH only, health system perspective

	Intervention total cost ($ million)	FH cost ($ million)	QALYs gained	Cost per QALY gained ($)
Base case	53.4	26.9	3,681	7,205
Improvement of risk reduction (risk of cancer after RRM or RRSO reduced by 5%)	52.7	26.9	3,721	6,930
Decrease in risk reduction (risk of cancer after RRM or RRSO increased by 5%)	54.1	26.9	3,643	7,481
Increase in uptake of RRM or RRSO (+3% uptake)	53.0	26.9	3,746	6,989
Decrease in uptake of RRM or RRSO (-7% uptake)	54.0	26.9	3,571	7,595
Increase in carriers identified through cascade testing (+5%)	54.9	28.2	3,866	6,896
Decrease in carriers identified through cascade testing (-5%)	51.9	25.5	3,497	7,546
Increase to genomic testing costs (+50%)	68.6	26.9	3,681	11,340
Decrease to genomic testing costs (-50%)	38.0	26.9	3,681	3,012

Source: Deloitte Access Economics calculations.

Expanding genomic screening to all breast cancer patients has the potential to be highly cost effective. This reflects other findings in international literature.[41] From a health system perspective, the intervention was modelled to cost $7,205 per QALY gained. This case study has only considered the benefits to improved screening for BRCA and the implications this has for reduction of breast cancer and ovarian cancer incidence. Genetic testing may also be used to detect other gene mutations linked to greater cancer incidence. For example, the testing currently available under the Medicare benefits schedule is capable of characterising germline gene variants for STK11, PTEN, CDH1, PALB2 and TP53.[44] These genes have been linked to additional cancer risk for carriers.[45,46,47,48,49] This case study did not include the additional benefits of identifying carriers of these mutations.

In addition to improving patient outcomes, reducing cancer incidence can have significant benefits to broader society. For instance, cancer leads to substantial productivity losses – particularly for those diagnosed at working age. One Australian based study estimated that people with no health conditions were three times more likely to be employed full time compared to people with cancer.[50] Furthermore cancer is one of the 10 most common health conditions in receipt of informal care giving in Australia.[51] Informal care poses additional productivity losses to society, by reducing the number of hours that the informal carer can work.

Figure 3.2: Patient stories

"Genetic testing for us a sister has been lifechaging, raw, emotional but above all empowering. Our lives could have been very different had we had not of known our risk. Every single person no matter what their story is can have a future and have hope"

– BRCA carrier

"The BRCA test is a powerful tool, with the potential to alter a person's genetic destiny. I am alive because I knew my risk and changed my future. I am one of the lucky ones. I am part of a generation of women who get to save our lives. All of us are linked to women who did not get that chance"

– BRCA carrier

"Knowing my risks has allowed me to make significant life choices and take action related to my physical and mental health, including having risk reducing surgery and those related to fertility preservation. Knowledge is power and it gives me options that others in my family were not lucky enough to have"

– BRCA carrier

A summary of the key clinical, economic and social benefits of genetic testing for BRCA mutation in all patients with breast cancer and relatives of affected individuals relative to FH testing alone is provided in Table 3.8.

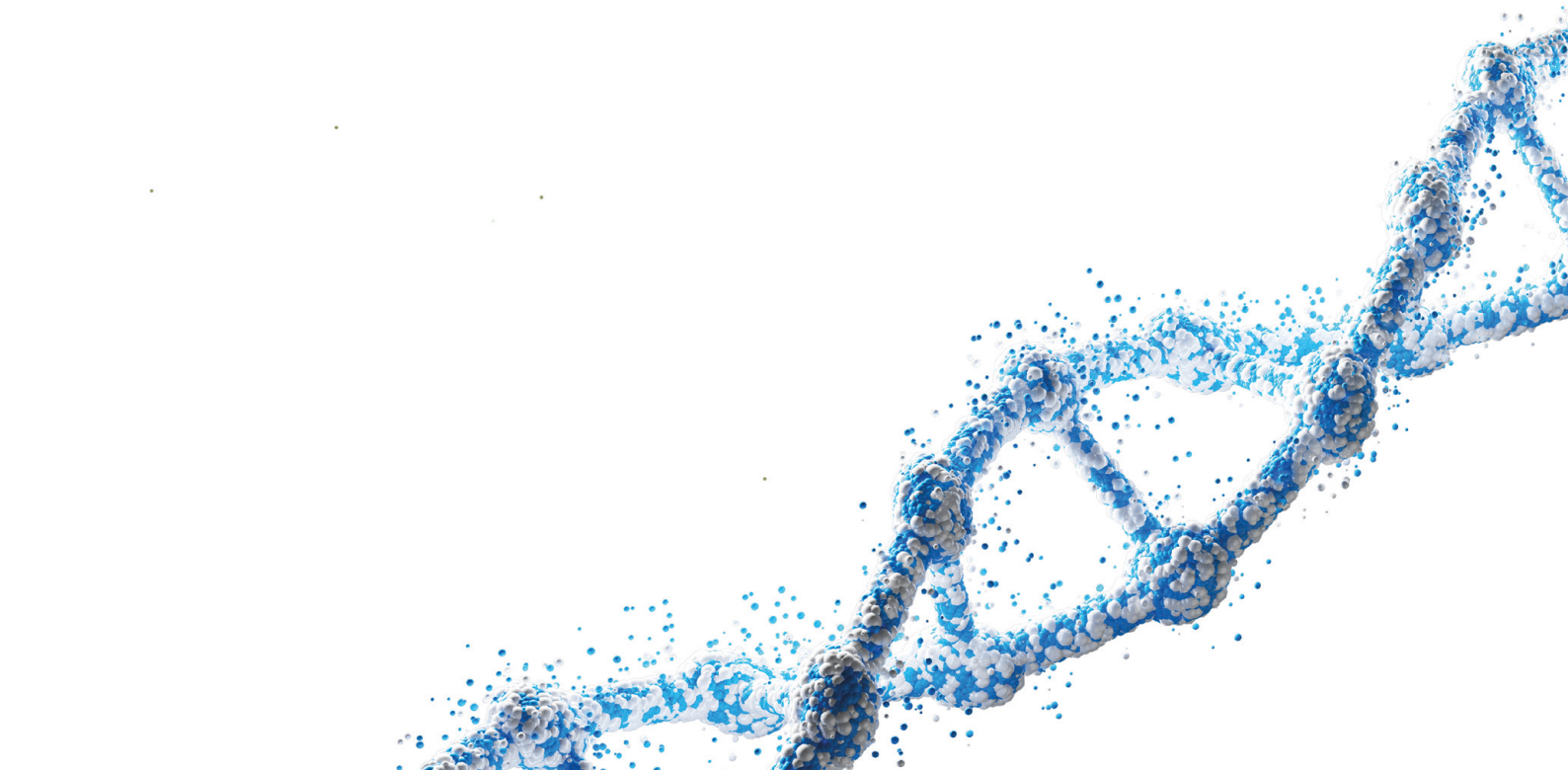


Table 3.8: Summary of the key clinical, economic and social benefits of genetic testing for BRCA mutation in all patients with breast cancer and relatives of affected individuals relative to testing based on FH only

Benefit	Outcome
Clinical benefits	
Improved identification of BRCA 1 and BRCA 2 carriers	The modelling estimated that by offering genetic testing to all people diagnosed with breast cancer in 2021 and relatives of affected individuals, an additional 1,145 unaffected relatives (i.e. people currently free of cancer) with a BRCA mutation would be identified, as compared with FH testing alone.
Reduced cancer incidence and mortality	Known carriers of BRCA mutations are more likely to proceed with risk reducing procedures which reduces their overall risk of developing cancer and in turn reduces their risk of dying from cancer. By identifying an additional 1,145 unaffected relatives (i.e. people currently free of cancer) with a BRCA mutation in 2021, the model estimated that over a lifetime horizon, the intervention would avoid 159 cases of breast cancer and 59 cases of ovarian cancer, relative to testing based on FH only. This resulted in 75 less deaths due to cancer.
Other economic and social benefits, by stakeholder beneficiary	
Individuals	BRCA screening provides the opportunity for relatives of a person affected by breast cancer to understand their personal risk of developing breast cancer. This information can then be used to decide if a risk reducing procedure is appropriate. As noted above, if these individuals decide to undergo risk reducing procedures, this will reduce their risk of cancer, and thereby improve their quality of life and life expectancy.
Health system	The intervention was significantly more costly than standard practice. The model estimated that the cost of offering genetic testing to all people diagnosed with breast cancer in 2021 and relatives of affected individuals was $30.5 million (or $1,200 per person) more than would be expected through FH testing alone. However, by reducing the incidence of cancer, testing costs are partially offset by longer-term health system savings (e.g. by reducing demand for health services such as hospital stays, palliative care etc.). The model estimated that, for those tested in 2021, over a lifetime horizon, the intervention relative to FH testing alone saves the health system: • a total of $12.8 million in cancer care costs, discounted to the year 2021, or • $11,650 in savings per BRCA mutation carrier identified or $503 in savings per person screened.
Families/carers and society	Breast and ovarian cancer patients often require a significant amount of support through informal care. One study reported that informal carers provide an average of 59 hours of care per month, with only 59% working in full-time employment.[52] In addition, while most people are able to return to work after diagnosis and treatment of breast cancer, the productivity impacts remain significant. Approximately one in ten people with breast cancer do not return to work two years post diagnosis, with unemployment remaining a challenge up to five to ten years post diagnosis.[53] For people tested in 2021, the intervention avoids the eventual incidence of cancer in an additional 218 people relative to FH testing alone. For these individuals, productivity losses attributable to the patient and their informal carers are removed entirely. The increase in workforce participation results in higher tax revenue for government, which in turn benefits the rest of society.

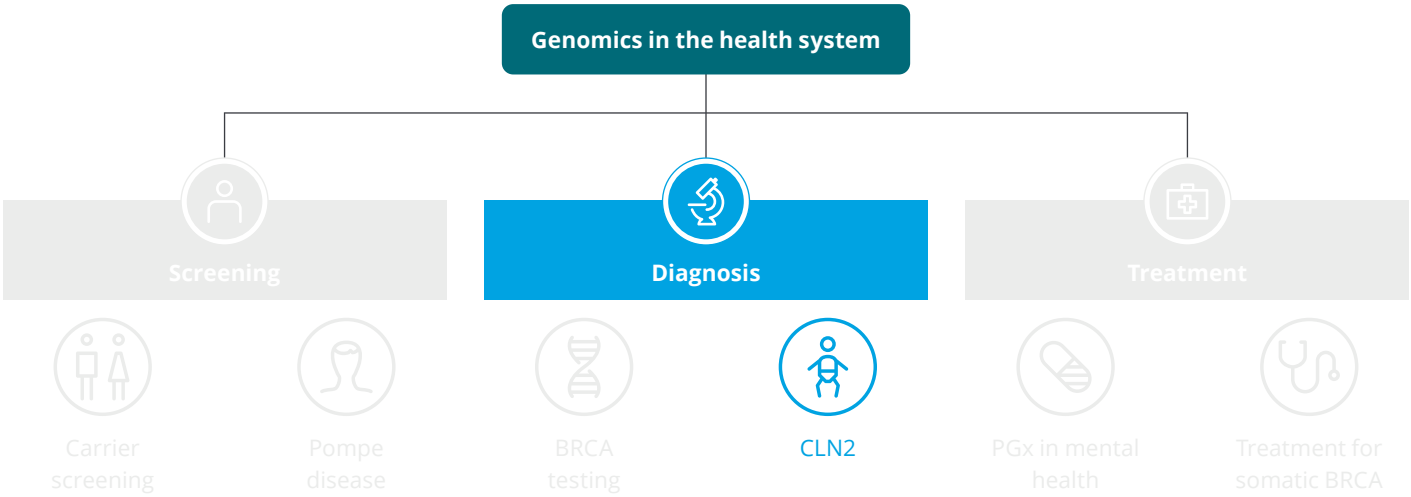
Source: Deloitte Access Economics calculations.

Box 6. Genetic testing for BRCA mutation in all patients with breast cancer and relatives of affected individuals – key takeaways

This case study evaluated the cost-effectiveness of testing all patients with breast cancer for BRCA1 or BRCA2 mutations, followed up with cascade testing for relatives. This was compared to testing based only on family history. The cost-effectiveness was evaluated over a lifetime horizon, from a health system perspective.

Genetic testing for all breast cancer patients was estimated to identify an additional 1,145 unaffected BRCA carriers in a year compared to the current strategy. Providing risk reducing interventions to these people was estimated to prevent almost 220 cases of breast or ovarian cancer, and 75 deaths from cancer. The intervention was highly-cost-effective when considered against common willingness to pay thresholds, estimated to cost $7,205 per QALY gained.

Current guidelines for genetic testing in breast cancer patients require a greater than 10% risk (i.e. family history) of the patient carrying a mutation. This case study demonstrates that this requirement could be removed in favour of testing for all breast cancer patients.



3.2.4 CLN2

A fourth application of genomics at the screening and diagnosis stage of the care continuum is its role in improving time to diagnosis for children with dementia. Childhood dementia represents a range of conditions defined by neurocognitive decline with multiple developmental skill losses overtime. Unlike conditions such as development delay or intellectual disability which are characterised by static or transient loss of skills, individuals with childhood dementia experience progressive loss of previously acquired development skills. There are over 70 types of childhood dementia and it is estimated that 1 in 2,800 children are born with a childhood dementia disorder in Australia.[54] Only less than five per cent of the 70 childhood dementia disorders have treatments, of which only four of the conditions have treatments listed on the federal government's Life Saving Drug Program.[53]

Figure 3.3: Patient stories

"Childhood dementia is every parent's worst nightmare. We've had to watch our beautiful seven-year-old daughter lose the ability to run, to walk, to dance. She's lost the ability to speak. She's going blind, she's finding it harder and harder to recognise family and friends."

– Carer of child with childhood dementia

"Childhood dementia strips children of the ability to engage, communicate and then strips them of their life – this is just evil."

– Carer of child with childhood dementia

One type of childhood dementia is neuronal ceroid lipofuscinosis type 2 (CLN2), caused by pathogenic variants in the gene encoding the tripeptidyl peptidase 1 (TTP1) enzyme. A deficiency of TPP1 causes an accumulation of lysosomal storage material that causes degenerative changes in neurons throughout the central nervous system and retina. Children with CLN2 are functionally normal until the age of two to four years. Over a period of four to six years, children begin to experience seizures, development delay, and rapid decline in motor, language, cognitive and visual function, and death by early adolescence (between 8 and 12 years).

Cerliponase alfa, a recombinant proenzyme form of human TPP1, is an ERT that is given by intracerebroventricular infusion to delay disease progression in patients. Treatment with cerliponase alfa in clinical trials showed children with CLN2 are significantly less likely to have a decline in CLN2 clinical rating scale assessment of motor and language scores than historical controls.[55]

The path to diagnosis for CLN2 is through a combination of enzymatic and genetic investigations after suspicion is raised that a child may have CLN2 after showing initial symptoms such as seizures. As part of the diagnostic procedures, children suspected of having CLN2 undergo an electroencephalogram (EEG) to monitor response to intermittent photic stimulation, magnetic resonance imaging (MRI) to identify patterns of brain atrophy and enzyme testing to detect low level of TPP1 enzyme activity.[56] Diagnostic delays are common in patients with CLN2, and the delay between the onset of initial symptoms and a confirmed diagnosis is usually two years with standard testing.

An Australian study found that CLN2 patients with a timely diagnosis utilised gene panels and whole exome sequencing followed by confirmatory enzymology, whilst older patients were diagnosed initially using enzymology followed by gene sequencing.

This may be explained by the increased clinical utility of genetic testing, where a genetic test can confirm the existence of pathogenetic variants in both copies of the CLN2 gene before detection of low level TTP1 enzyme activity through enzymology.[55]

Methodology

The purpose of this case study was to determine if diagnosis with genomic and standard testing (EEG, MRI and TPP1 enzyme activity test) is a cost-effective means to diagnose cases of CLN2 disease in children, as compared with standard diagnostic tools. The cost of genomic testing was assumed to be $3,000.[57] Cost-effectiveness was evaluated from a healthcare system perspective, over a lifetime horizon.

The standard testing arm was assumed to incur no cerliponase alfa cost in the first five years of the model, and only incurs these costs from year five onwards, once the child has a confirmed diagnosis of CLN2.[58] In the genetic and standard testing arm, it is assumed that newborn children CLN2 would get genetic testing for pathogenic variants in the CLN2 gene as soon as first presentation of symptoms (usually seizures) which is usually around age three. If detected, these children were assumed to start treatment with cerliponase alfa at the age of three to delay further disease progression.

The prevalence of Batten disease (name of all CLN conditions) in Australia is not reported, however, it has been estimated that approximately 35 people live with Batten disease at any one time.[59] Approximately 26% of CLN conditions are CLN2, which means there is an estimated nine people with CLN2 in Australia.[60] A Markov model was constructed which consisted of 10 health states based on the CLN2 clinical rating scale. This modelling approach is consistent with previous economic evaluations.[61,62] Medical costs (e.g. medical appointments, hospitalisations etc.) and QALYs were attached to each CLN2 health state and accrued over time, using a cycle length of one year.

Starting states at diagnosis (and commencement of treatment) were more skewed toward the severe states for the standard testing arm, as it was assumed these children would be diagnosed two years later than children in the standard testing arm – by which point the disease had declined (reflecting the natural history of the disease).

The Markov model was used to analyse patient progression over a child's lifetime with genetic testing and standard testing, compared to standard testing alone. Transition probabilities (i.e. the chance of progressing from one health state to another each year) were based on a previous cost-effectiveness analysis of cerliponase alpa in children with CLN2.[63] Transition probabilities once diagnosed and treated reflect the efficacy of cerliponase alpa in stabilising CLN2 symptoms.

Additional details on the model structure and inputs used are provided in Appendix B.

Results and discussion

Using genetic and standard testing to diagnose CLN2 in symptomatic children was estimated to result in 38 QALYs per child diagnosed over a lifetime horizon. This is in comparison to the standard testing arm which was estimated to total 27 QALYs per child diagnosed over the same period. The increased QALYs associated with the genomic and standard testing arm was primarily driven by earlier diagnosis, which allowed children to be treated with cerliponase alfa two years earlier than the standard testing arm.

The modelling estimated that genomic and standard testing for the diagnosis of CLN2 at symptom presentation compared with standard testing alone costs approximately $313,706 per QALY gained. The relatively high ICER reflects longer time spent receiving the life-saving drug, cerliponase alfa, for children in the genetic and standard testing arm. These results are shown in Table 3.9.

Table 3.9: Base case and one-way sensitivity analysis for cost-effectiveness of standard testing coupled with genomic testing for confirmation of CLN2 relative to standard testing

	Standard testing cost ($ million)	Genomic and standard testing cost ($ million)	QALYs gained	Cost per QALY ($)
Base case	227.6	259.5	102	313,7060
Low ERT (-90%)	33.5	38.9	102	53,220
High ERT (90%)	421.8	481.1	102	574,191

Source: Deloitte Access Economics calculations.

While the base-case cost-effectiveness estimate of genomic testing for CLN2 is above traditional WTP thresholds when evaluated from a health system perspective, the use of genomic testing alongside standard testing still demonstrates significant value to the individuals affected. Earlier treatment could allow patients to maintain their independence and bodily function for a longer period, and results in improved overall quality of life.

It is also noted that while testing for CLN2 alone may not be cost effective, larger panel testing or WGS would be capable of detecting cases of CLN2 as well as other potential causes of childhood dementia. Large panel testing is likely to prove significantly more cost effective due to the economies of scale and should be considered for rare diseases such as CLN2.

It is important to note that other benefits are not included in the modelling, which would improve the cost-effectiveness ratio. Reduced time to diagnosis and earlier treatment provides value to the affected individual's families/carers, with significantly fewer hours of informal care required for individuals with mild symptoms. This in turn could improve families/carers productivity, with flow-on impacts to the government such as increased taxation revenue. The annual economic cost of childhood dementia in Australia has been estimated to be $389 million.[53] This cost is primarily driven by the short life expectancy of childhood dementias of around 28 years, and the large burden of care disproportionately met by the patient's families/carers due to the lack of treatment options for childhood dementias. Earlier diagnosis and treatment will go some way to reducing the cost burden of childhood dementia such as CLN2. Diagnosis of a child can also support families in future family planning decisions.

It should be noted that this case study only provides a snapshot of the benefits of genomics in diagnosing childhood dementia conditions, noting that CLN2 is only one of many conditions. Further, genomic testing also offers benefits for conditions with no regulatory approved treatment. An earlier diagnosis of such a condition could result in improved access to clinical trials, with the opportunity to receive a new and novel treatment that could stabilise symptoms and improve quality of life.

A summary of the key clinical, economic and social benefits of standard testing coupled with genomic testing to diagnose cases of CLN2 in children when symptoms first present relative to standard testing alone is outlined in Table 3.10.

Table 3.10: Summary of the key clinical, economic and social benefits of standard testing coupled with genomic testing to diagnose cases of CLN2 in children when symptoms first present relative to standard testing alone

Benefit	Outcome
Clinical benefits	
Improved time to diagnosis	The literature indicates that standard testing coupled with genomic testing for children diagnosed with CLN2 could result in a two year improvement on the typical time to diagnosis.[57] Because of the improved time to diagnosis, it was modelled that up to 65% of children diagnosed with genetic testing would be diagnosed in the earliest stage of disease progression (health stage 1 and 2). Comparatively, only 16% of children were diagnosed at this stage under standard testing.
Reduction in symptom progression	While there is no cure for CLN2, early diagnosis with genomic and standard testing significantly delays severe symptom onset. The model estimated that at ten years post diagnosis, 55% of patients diagnosed with genomic testing had remained in the mild symptoms health states (i.e. the first two CLN2 health state), which are characterised by a marginal decrease in quality of life. Conversely, only 13% of patients under standard testing remained in this health state, with around 16% of patients having progressed to the most severe symptoms (health state 6 to 9) or death.
Other economic and social benefits, by stakeholder beneficiary	
Individuals	For children with CLN2, standard testing coupled at first presentation of symptoms results in improved quality of life. Over a lifetime horizon, the use of genetic testing relative to diagnosis through standard testing alone was estimated to gain: • a total of 102 QALYs, across all cases of CLN2 identified in children in a given year, or • 11 QALYs per child diagnosed with CLN2. Genomic testing also offers benefits for many childhood dementia conditions such as CLN2 with no regulatory approved treatment. An earlier diagnosis of such a condition could result in improved access to clinical trials, with the opportunity to receive a new and novel treatment that could stabilise symptoms and improve quality of life.
Health system	Using genomic and standard testing to confirm a diagnosis of CLN2 relative to standard testing was expected to increase costs incurred by the health system. This is because the intervention is able to prolong life – and thereby, time receiving cerliponase alfa, which is a relatively costly treatment. Given that there is no cure for CLN2, the increases in health system costs is expected when patient life expectancy increases.
Society	Reduced time to diagnosis and effective treatment provides value to the affected individual's families/carers, with significantly fewer hours of informal care required for individuals with mild symptoms. This in turn could improve families/carers' productivity, with flow-on impacts to government such as increased taxation revenue. Another benefit is providing timely information for personalised care and future family planning. This allows couples to make the best decision for themselves and their family.

Box 7. Genetic testing for conformation of one form of childhood dementia, CLN2 – key takeaways

This case study evaluated if genomic and standard testing is a cost-effective means to diagnose cases of CLN2 in children when symptoms (usually seizures) first present, compared to standard testing alone. The CEA was performed over lifetime horizon, from a health system perspective.

Including genomic testing with standard testing when symptoms first present resulted in a cost-effectiveness ratio above traditional WTP thresholds, because the genomic technology was able to prolong life – and thereby, time receiving treatment. However, the intervention demonstrated strong clinical value by increasing time to diagnosis, time to effective treatment, and preventing symptom onset/progression. This resulted in an additional 11 QALYs per child diagnosed, over their lifetime.

Given that most rare diseases are genetic in origin, the potential of genomics to diagnose rare disease, such as CLN2, more quickly, will improve the quality of life of thousands of patients and their families. Ongoing research and funding will contribute to the diagnosis and management of rare diseases.

3.3 Benefits in treatment

In addition to enhancing screening and diagnostic processes, genomic medicine is also used to improve the treatment of disease and care of patients. As noted in Section 2.2.2, genomic knowledge can be applied to understand how medicine interacts with inherited genes. PGx is a form of genetic testing that looks for small variations within genes to assess how these genes may affect a person's response to specific drugs, and may contribute to the chance of side effects. Test results help the doctor choose the safest and most effective drug and dose.

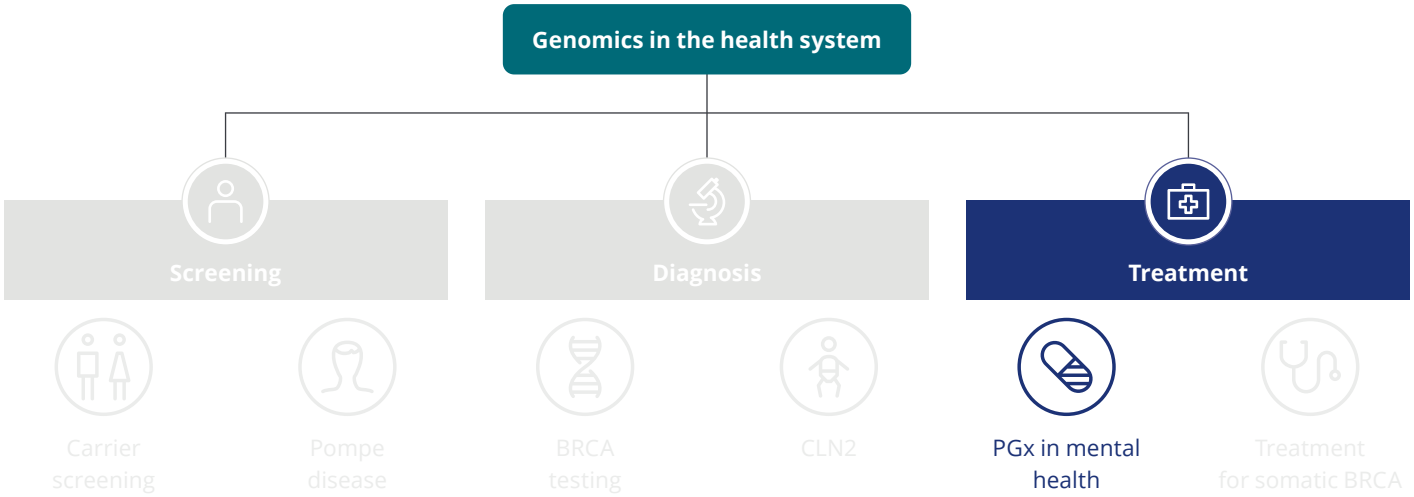
For patients and family/carers, improved treatment efficacy results in improve quality of life, as well as improved safety from a reduction in adverse side effects. In addition, patients and their families/carers achieve personal utility from receiving more timely and efficacious treatment.

For the health system, by eliminating the trial and error approach to prescribing, genomics-guided treatment choices will minimise drug waste, thereby reducing costs on the health system and government. This application also serves to reduce adverse side effects due to therapeutic toxicity, which may result in hospitalisations. Further efficiencies are realised in the form of longer-term cost-savings to the health system, as patients remain healthier and are less reliant on health services.

For the genomics industry, benefits include improved research and development output, a potential increase in the number of successful clinical trials for new treatments and timeliness of market approval, and development of new therapeutic applications for existing drugs.

For society, similar benefits to those described in Section 3.2 are achieved, as healthier patients improve workforce participation (among both patients and their families/carers), which results in productivity benefits for society as a whole.

These benefits are profiled at a more granular level in the following sections which use case studies to explore the incremental costs and benefits of using genomic testing to guide treatment choice relative to standard approaches to drug selection.



3.3.1 Pharmacogenetics for depression

PGx allows for the possibility to personalise medication and treatment to improve efficacy and decrease side effects for patients. One of the significant applications of PGx is for people with major depressive disorder (MDD). MDD describes people who experience sadness and depression for extended periods of time, affecting the person's everyday life. It has been estimated that 1 in 5 women and 1 in 8 men will experience MDD at some point in their lives.[64] The Institute for Health Metrics and Evaluation reported a prevalence of MDD in Australia of almost 900,000 people.

While there are many different antidepressant medications available, these have varying levels of efficacy and side effects for different people. PGx research has established an understanding of how variants in genes coding for the cytochromes involved in antidepressant metabolism (CYP2D6 and CYP2C19) affect a person's response to antidepressant medication. For example, metabolism of medications by these enzymes affects the drug levels in the blood. A poor metaboliser for a drug will ultimately lead to high drug blood levels which increases the potential for side effects.[65] Adverse reactions of antidepressant drugs may include bleeding, cardiovascular side effects, dry mouth, gastrointestinal side effects, hepatoxicity, seizure, suicidality, sexual dysfunction, weight gain and others.[66] A meta analysis of randomised controlled trials suggests that PGx guided antidepressant treatment produces superior clinical outcomes than heuristic trial and error prescribing.[67]

Australians have access to an extensive range of genetic tests, including PGx.[68] PGx tests detect clinically important genetic variants that affect drug metabolism – information which can be used to predict whether a drug is likely to be effective for a patient. PGx tests can by requested by any medical practitioner and will cost the patient two hundred dollars out of pocket.[69] However, the uptake of these tests is limited, with most general practitioners not trained to understand how PGx tests are generated and how this enhances prescribing guidance.[70] This presents a challenge for the widespread implementation of PGx into the health system. The following case study profiles a scenario where GPs appropriately identify when PGx testing is an option and are informed in how to interpret/act on the information when selecting drug treatment for a patient.

Methodology

This case study focuses on the effectiveness of combinatorial gene testing (CPGx), which is the approach of combining genetic markers to present a more complete picture of a patient. Compared to individual gene testing which reveals specific information about a single gene and may only be relevant to select medications, CPGx attempts to encompass more complete genomic information by combining moderate risk alleles and synergistically viewing these results from the perspective of the medication.[71]

CPGx tests involve an initial swab of the inside of a person's cheek, with the sample sent to the lab for analysis. Results from the sample are typically available after 2 days. The test looks at both pharmacokinetic Genes[x] and Pharmacodynamic Genes.[xi] These genes are then evaluated with respect to more than 60 different medications. This information is then provided to doctors, who are able to make an informed decision on which drug to prescribe to the patient. Previous studies on CPGx testing have reported statistically significant increases in response and remission rates for patients with CPGx guided treatment choices compared to those with standard drug selection (ie. no genetic testing).[72]

[x] Pharmacokinetic genes give information as to how a patient's body will break down medication. The genes evaluated include CYP2D6, CYP2B6, CYP2C19, CYP1A2, CYP2C9, UGT1A4, CYP3A4, UGT2B15, CES1A1.

[xi] Pharmacodynamic Genes give information as to the likelihood of response to and/or the risk of side effects for certain medications. The genes evaluated include SLC6A4, HTR2A, HLA-A*3101, HLA-B*1502, ADRA2A.

The case study assumed a cohort of 75,000 Australians would receive CPGx guided treatment instead of the standard approach to drug selection. The cost of testing was assumed to be $2,700.[73] Outcomes were modelled over a five year time horizon, from both a health system and a societal perspective. It was assumed that CPGx guided treatment would lead to increased rates of remission, and lower rates of relapse, based on outcomes from clinical trial data.[71] For example, the first year of CPGx guided treatment was modelled to result in more than 14,000 people alive and in remission, compared with 9,600 in the usual care arm. It was assumed that CPGx guided drug selection for MDD increased the chance of a drug being effective in moving a patient into remission and reducing relapse for 3 years post-test, relative to standard testing.[74] After this time, it was assumed that the standard approach to drug selection would be just as effective.

Additional details on the model structure and inputs used are provided in Appendix B.

Results and discussion

Over a five year period, in a cohort of 75,000 people tested, CPGx guided treatment was expected to provide 7,600 additional QALYs, or 0.1 QALYs per person, when compared with the standard approach to drug selection. This improvement to quality of life was generated from an increased chance of being in remission and lower rates of death (driven by lower rates of suicide). From a health system perspective, the intervention was highly cost effective, with an ICER of $9,465 per QALY gained. Other international literature has found that CPGx may be cost saving to the health system.[71] Health system costs included drug costs, consultations with general practitioners and counsellors, emergency department presentations and hospitalisations. CPGx was modelled to reduce costs to the health system by almost $1,800 per patient receiving CPGx over the model time horizon.

From a societal perspective, CPGx guided treatment was found to be cost saving, by generating an estimated $167 million in productivity savings over the model time horizon, for the cohort of 75,000 people tested.

Table 3.11: Base case and one-way sensitivity analysis for cost-effectiveness of CPGx guided drug treatment for people with depression relative to standard drug selection, hypothetical cohort of 75,000 patients, health system perspective and societal perspective

	Standard testing cost ($)	Genomic and standard testing cost ($)	QALYs gained	Cost per QALY gained ($)
Base case (health system perspective)	1,358	1,430	7,645	9,465
High rates of remission (+50%)	1,246	1,293	7,928	5,986
Low rates of remission (-20%)	1,403	1,497	6,534	14,277
Base case (societal perspective)	2,341	2,246	7,645	Cost saving

Source: Deloitte Access Economics calculations.

CPGx has significant potential to improve outcomes for people with MDD in Australia. The intervention could have a wide-ranging impact, with almost one million Australians affected by MDD in any given year. When accounting for the significant productivity impacts MDD can have, the intervention is cost saving. Work productivity costs due to depression totalled more than $8,000 per person in Australia in 2007.[75] Based on international evidence of the productivity impacts of depression, the costs of absenteeism and presenteeism alone may total more than $10,000 in 2020.[76] The post pandemic period is likely to see a spike in cases of MDD.

The modelling considered a conservative productivity improvement which included a 14 day reduction in absenteeism and an 11 day reduction in presenteeism per year for individuals in remission. Individuals in remission were estimated to improve productivity by $3,700 each year when accounting for their average earnings and their likelihood of being employed. At the end of the five-year time horizon, 12,000 additional people were in remission under CPGx guided treatment – each of whom capable of contributing additional productivity improvements to society.

A summary of the key clinical, economic and social benefits of CPGx to guide treatment for depression relative to standard drug selection is provided in Table 3.12.

Table 3.12: Summary of the key clinical, economic and social benefits of CPGx guided drug treatment for people with depression relative to standard drug selection

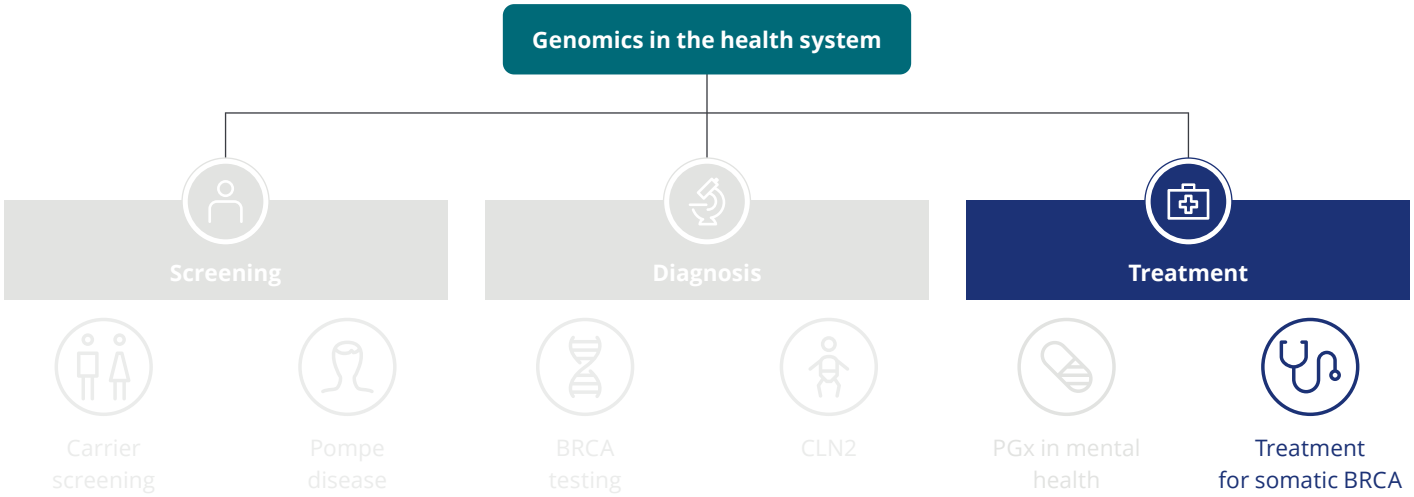
Benefit	Outcome
Clinical benefits	
Improved remission rates	CPGx guided drug treatment for patients with depression leads to significantly higher remission rates when compared with standard approaches to drug selection. Over a model period of five years, 48% of the starting population were alive and in remission after receiving CPGx guided treatment. Comparatively only 32% of the starting population were alive and in remission in the usual care arm. In a hypothetical cohort of 75,000 patients tested, CPGx guided drug selection was estimated to prevent 11 suicides and improve the number of people in remission by 12,000 at five-year follow-up.
Reduced rates of relapse	Patients receiving CPGx guided treatment are more likely to remain in remission. Based on clinical trial results, annual relapse rates under CPGx guided treatment were estimated to be 9.9% compared to 18.9% under standard care.
Other economic and social benefits, by stakeholder beneficiary	
Individuals	CPGx guided drug selection for people with depression improves remission rates, and thereby facilitates improved quality of life and life expectancy relative to standard approaches to drug section. Over a five-year time horizon, CPGx guided drug selection relative to standard drug selection was estimated to gain: • a total of 7,600 QALYs in a hypothetical cohort of 75,000 people tested, or • 0.1 QALYs per person tested.
Health system	In a hypothetical cohort of 75,000 tested, CPGx guided treatment was estimated to cost an additional $205 million in testing costs. However, these costs are partially offset by the downstream health system cost savings when accounting for the reduction in hospital admissions, emergency department presentations and GP or specialist visits. Over a five-year period, the model estimated that CPGx guided drug selection relative to standard drug selection saves the health system: • a total $132 million in treatment costs, discounted to the year 2021, in a hypothetical cohort of 75,000 tested, or • $1,750 per person tested.
Society	Individuals who are able to remain in remission after receiving CPGx guided treatment are more likely to be more productive at work. Measured by the number of days a person takes off work (absenteeism) and a person's lost productive time while at work (presenteeism), it was estimated that, over a five-year period, CPGx guided treatment could improve productivity by $2,230 per person tested relative to standard drug selection. For a hypothetical cohort of 75,000 people receiving CPGx guided drug treatment, this equated to approximately $167 million in productivity savings over the five-year time horizon, discounted to the year 2021.

Box 8. Combinatorial gene testing (CPGx) to guide treatment of depression compared to standard drug selection – key takeaways

This case study assessed the cost effectiveness of providing CPGx to guide drug selection for patients with MDD. This was compared to standard drug selection. The CEA was performed over a five year time horizon, evaluated from a both a health system and a societal perspective.

CPGx guided treatment of patients with MDD was a cost-effective intervention in the base case, estimated to be cost saving from a societal perspective as compared with standard drug selection. Over a five-year period, of 75,000 patients tested, CPGx guided drug selection was estimated to prevent 11 suicides and improve the number of people in remission by 12,000.

This case study demonstrates the significant value that PGx could have for guiding treatment of MDD in Australia. The recent investment in PGx mental health research as part of the Medical Research Future Fund is a positive step in accelerating the shift toward use of PGx to guide prescribing decisions for mental health patients in Australia.



3.3.2 Breast cancer gene 1 and 2

Another application of PGx is in the context of treatment choice for metastatic cancer patients, based on an understanding of BRCA1 and BRCA2 mutation. Mutation of BRCA1 and BRCA2 can increase the risk of several cancers most notably breast, ovarian, prostate and pancreatic cancer.[77] In normal cells, DNA repair during cell division involves BRCA1 and BRCA2 proteins. However, in people who have mutations in BRCA1 and BRCA2 genes, DNA repair is mediated through alternative pathways and involves a protein called poly (ADP-ribose) polymerase (PARP). Treatments exist that stop PARP enzymes from repairing DNA, leading to cancer cell death.

In Australia, olaparib is listed on the PBS for treatment use for metastatic ovarian patients with a germline BRCA mutation, and for patients receiving maintenance therapy.[78] Olaparib is also used to treat patients with somatic BRCA mutation and metastatic cancers of the prostate, pancreas and breast, though its use in these conditions are not listed on the PBS. The benefits of prolonged progression-free survival in patients with somatic BRCA mutations have shown to be similar to that of the germline BRCA cohort through the use of olaparib.[79] Confirmation of BRCA1 and BRCA2 mutation through genetic testing will allow patients to undergo olaparib treatment, which has been found to be a cost-effective treatment in metastatic pancreatic cancer. For example, in one study, metastatic pancreatic cancer patients treated with olaparib produced an additional 9 QALYs compared with patients on placebo maintenance therapy and yielded an ICER of $13,327 per QALY gained.[80]

In men with metastatic castration-resistant prostate cancer (MCRPC), despite effective treatment options such as hormone therapy, the prognosis is still poor with overall survival ranging from 9 to 13 months.[19] Previous cost-effectiveness modelling indicates that olaparib yielded an additional 0.100 overall life years and 0.063 QALYs in patients with MCRPC which had at least one gene alteration in BRCA1, BRCA2 and ATM compared to men assigned to standard care (hormone therapy).[81] Olaparib treatment led to an ICER of $116,903 per QALY gained, indicating that although the treatment arm was costly, it also incurred more benefits in the form of progression-free disease to the patient.

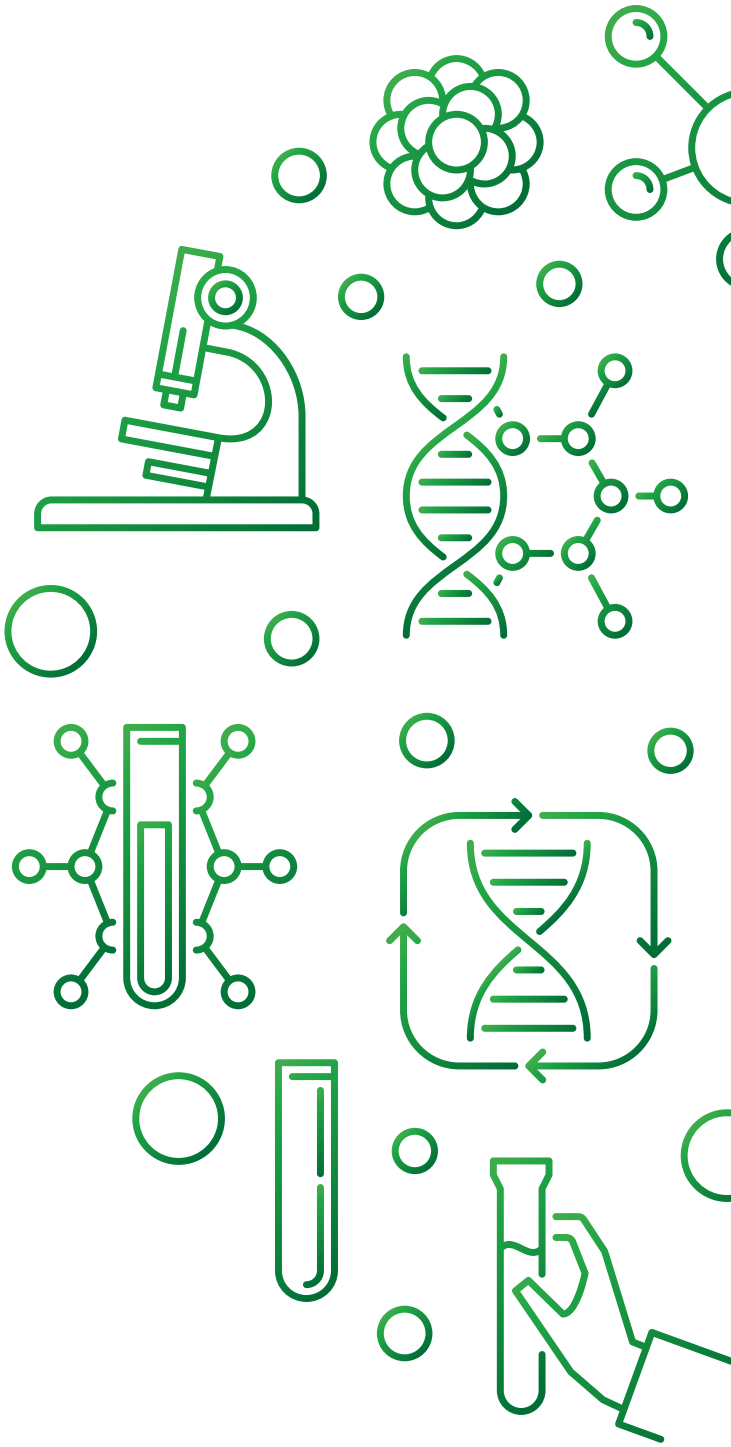
This evidence shows there are benefits to genetic testing for BRCA mutations outside of traditional applications in screening for germline risk of breast and ovarian cancer. There is value in using genetic testing to assess for somatic and germline BRCA mutations in metastatic cancer patients across a variety of tumour types to enhance the efficacy of treatment choices.

Box 9. Application of PGx to guide the treatment choice for metastatic cancer patients with BRCA gene mutations – key takeaways

This case study summarised literature to highlight the benefit of genetic testing for BRCA mutations outside of traditional applications in testing for germline risk of cancers.

Treatment with olaparib is confirmed through genetic testing of BRCA gene mutations. Published CEA findings indicate olaparib treatment is a cost-effective treatment in metastatic pancreatic cancer patients. Although by traditional WTP thresholds olaparib treatment is not cost-effective in prostate cancer, it still incurs benefits in the form of progression-free disease to metastatic prostate cancer patients.

There is value in using genetic testing to assess for somatic and germline BRCA mutations in metastatic cancer patients across a variety of tumour types to enhance the efficacy of treatment choices.



4. Implementation and considerations

This chapter provides an overview of the key actions required to achieve the full potential of genomics and successfully integrate it within the Australian health system.

The analysis presented in Chapter 3 provides a strong clinical and economic case for further investment and focus on embedding genomics within the Australian health system. Noting that the analysis presented in this report only provides a snapshot of the true value that genomic medicine offers Australia.

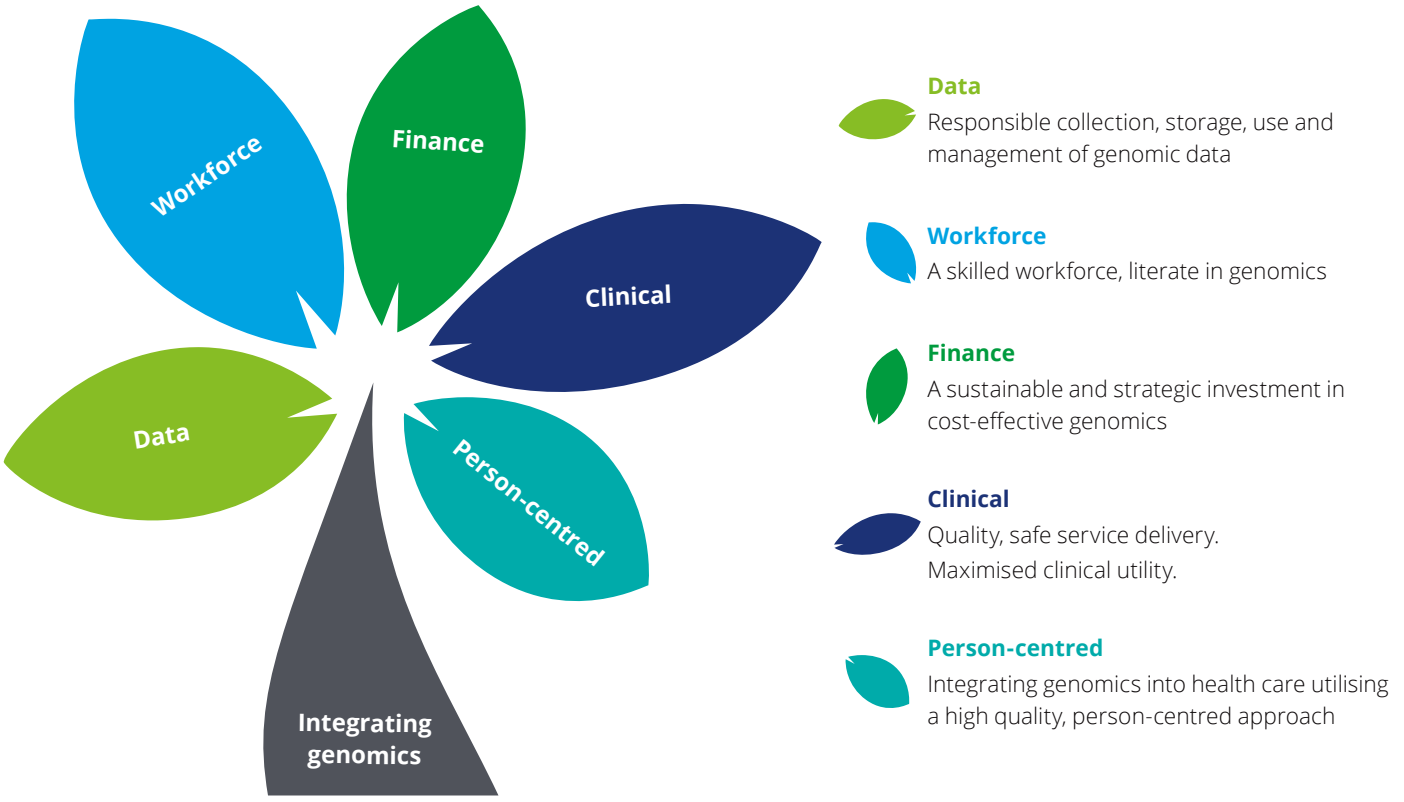
The genomics health ecosystem is extremely complex, involving multiple different types of industry players, providers (such as laboratories and hospitals), researchers, government bodies and most importantly, consumers of healthcare and their families/ carers. The implementation of genomic applications in the health system is equally complex, requiring a range of advances in technology, workforce, policy, community awareness, and funding mechanisms. A suite of recommendations that serve to guide the successful integration, maintenance, and delivery of genomics within the health system are outlined in Section 4.1.

4.1 Recommendations for integrating genomics in Australia

A national and coordinated approach to genomic medicine is key to the successful implementation and integration within the health system. The National Health Genomics Policy Framework highlights the importance of collaborative partnerships between health, academic, industry and government stakeholders, both nationally and internationally, to address the most important issues and meet the future age of genomics. The Framework outlines five strategic priority areas considered essential to harness the health benefits of genomic knowledge and technology into the Australian health system (see Figure 4.1).

The recommendations detailed below are based on insights gleaned through consultation with key opinion leaders and align with each of the priority areas identified in the Framework.

Figure 4.1: Priority areas for integrating genomics into the Australian health system



Source: Deloitte Access Economics using National Health Genomics Policy Framework (2018).

1. Enable cost-effective and efficient use of finances by adapting existing health technology assessment approaches and pathways.

Finance should be targeted toward cost effective technologies that achieve the best outcomes for Australians, while providing value for money. This report highlights that many potential diagnostic applications of genomics in healthcare are cost-effective and/or provide significant clinical benefit relative to standard practice.

To ensure these technologies are accessible to all Australians, regardless of circumstance or background, approval by health technology assessment (HTA) bodies is critical. However, current HTA systems need to adapt to the unique complexities of genomic technology and precision medicine. This report has shown that the clinical and economic benefits of genomics are broad and diverse, and often fall outside of the traditional metrics evaluated by HTA bodies in Australia, such as survival end points and cost per QALY evaluated only from a health system perspective. Metrics more relevant to genomic technologies, particularly in a rare disease context, include:

- time to diagnosis
- time to effective treatment
- prevention/onset delay
- cost per QALY, evaluated from a societal perspective (i.e. including productivity costs for patients and informal carers).

There is an evolving need for new metrics and approaches that build out the tools to quantifying these benefits, as well as a need to adapt HTA guidelines to accommodate their use.

Other factors unique to genomic technologies that limit approval under existing HTA guidelines include: smaller patient cohorts for rare diseases; lag time in realisation of clinical outcomes that often require real world evidence; and increased utility over time as more clinical data is gathered and mutations are identified.

2. Develop education and awareness campaigns in partnership with consumer groups and the broader ecosystem to build public understanding of genomics.

Creating evidence-based information and education materials for consumers will contribute to building community understanding of genomic medicine and its use across the care pathway, particularly for preventive purposes. Greater understanding of genomic medicine and technology will enable early patient engagement. Dedicated resources should also seek to explain genetic test results to ensure patients can make informed decisions as part of care planning.

3. Continue to build the genomics workforce, by offering ongoing education and training to existing health professionals.

Support the ongoing development of resources for upskilling of health professionals which are flexible to adapt to the changing and evolving nature of genomic medicine. For example, as outlined in the PGx in mental health case study, one of the barriers to widespread implementation of PGx in Australia is the interpretation capability by prescribing healthcare professionals. Developing guidelines and protocols, alongside creating awareness and effective education will support health professionals to build their genomic knowledge and capabilities and enable widespread integration of genomic technology into the health system.

In addition to capability, there is also a need to build the capacity of the genomic workforce. This may require the introduction of appropriate incentives to achieve an appropriately sized workforce to meet growing demands in genetic counselling, genetic pathology, bioinformatics, clinical trial design and execution and cybersecurity. Early introduction of genomic and other multi-omic sciences in higher education streams will create new talent pathways and prepare Australia's future workforce and leaders in this field.

Integration of genomics across the health system requires partnerships and networks to promote and support sharing of knowledge and to build a multidisciplinary team across the health system. This could be supported through establishing partnership workforce arrangements, through secondments and mentorships between industry and public and private sectors.

4. Establish national standards for data collection, storage, analysis and sharing to be accessible to those who require it, while ensuring privacy, consent and confidentiality remain a priority.

Data will need to be available to health professionals so that they have the requisite information about the patients they care for. Key to this will be centralising storage of genomic information on an accessible national database to enable genomic data to be reinterrogated and avoid duplication of testing. This will also be aided by a transition towards using large panel testing over individual tests which would reduce the number of tests required and streamline the data storage process.

Researchers should have access to de-identified genomic data with the purpose of improving the diagnosis of rare diseases, understanding the causes of these diseases and ultimately developing new treatments that better target the genetic basis of disease based on real world evidence. Access to data should also extend beyond health practitioners and researchers, to include sponsors of medical innovations. This will enable sponsors to develop evidence-based health technology assessment submissions (e.g. in the same way they can currently access PBS and MBS data).

To ensure that genomics data is available to health professional and researchers, while maintaining the confidentiality and consent of patients, there will likely need to be legislation outlining global best practice on data sharing practices, sharing of data across geographic boundaries and dynamic patient consent. Further, significant investment and infrastructure will be required to ensure data linkage and data sharing is available, both nationally and internationally.

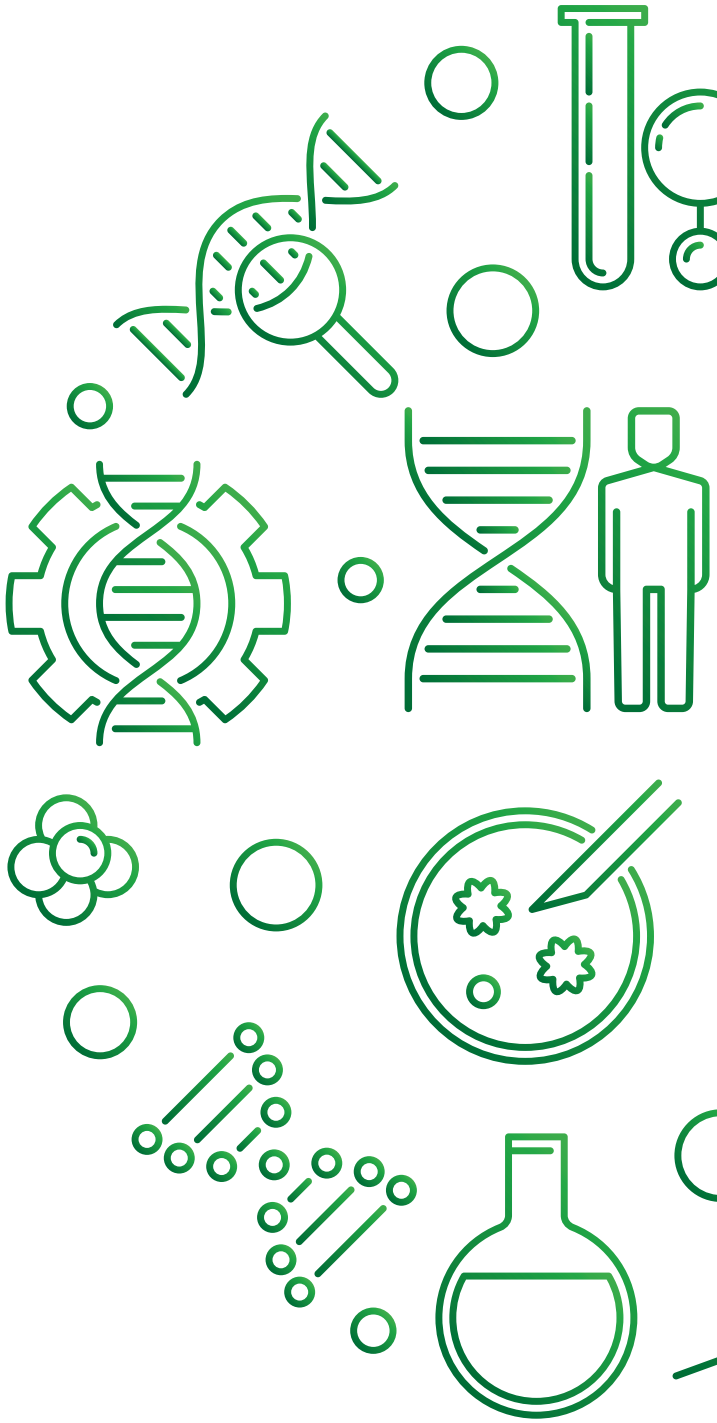
5. Promote centres of excellence to drive research agendas and set the standard for best-practice across the sector.

Centres of excellence (CoE) provide the opportunity to accelerate innovation by bringing together multidisciplinary leaders in the field across Australia. CoEs could serve to ensure a nationally consistent approach to guidelines, regulations and standards, with a view to supporting the quality and safe use of genomics in healthcare. A CoE should be established to report on the long-term return on investment of funded genomics technologies in Australia on behalf of the Department of Health. Further, CoEs could be used to set research priorities based on emerging evidence in the clinical literature and the needs of the Australian population, and advocate for initiatives such as projects similar to the 100,000 Genome Project in the UK.

A current example in Australia is the Centre for Population Genomics, which aims to solve the critical scientific, regulatory, and technical problems currently limiting the development of genomic medicine in Australia.[82]

6. Advocate for national uniform legislative frameworks which will support the implementation of policy surrounding the integration of genomics within the health system.

Key stakeholders across the sector such as government, researchers, and industry currently operate in siloes, which is impedes progress. Policy could inform consistent data collection and storage to allow for streamlined knowledge sharing within the sector. Policy can also be used to develop consistent guidelines across genetic laboratories, guidelines related to using PGx to inform prescribing, and in ensuring the translation of research to clinical settings through implementation science principles. National uniform legislative frameworks detailing the rights and responsibilities of people and organisations will ensure harmonisation of services, while protecting those whom the legislation applies.



Appendix A – Cost-effectiveness methodology

A cost-effectiveness analysis is performed to assess the value for money of a particular intervention. A cost-effectiveness analysis calculates the incremental net costs and benefits of an intervention relative to a comparator, by providing evidence to answer the question – *do the extra benefits outweigh the extra costs?*

Two perspectives were used in the case studies to evaluate cost-effectiveness. A *health system perspective* evaluates the change in health system costs relative to the change in QALYs. A *societal perspective* includes the change in health system costs but also factors in changes to productivity. Productivity changes include costs such as absenteeism, presenteeism or informal care. A societal perspective was only adopted for the case studies where reliable inputs were readily available.

In each case study, a cost-effectiveness analysis model was construed to assess the value of different genomics applications relative to current practice. A cost-effectiveness analysis model is structured using a series of "branches", which represent the progression through the model by a hypothetical cohort of people. A model was developed for each of the case studies, which are shown in this chapter by case study. Each of the five case studies utilised either a decision tree or a decision tree coupled with a Markov model.

A decision tree models decision points and their possible consequences. At each "fork" in the model, the cohort is split into a variety of potential model pathways, depending on the probabilities assigned to each of the branches which split off from the fork. Each model contains the following nodes:

- **decision node (represented by rectangles)** – each model begins with a decision to place the hypothetical cohort in the intervention model arm or the comparator model arm.
- **chance nodes (represented by circles)** – the cohort progresses through the branches of the model according to the probabilities at each node. For example, in carrier screening, a couple has a chance of being an 'at risk' couple based on the estimated prevalence rate of at risk couples. Similarly, if that couple proceeds with conception, their child is assigned probabilities of having a genetic condition or not.
- **end nodes (triangles)** – represent the end period outcomes for the total patient cohort in terms of costs and disutility.

A Markov process within a cost-effectiveness analysis model represents a series of transitions through the model which take place over a defined period of time, where the cohort in the model "loops" through the model a set number of times depending on the time horizon for the model and the length of each cycle.

For example, in a model with a five-year horizon and a cycle length of one year, the cohort would loop through the Markov component of the model five times, before the model concludes and the outcomes are evaluated. The changes in health states in the model are determined by the "transition probabilities", which reflect the probability of a new health state based on the present health state.

The model pathways and time horizons are bespoke to each case study, as they are selected to the reflect the specific course of disease, impact of the intervention, and the available data. Note that each model pathway and time horizon is consistent with previous cost-effectiveness analyses in the literature related to the intervention of interest.

Costs and QALYs are applied to each state to determine the costs and outcomes associated with a person living in a given health state. Costs and QALYs are accrued over time as each person in the cohort cycles through the model. A five percent discount rate was used. All case studies utilised a health system perspective, which meant they included the following costs include:

- costs associated with screening, diagnosis or treatment using genomics
- costs associated with comparator screening, diagnosis or treatment
- other medical treatment costs utilised over the time horizon of the model, including costs from genetic counselling, general practitioner visits, and visits to other specialists, drug costs, surgeries, emergency department presentations and hospitalisations etc.
- costs associated with informal care providers by families/carers over the time horizon of the model (only included in the Pompe disease case study).

Discounted costs and QALYs are summed in both the intervention arm and the comparator arm, and the compared. Results are then reported in the form of an ICER. This ratio is calculated as the difference between the discounted costs of the two simulations, over the difference between the discounted QALYs. It is interpreted as the additional cost required to gain one QALY. If this value if less than approximately $50,000, the use of genomics is considered cost-effective based on common willingness to pay thresholds. For each model one-way analysis was undertaken to determine the impact that variation in a single parameter has on the overall cost effectiveness of the intervention. This analysis was performed by allowing key parameters to vary individually from their base value.

Appendix B – Case study model details and inputs

An overview of the approach and key inputs used to inform each of the cost-effectiveness analyses presented in the report is provided below.

The five case studies include:

- B.1 – Preconception expanded carrier screening
- B.2 – Newborn screening and genetic testing for infantile onset Pompe disease
- B.3 – Genetic testing for BRCA1 and BRCA2 mutations in patients with breast cancer and their families
- B.4 – Genetic testing to confirm a diagnosis of one form of childhood dementia, CLN2, when symptoms first present
- B.5 – Combinatorial gene testing to guide drug selection for patients with MDD.

B.1. Carrier screening

This case study estimates the potential benefits of expanded carrier screening, using next-generation sequencing to screen for 176 conditions. Unlike traditional carrier screening, expanded carrier screening tests for as many genetic carrier mutations as is practically possible. As a result, expanded carrier screening may detect additional carriers of a genetic condition that would not be found using traditional screening. Table B.1 details the most prevalent genetic conditions included in this approach.

Table B.1: Most common genetic conditions with carrier screening (number of births per case)

Condition	Number of births per case
Hb beta chain-related hemoglobinopathy	2,174
Cystic fibrosis	2,511
Fragile X syndrome	2,939
Dystrophinopathy (including Duchenne/Becker muscular dystrophy)	3,571
GJB2-related DFNB1 nonsyndromic hearing loss and deafness	6,191
Phenylalanine hydroxylase deficiency	8,683
Congenital adrenal hyperplasia	10,230
Spinal muscular atrophy	10,879
Smith-Lemli-Opitz syndrome	12,243
Fabry disease	12,861

Source: Deloitte Access Economics estimates based on Beauchamp et al (2019).

Model overview – The purpose of this cost-effectiveness analysis was to determine if preconception carrier screening is a cost-effective approach to detecting carriers of genetic conditions relative to no screening. Cost effectiveness was evaluated from a health system perspective, over a lifetime, one year and five year horizon. While the target population is all women aged 18 to 44, this model presents the cost-effectiveness for a hypothetical cohort of 300,000 women.[xiii] Carrier screening was assumed to detect up to 176 genetic conditions.[18]

Model structure – A decision-tree model was constructed using Microsoft Excel to analyse the patient pathways with and without screening. Couples identified as 'at risk'[xiv] were offered genetic counselling, and based on their results chose to proceed with conception (base case = 50 per cent), proceed with a reproductive intervention (base case = 30 per cent), or not proceed with conception (base case = 20 per cent).

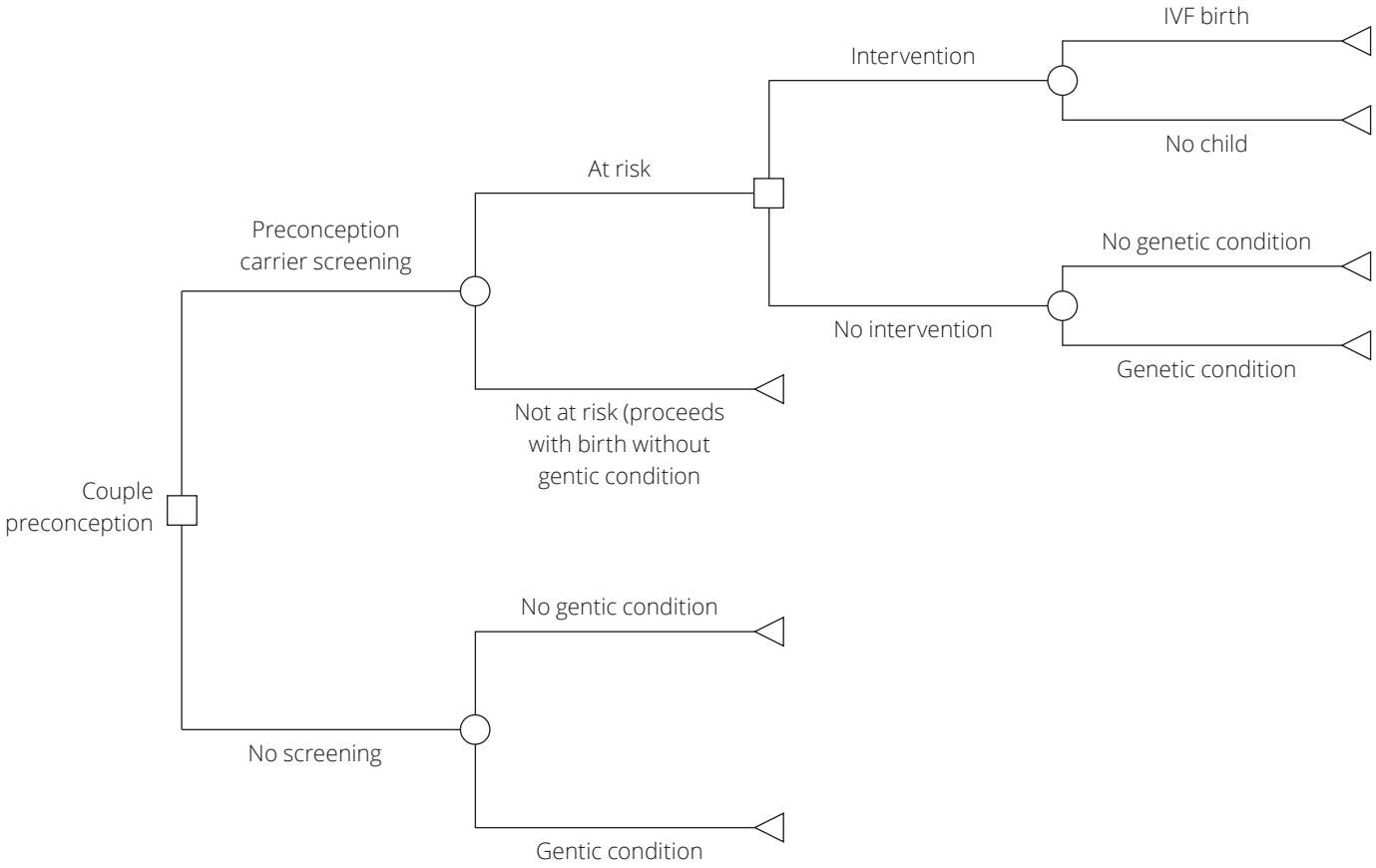
[xiii] There are approximately 300,000 births in Australia each year, so genetic carrier screening is assumed to be relevant to approximately this many couples each year.

[xiv] At risk couples have a 25 per cent chance of giving birth to a child with a severely debilitating or life limiting genetic condition.

Health benefit measurement – The primary measurement was the number of children born with and without severely debilitating or life limiting genetic conditions in both model arms. The model measured the number of children who are born healthy with reproductive interventions where otherwise this child would have had a severe genetic disorder without screening. QALYs were used to estimate the improvement in quality of life resulting from less children born with these genetic conditions. QALYs were based on the estimated life years lost for each of the 176 genetic conditions, based on the utility values by condition reported in Beauchamp et al.[18]

Cost measurement – Health system costs were based on the lifetime resource utilisation for each condition, informed by a literature survey undertaken by Beauchamp et al on average healthcare resource utilisation associated with each of the 176 genetic conditions.[18] All estimates were converted to 2021 AUD.

Figure B.1: Carrier screening decision tree



Source: Deloitte Access Economics analysis. Adapted from Beauchamp et al (2019).

B.1.2. Model inputs

Table B.2: Model inputs for carrier screening

Input type	Model input	Source
Population	300,000	ABS (2021)[20]. This is the approximate number of births each year which has been used as a proxy for the number of couples who would receive genetic testing in a given year.
Proportion of at risk couples	1.2%	Beauchamp et al (2019)[18]
Disease risk	0.3%	Beauchamp et al (2019)[18]
Probability of conceiving at risk (at risk couples)	50%	Azimi et al (2016)[83]
Probability of pursuing assisted reproduction (at risk couples)	30%	Azimi et al (2016)[81]
Probability of not pursuing conception (at risk couples)	20%	Azimi et al (2016)[81]
Cost of carrier screening	$1,054	Estimated cost of screening from *Mackenzie's Mission*. Includes costs associated with genetic counselling.
Annual health system cost of an affected birth	$161,200	Based on the weighted average annual cost of 176 conditions. Beauchamp et al (2019)
Average life years lost for an affected birth	26 years	Based on the weighted average life expectancy of an affected birth compared to the life expectancy of a normal birth. Beauchamp et al (2019)[18]
Cost of IVF	$10,000	IVF Australia (2020)[84]

Source: As noted. Deloitte Access Economics calculations.

B.2. Pompe disease inputs

Model overview – The purpose of this cost effectiveness analysis is to determine if NBS is a cost-effective means to diagnose cases of infantile onset Pompe disease. This was compared with clinical diagnosis which is often delayed. Cost effectiveness was evaluated from a societal perspective, over a ten-year time horizon. The target population was all newborns in Australia (approximately 300,000).

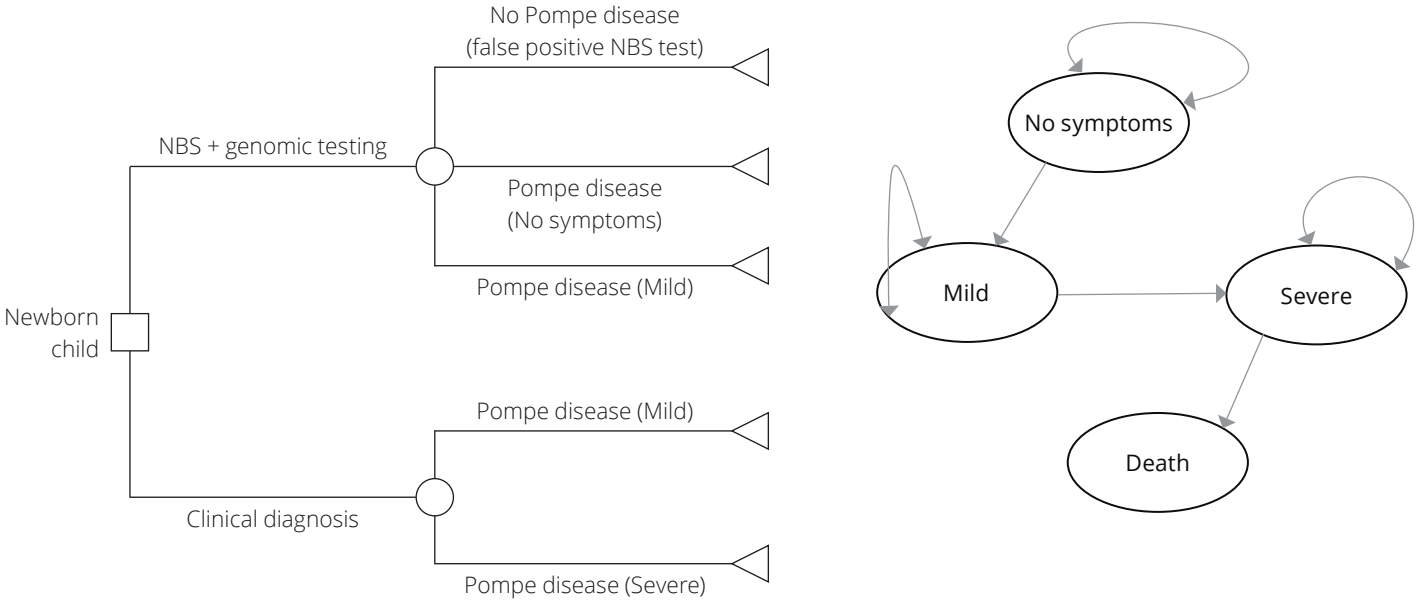
Model structure – A Markov model constructed in Microsoft Excel was used to analyse patient progression over a ten year time horizon using a one year cycle length. It was assumed that patients diagnosed with NBS achieved a better starting state and a lower probability of developing severe complications from Pompe disease. The transition probabilities were based on an existing cost effectiveness analysis by Richardson et al.[31] Due to the low rates of natural death at this age, all mortality was assumed to be attributed to infantile onset Pompe disease. It was assumed that death from Pompe disease would only occur after first progressing to severe Pompe disease.

Health benefit measurement – The modelling measured the change in QALYs, assuming changes to quality of life were dependant on the person's current health state. Patients with no symptoms were not attributed any reduction to quality of life, while utility values for mild Pompe disease were 0.799 (characterised by mechanical ventilator free survival) and 0.399 for severe Pompe disease (characterised by mechanical ventilator dependant survival). QALY values by severity of condition were sourced from the values reported in Richardson et al.

Cost measurement – Health system resource utilisation was predominantly driven by the estimated cost of ERT, but also the expected health system utilisation for mild Pompe and severe Pompe disease. This included visits with specialists, other medications, emergency room presentations, laboratory tests and additional procedures. These costs were informed using the MBS and Richardson et al[31], with costs converted to AUD 2021, where appropriate.

In conducting the modelling from a societal perspective, the productivity costs of care requirements were included based on the expected number of hours of formal and informal care required. A human capital approach was used, with the total cost of an hour of care based on the carer's expected wage (after taking into account the chance of being employed).

Figure B.2: Pompe disease decision tree and Markov model



Source: Deloitte Access Economics. Adapted from Richardson et al (2020).

B.2.2. Model inputs

Table B.3: Model inputs for Pompe disease

Input type	Model input	Source
Newborn population	305,832	ABS (2021)[20]
Pompe disease prevalence	1/27,800	Prosser et al (2018)[32]
Proportion of infantile onset Pompe disease	28%	Prosser et al (2018)[32]
Transition probabilities	Various	See Richardson et al (2020)[31]
QALYs for Mild Pompe disease	0.799	Richardson et al (2020)[31]
QALYs for Severe Pompe disease	0.399	Richardson et al (2020)[31]
Enzyme Replacement therapy cost	$200,000/year	Denaro and Martin (2016)[85]
Diagnosis delay in clinical arm	0.33 years	Modelling assumption
NBS screening cost	$10	Richardson et al (2020)[31]
Additional genetic screening for positive tests	$3,462	Richardson et al (2020)[31]
Mild Pompe disease other health system costs	$41,862	Including visits with specialists, other medications, emergency room presentations, laboratory tests and additional procedures. See Richardson et al (2020).[31]
Severe Pompe disease other health system costs	$184,470	Including visits with specialists, other medications, emergency room presentations, laboratory tests, equipment, and additional procedures. See Richardson et al (2020).[31]
Informal care for Mild Pompe disease	14 hours/week	Richardson et al (2020[31]
Informal and formal care for Severe Pompe disease	24 hours/day	Richardson et al (2020)[31]

Source: As noted. Deloitte Access Economics calculations.

B.3. Breast cancer inputs

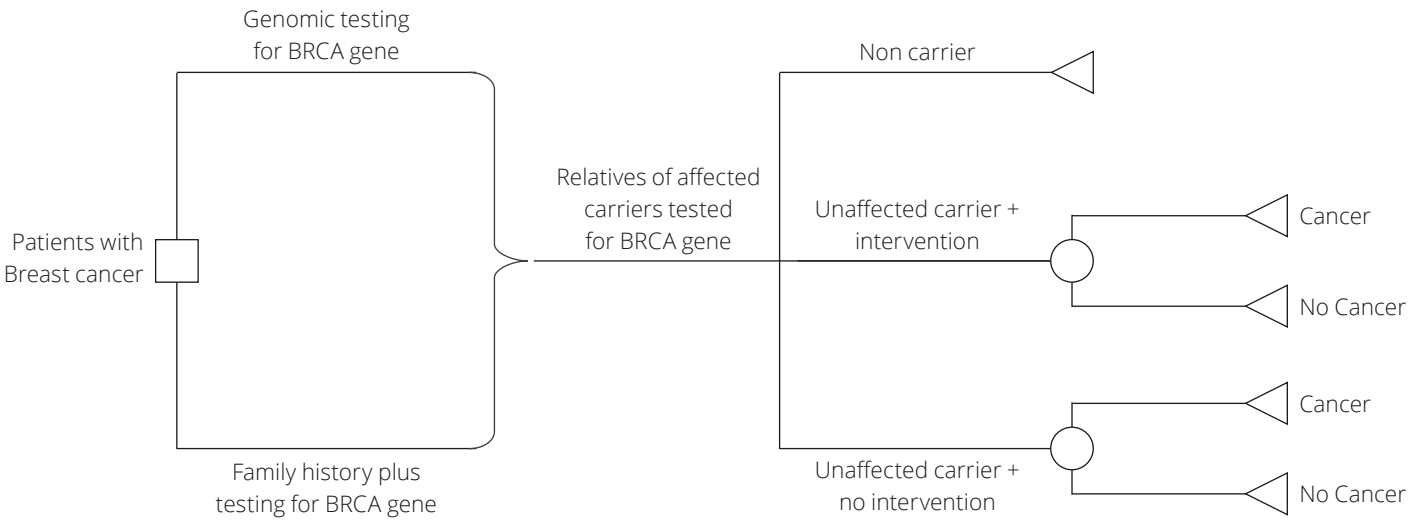
Model overview – The purpose of this cost effectiveness analysis is to determine if genomic testing of all breast cancer patients with subsequent cascade testing for relatives is a cost effective means to identify BRCA carriers and reduce the incidence of breast and ovarian cancer. This was compared to current testing, where only breast cancer patients with a greater than 10 per cent chance of being a BRCA carrier (based on FH) were tested. The modelling was conducted over a lifetime horizon, from a health system perspective.

Model structure – A decision tree model was constructed in Microsoft Excel to analyse the effect of BRCA genomic testing. Relatives who were identified as carriers of BRCA mutations who did not already have breast cancer (referred to as unaffected carriers) were given the option of RRM, RRSO or no intervention. RRM and RRSO were assumed to decrease the likelihood of an unaffected carrier developing breast or ovarian cancer. A lifetime Markov model with a cycle length of one-year was used to estimate the number of cancer cases and deaths that would occur with and without the intervention. Annual transition probabilities were used based on the lifetime cancer incidence rates for BRCA carriers, and the estimated reduction in cancer incidence from risk reducing procedures.

Health benefit measurement – The model measured the change in QALYs from the intervention, based on the reduction in the number of people who developed cancer, and the reduction in mortality that resulted. QALYs were adjusted to account for the disutility of risk reducing procedures in the first year. QALYs associated different cancer states (i.e. diagnosis year, continuing years, and terminal years) were drawn from the values reported in the Australian Institute of Health and Welfare's Burden of Disease Study.[86]

Cost measurement – Health system costs were based on reported cancer costs for breast and ovarian cancer, converted to AUD where appropriate.[86,90]

Figure B.3: Breast cancer decision tree



Source: Deloitte Access Economics. Adapted from Guzauskas et al (2020) and Sun et al (2019).

B.3.2. Model inputs

Table B.4: Model inputs for BRCA testing

Input type	Model input	Source
Yearly diagnosed cases of breast cancer	20,030	National Breast Cancer Foundation (2021)
Proportion of BRCA1/2 carriers	4.64%	Sun et al (2019)[41]
Number of unaffected carriers per affected carrier	1.44	Sun et al (2019)[41]
RRM risk reduction (breast cancer)	0.91	Sun et al (2019)[41]
RRSO risk reduction (breast cancer)	0.41	Sun et al (2019)[41]
RRM+RRSO risk reduction (breast cancer)	0.95	Sun et al (2019)[41]
RRM risk reduction (ovarian cancer)	0	Sun et al (2019)[41]
RRSO risk reduction (ovarian cancer)	0.96	Sun et al (2019)[41]
RRM+RRSO risk reduction (ovarian cancer)	0.96	Sun et al (2019)[41]
Probability of RRM	0.21	Sun et al (2019)[41], Guzauskas et al (2020)
Probability of RRSO	0.29	Sun et al (2019)[41], Guzauskas et al (2020)[86]
Probability of RRM + RRSO	0.26	Sun et al (2019)[41], Guzauskas et al (2020)[86]
Breast cancer survival (5 year)	91%	Cancer Australia (2020)
Ovarian cancer survival (5 year)	46%	Ovarian Cancer Australia
Disability weight – diagnosis year	0.13	Global burden of disease[84]
Disability weight – continuing phase	0.05	Global burden of disease[84]
Disability weight – terminal phase	0.52	Global burden of disease[84]
Genetic testing cost for BRCA1/2	$1,200	Medicare benefits schedule – Item 73296
Breast cancer costs – diagnosis year	$46,500	Goldsbury et al (2018)
Breast cancer costs – continuing phase	$5,100	Goldsbury et al (2018)[90]
Breast cancer costs – terminal phase	$49,200	Goldsbury et al (2018)[90]
Ovarian cancer costs – diagnosis year	$74,000	Goldsbury et al (2018)[90], Guzauskas et al (2020)[86]
Ovarian cancer costs – continuing phase	$9,300	Goldsbury et al (2018)[90], Guzauskas et al (2020)[86]
Ovarian cancer costs – terminal phase	$67,300	Goldsbury et al (2018)[90], Guzauskas et al (2020)[86]
Cost of RRM	$10,580	Medibank (2021)
Cost of RRSO	$5,665	Medibank (2021)
Incremental risk of breast cancer by age	Various	Guzauskas et al (2020)[86]
Incremental risk of ovarian cancer by age	Various	Guzauskas et al (2020)[86]

Source: As noted. Deloitte Access Economics calculations.

B.4. CLN2 inputs

Model overview – The purpose of this cost-effectiveness analysis is to determine if genomic and standard testing is a cost-effective means to diagnose cases of CLN2 in children when symptoms (usually seizures) first present, compared to standard testing alone. Cost-effectiveness was evaluated from health system perspective, over a lifetime horizon.

The target population was newborn siblings with CLN2. To derive the starting population, the proportion of CLN conditions which were CLN2, was applied to the prevalence of children living with Batten disease in Australia.[58,59]

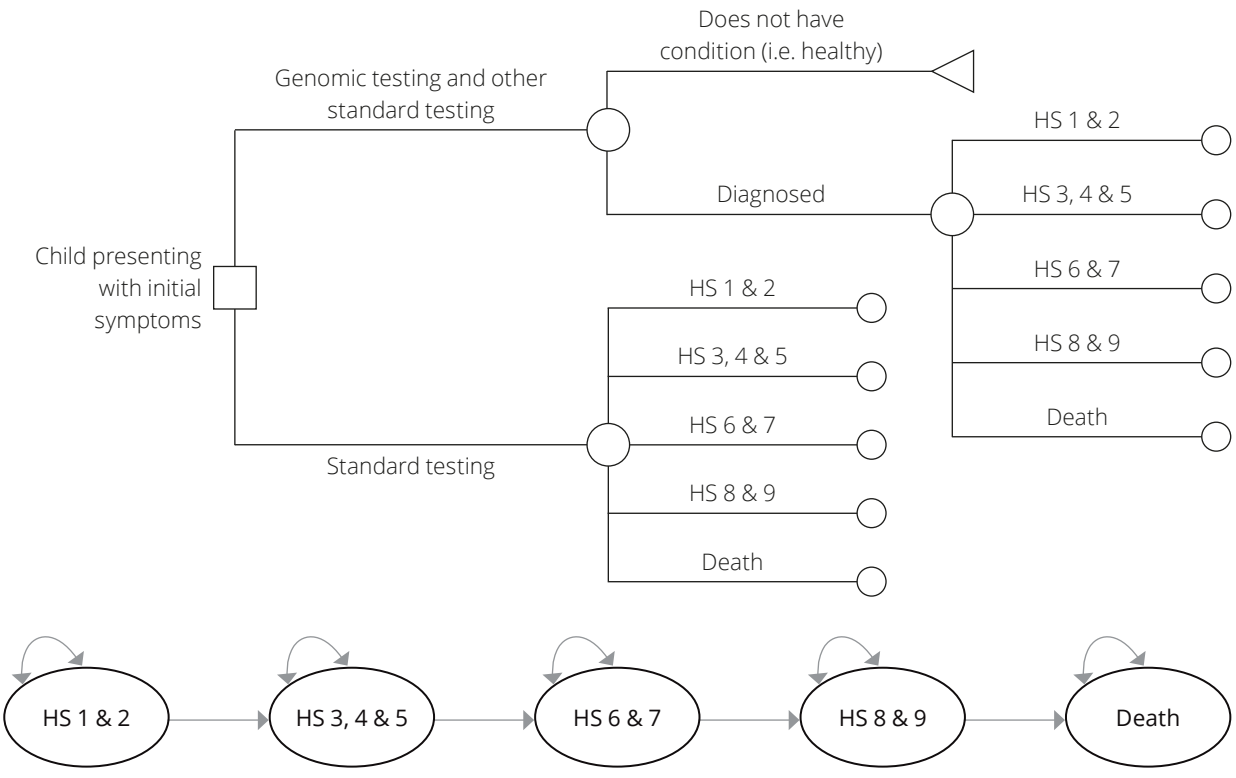
Model structure – A decision tree and Markov model was constructed using Microsoft Excel to analyse the patient progression with and without genetic testing (alongside standard testing including EEG, MRI and TTP1 enzyme testing) over a lifetime time horizon using a one-year cycle length. Starting states at diagnosis (and commencement of treatment) were more skewed toward the severe states for the standard testing arm, as it was assumed these children would be diagnosed two years later than children in the genetic testing arm – by which point the disease had rapidly declined (reflecting the natural history of the disease).

The Markov model consisted of ten health states based on the CLN2 clinical rating scale. These health states are consistent with previous economic evaluations.[60,61] Transition probabilities once treated (i.e. the chance of progressing from one health state to another each year) were based on a previous cost-effectiveness analysis of cerliponase alpa in children with CLN2.[62]

Health benefit measurement – The modelling measured the change in QALYs between the two arms. QALYs associated with a year spent in each CLN2 state were drawn from a study by Gissen et al.[93]

Cost measurement – Health system resource utilisation was predominately driven by the estimated cost of cerliponase alpa, as well as the expected ongoing treatment cost for a child with CLN2. Ongoing treatment included specialist clinicians, nurses, GPs, community paediatricians, speech/language therapist, physiotherapies, hospitalisation days, palliative care and additional procedures. These annual healthcare costs were drawn from a study by Akehurt et al and converted to 2021 AUD.[62]

Figure B.4: CLN2 decision tree and Markov model



Source: Deloitte Access Economics. Adapted from CADTH Common Drug Review Pharmacoeconomic Review Report Cerliponase Alfa (2019).
Note: HS = health state.

B.4.2. Model inputs

Table B.5: Model inputs for childhood dementia (Batten disease)

Input type	Model input	Source
Batten disease prevalence cases	35	Batten Disease Support and Research Association Australia (2021)[58]
Proportion of Batten disease which is CLN2	26%	Modelling assumption, informed by Mole et al (2015)
QALY for health state 1 & 2 (with cerliponase alpa)	0.874	Gissen et al (2021)
QALY for health state 3, 4 & 5 (with cerliponase alpa)	0.486	Gissen et al (2021)[93]
QALY for health state 6 & 7 (with cerliponase alpa)	0.028	Gissen et al (2021)[93]
QALY for health state 8 & 9 (with cerliponase alpa)	-0.205	Gissen et al (2021)[93]
QALY for health state death (with cerliponase alpa)	0	Gissen et al (2021)[93]
QALY for health state 1 & 2 (without cerliponase alpa)	0.866	Gissen et al (2021)[93]
QALY for health state 3, 4 & 5 (without cerliponase alpa)	0.342	Gissen et al (2021)[93]
QALY for health state 6 & 7 (without cerliponase alpa)	-0.147	Gissen et al (2021)[93]
QALY for health state 8 & 9 (without cerliponase alpa)	-0.358	Gissen et al (2021)[93]
QALY for health state death (without cerliponase alpa)	0	Gissen et al (2021)[93]
Diagnosis delay in standard treatment arm	2 years	Modelling assumption, informed by Specchio et al (2020)[57]
Annual cost of cerliponase alpa per dose 300mg	$1,064,717.18 ($106,471.72 - $2,022,962.65)	Akehurt et al (2018)[62] converted to 2021 Australian dollar
Annual cost of cerliponase alpa per dose 200mg	$709,811.45 ($70,981.15 - $1,348,641.76)	Akehurt et al (2018)[62] converted to 2021 Australian dollar
Annual cost of cerliponase alpa per dose 150mg	$532,358.59 ($53,235.86 - $1,011,481.32)	Akehurt et al (2018)[62] converted to 2021 Australian dollar
Annual cost of cerliponase alpa per dose 100mg	$354,905.73 ($35,490.57 - $674,320.88)	Akehurt et al (2018)[62] converted to 2021 Australian dollar
Once off cost for insertion intracerebroventricular infusion	$19,436.23	Akehurt et al (2018)[62] converted to 2021 Australian dollar
EEG cost	$110.00	MBS (2021)
MRI cost	$403.20	MBS (2021)
Enzyme (TTP1) test	$51.95	MBS (2021)
Genetic sequencing cost	$3,000.00	Wu et al (2021)[56]
Clinical geneticist appointment cost	$272.15	Wu et al (2021)[56]
Paediatric neurologist appointment cost	$276.25	MBS (2021)
General practitioner appointment cost	$108.85	MBS (2021)

Input type	Model input	Source
Annual ongoing treatment cost (first year) health state 1 & 2	$16,639.28	Akehurt et al (2018)[62] converted to 2021 Australian dollar
Annual ongoing treatment cost (first year) health state 3, 4 & 5	$39,309.18	Akehurt et al (2018)[62] converted to 2021 Australian dollar
Annual ongoing treatment cost (first year) health state 6 & 7	$65,172.54	Akehurt et al (2018)[62] converted to 2021 Australian dollar
Annual ongoing treatment cost (first year) health state 8 & 9	$54,887.95	Akehurt et al (2018)[62] converted to 2021 Australian dollar
Annual ongoing treatment cost (subsequent year) health state 1 & 2	$15,655.08	Akehurt et al (2018)[62] converted to 2021 Australian dollar
Annual ongoing treatment cost (subsequent year) health state 3, 4 & 5	$38,324.99	Akehurt et al (2018)[62] converted to 2021 Australian dollar
Annual ongoing treatment cost (subsequent year) health state 6 & 7	$64,188.34	Akehurt et al (2018)[62] converted to 2021 Australian dollar
Annual ongoing treatment cost (subsequent year) health state 8 & 9	$54,395.85	Akehurt et al (2018)[62] converted to 2021 Australian dollar

Source: As noted. Deloitte Access Economics calculations.

B.5. Pharmacogenetics inputs

Model overview – The purpose of this cost effectiveness analysis was to determine if CPGx is an effective means to inform treatment pathways for people with MDD. Two pathways were modelled, one where patients were given CPGx guided treatment, while the other relied on standard drug selection. The modelling was evaluated from both a health system and a societal perspective, over a five year time horizon. The target population was people with MDD in Australia, approximately 900,000 people each year, however it was conservatively assumed that only 75,000 people would undergo PGx testing.[101]

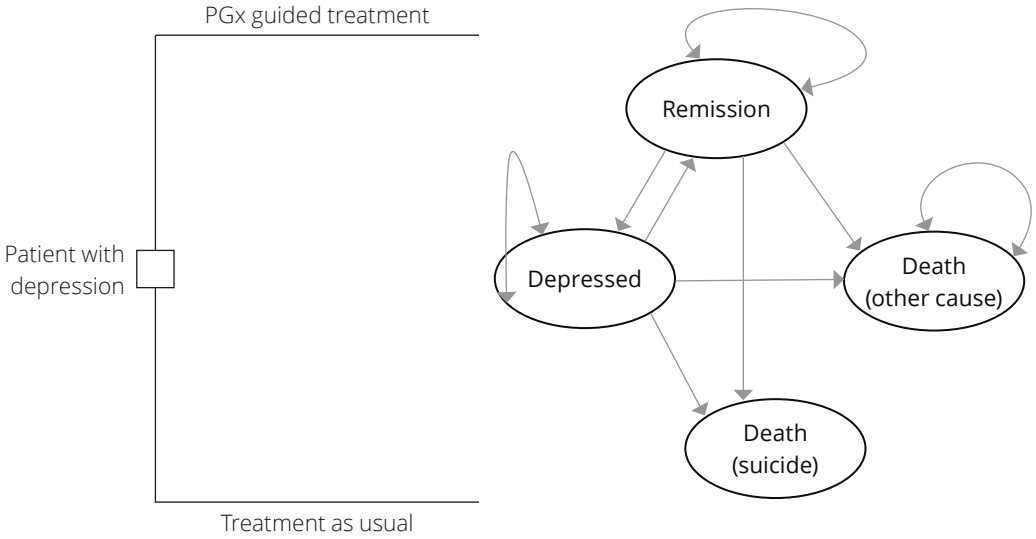
Model structure – A Markov model was constructed using Microsoft Excel to analyse the patient progression in both arms of the model. A cycle length of one year was used over a five year time horizon. It was assumed that patients in the CPGx model were more likely to achieve remission (i.e.. the transition probability from the depressed state to the remitted state) and less likely to relapse (i.e.. transition from the remitted state to the depressed state), based on outcomes reported in a clinical trial by Tanner et al.[71] It was assumed that CPGx guided drug selection for MDD increased the chance of a drug being effective in moving a patient into remission for 3 years post-test.[102] After this time, it was assumed that the standard approach to drug selection would be just as effective in moving a patient into remission.

Health benefit measurement – The model measured the number of QALYs gained, achieved through a greater number of people entering into, and remaining in, remission, and through lower rates of death due to suicide. QALY estimates attached to each health state were drawn from Tanner et al.[71]

Cost measurement – The model measured health system costs by multiplying medical resource use (drug costs, GP monitoring costs, counselling costs and hospital admissions) in each health state per year by the unit cost of these items. Units costs were largely drawn from MBS items. Resource use estimates per year per health state were based on previous Deloitte Access Economics modelling. For example, it was assumed that patients in the non remission stage of the model would receive double the amount of GP monitoring sessions annually compared to those in remission. Non remission patients were assigned additional average costs for hospitalisation and emergency department visits based on their probability of hospitalisation.

In conducting the modelling from a societal perspective, the productivity costs of absenteeism and presenteeism were estimated. A human capital approach was used by applying the total cost of an hour of presenteeism/absenteeism each year based on the person's expected wage (after taking into account the chance of being employed).

Figure B.5: PGx for depression decision tree and markov model



Source: Deloitte Access Economics. Adapted from Tanner et al (2020)

B.5.2. Model Inputs

Table B.6: Model inputs for CPGx testing

Input type	Model input	Source
Population with MDD	898,000	IHME (2021)
Remission rate (TAU)	12.8%	Tanner et al (2020)[71]
Remission rate (CPGx)	18.9%	Tanner et al (2020)[71]
Relapse rate (TAU)	23.2%	Tanner et al (2020)[71]
Relapse rate (CPGx)	9.9%	Tanner et al (2020)[71]
Suicide mortality rates (remission)	0.04%	Tanner et al (2020)[71]
Suicide mortality rates (non-remission)	0.01%	Tanner et al (2020)[71]
Natural death rates	0.16%	ABS life tables
Cost of CPGx	$2,737	Tanner et al (2020)[71]
Utility (remission)	0.83	Tanner et al (2020)[71]
Utility (non-remission)	0.55	Tanner et al (2020)[71]
Drug costs (annual, remission and non-remission)	$143	Pharmaceutical Benefits Scheme[103]
Hospital admission inc. emergency department presentations (annual, non-remission)	$582	National Hospital Cost Data Collection[104]
GP monitoring costs (annual, remission)	$1,500	MBS (2021)[105]
GP monitoring costs (annual, non-remission)	$3,000	MBS (2021)[103]
Counselling costs (annual, non-remission)	$840	MBS (2021)[106]
Absenteeism days	14	Evans-lacko et al[107], Cocker et al (2014)[108]
Presenteeism days	11	Evans-lacko et al[109], Cocker et al (2014)[110]

Source: As noted. Deloitte Access Economics calculations.

Endnotes

1. Department of Health, *National Health Genomics Policy Framework* (2017) <https://www1.health.gov.au/internet/main/publishing.nsf/Content/FD973B58DE82BCFFCA2581CC007D4682/$File/National-Health-Genomics-Policy-Framework.pdf>.
2. Department of Health, *Implementation Plan National Health Genomics Policy Framework Driving National Action 2018*-2021 (2018) <https://www1.health.gov.au/internet/main/publishing.nsf/Content/FD973B58DE82BCFFCA2581CC007D4682/$File/Implementation-Plan-to-the-Framework.pdf>.
3. Diana Mowman et al 'Newborn screening cards: a legal quagmire' (2011) 194(4) *Medical Journal of Australia* 319.
4. Genomics England, *The 100,00 Genomes Project*, *2020*, accessed July 2021. <https://www.genomicsengland.co.uk/about-genomics-england/the-100000-genomes-project/>.
5. Genomics England, *First patients diagnosed through the 100,000 Genomes Project, 2020,* accessed July 2021. <https://www.genomicsengland.co.uk/first-patients-diagnosed-through-the-100000-genomes-project/>.
6. Cinnamon Bloss et al 'Genomics for Disease Treatment and Prevention' (2011) 34(1) *Psychiatric Clinics of North America* 147.
7. Victor E Ortega et al 'Pharmacogenetics: implications of race and ethnicity on defining genetic profiles for personalized medicine' (2014) 133(1) *Journal of allergy and clinical immunology* 16.
8. Department of Health, *Pharmacogenomics research funding to improve mental health care,* 2019, accessed July 2021. <https://www.health.gov.au/ministers/the-hon-greg-hunt-mp/media/pharmacogenomics-research-funding-to-improve-mental-health-care>.
9. Gabriel Vachey et al 'CRISPR/Cas9-Mediated Genome Editing for Huntington's Disease' (2018) 1780 *Methods in Molecular Biology* 463.
10. Aaishwariya Gulani and Tracey Weiler, 'Genetics, Autosomal Recessive' (2020) StatPearls Publishing.
11. Cystic Fibrosis, 'CF carrier screening' available at < https://www.cysticfibrosis.org.au/get-involved/support-and-services/support-and-services-information/cf-carrier-screening#WhenShouldSomeoneHaveCFCS>.
12. Muscular Dystrophy Australia, 'Spinal Muscular Atrophy – An Overview' available at < https://www.mda.org.au/disorders/spinal-muscular-atrophy-an-overview/>.
13. Australian Genomics, 'Mackenzie's Mission' available at <https://www.australiangenomics.org.au/our-research/disease-flagships/mackenzies-mission/#:~:text=Mackenzie's%20Mission%20is%20a%20research,or%20are%20in%20early%20pregnancy.>.
14. News GP, 'Genetic carrier screening: What GPs need to know' (2020) available at < https://www1.racgp.org.au/newsgp/clinical/genetic-carrier-screening-what-gps-need-to-know>.
15. Australian Bureau of Statistics, 'National state and territory population' (2021) available at < https://www.abs.gov.au/statistics/people/population/national-state-and-territory-population/dec-2020>.
16. MSAC application 1165 'Assessment of preimplantation genetic diagnosis' (April 2015) Assessment Report.
17. Department of Health, *$354 million to support the health and wellbeing of Australia's women* (2021) <https://www.health.gov.au/ministers/the-hon-greg-hunt-mp/media/354-million-to-support-the-health-and-wellbeing-of-australias-women>.
18. Kyle Beauchamp et al, 'Clinical impact and cost-effectiveness of a 176-condition expanded carrier screen' (2019) 21(9) Genetics in Medicine 1948.
19. Lugeng He et al 'Metastatic castration-resistant prostate cancer' (2020) 99(15) *Medicine* e19760.
20. Australian Bureau of Statistics, 'Births, Australia' (2020) available at <https://www.abs.gov.au/statistics/people/population/births-australia/2019>.
21. Deloitte Access Economics 'The social and economic costs of cystic fibrosis in New Zealand' (2020) Report commissioned by Cystic Fibrosis New Zealand.

22. Michelle A Farrar et al, 'Financial, opportunity and psychosocial costs of spinal muscular atrophy: an exploratory qualitative analysis of Australian carer perspectives' (2018) 8(5) *British Medical Journal Publishing Group* e020907.

23. Deloitte Access Economics 'The social and economic costs of cystic fibrosis in New Zealand' (2020) Report commissioned by Cystic Fibrosis New Zealand.

24. Michelle A Farrar et al, 'Financial, opportunity and psychosocial costs of spinal muscular atrophy: an exploratory qualitative analysis of Australian carer perspectives' (2018) 8(5) *British Medical Journal Publishing Group* e020907.

25. Lara Kohler et al, 'Pompe disease: from basic science to therapy' (2018) 15(4) *Neurotherapeutics* 928.

26. Priya Kishnani et al, 'A retrospective, multinational, multicenter study on the natural history of infantile-onset Pompe disease' (2006) 148(5) *The Journal of Pediatrics* 671.

27. Tchan Michel et al, 'Is it Pompe Disease? Australian diagnostic considerations' (2020) 30(5) *Neuromuscular Disorders* 389.

28. Priya Kishnani et al 'Timing of diagnosis of patients with Pompe disease: data from the Pompe registry' (2013) 161(10) *American Journal of Medical Genetics Part A* 2431.

29. Yin-Hsiu Chien et al, 'Long-term prognosis of patients with infantile-onset Pompe disease diagnosed by newborn screening and treated since birth' (2015) 166(4) *The Journal of Pediatrics* 985.

30. Jennifer Kwon and Robert Steiner, '"I'm fine; I'm just waiting for my disease": the new and growing class of presymptomatic patients' (2011) 77 *Neurology* 522.

31. John S Richardson et al, 'Health and economic outcomes of newborn screening for infantile-onset Pompe disease' (2021) 23(4) *Genetics in Medicine* 758.

32. Lisa A Prosser et al, 'Using decision analysis to support newborn screening policy decisions: A case study for Pompe disease' (2018) 3(1) *MDM Policy & Practice* 1.

33. Andrea M Atherton and Debra Day-Salvatore, 'The role of genetic counseling in Pompe disease after patients are identified through newborn screening' (2017) 140(supplement 1) *Pediatrics* S46.

34. National Cancer Institute, 'BRCA Gene Mutations: Cancer Risk and Genetic Testing' (2021) available at <https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet>.

35. Sandhya Pruthi et al, 'Identification and management of women with BRCA mutations or hereditary predisposition for breast and ovarian cancer' (2010) 85(12) *Mayo Clinic Proceedings* 1111.

36. Robert Pilarski, 'The role of BRCA testing in hereditary pancreatic and prostate cancer families' (2019) 39 *American Society of Clinical Oncology Educational Book* 79.

37. National Breast Cancer Foundation, 'BRCA: The Breast Cancer Gene' (2020) available at <https://www.nationalbreastcancer.org/what-is-brca>.

38. 'Men with BRCA mutations have much higher risk of cancer' *Breastcancer.org* (2017) < https://www.breastcancer.org/research-news/brca-mutations-up-cancer-risk-in-men>.

39. Chiyan Lau, Graeme Suthers, 'BRCA testing for familial breast cancer' (2011) 34 *Australian Prescriber* 49.

40. National Breast Cancer Foundation, 'Breast Cancer Statistics' (2021) available at < https://nbcf.org.au/about-breast-cancer/breast-cancer-stats/>.

41. Li Sun et al, 'A cost-effectiveness analysis of multigene testing for all patients with breast cancer' (2019) 5(12) *American Medical Association* 1718.

42. Ranjit Manchanda, 'Current detection rates and time-to-detection of all identifiable BRCA carriers in the Greater London population' (2018) 55(8) *Journal of medical genetics* 538.

43. Courtney Macdonald et al, 'Breast Cancer Chemoprevention: Use and Views of Australian Women and Their Clinicians' (2021) 14(1) *Cancer Prevention Research* 131.

44. 'Medicare Benefits Schedule – Item 73296' Department of Health < http://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=73296&qt=item>.

45. Antonis C Antoniou et al 'Breast-cancer risk in families with mutations in PALB2' (2014) 371(6) *New England Journal of Medicine* 497.

46. Asma Alkaf et al, 'Expression of STK11 gene and its promoter activity in MCF control and cancer cells' (2017) 7(6) *Biotech* 1.

47. Joanne Ngeow et al 'Breast cancer risk and clinical implications for germline PTEN mutation carriers' (2017) 165(1) *Breast cancer research and treatment* 1.

48. Parry Guilford et al, 'Hereditary diffuse gastric cancer: translation of CDH1 germline mutations into clinical practice' (2010) 13(1) *Gastric cancer* 1.

49. Thomas P Slavin, 'The contribution of pathogenic variants in breast cancer susceptibility genes to familial breast cancer risk' (2017) 3(1) *NPJ breast cancer* 1.

50. Nicole Bates et al 'Labour force participation and the cost of lost productivity due to cancer in Australia' (2018) 18(1) *BMC Public Health* 1.

51. Palliative Care Australia. The hardest thing we have ever done: The social impact of caring for terminally ill people in Australia, 2004.

52. J Gout-Zwart et al 'The burden of informal care for breast cancer patients in the Netherlands' (2018) 21 *Value in Health* S81.

53. Michael Schaapveld et al 'Changes in employment status, barriers to, and facilitators of (return to) work in breast cancer survivors 5–10 years after diagnosis' (2020) 42(21) *Disability and rehabilitation* 3052.

54. Tilden D et al 'Childhood dementia in Australia: quantifying the burden on patients, carers, the healthcare system and our society'. Report for Childhood Dementia Initiative. THEMA Consulting Pty Ltd.

55. Angela Schulz et al 'Study of Intraventricular Cerliponase Alfa for CLN2 Disease' (2018) 387(20) *New England Journal of Medicine* 1898.

56. Alexandra Johnson et al 'Neuronal ceroid lipofusciosis type 2: an Australian case study' (2020) 56 *Journal of Paediatrics and Child Health* 1210.

57. You Wu et al 'Genomic sequencing for the diagnosis of childhood mitochondrial disorders: a health economic evaluation' (2021) Online ahead of print. *European Journal of Human Genetics* 1.

58. Nicola Specchoi et al 'Changing Times for CLN2 Disease: The Era of Enzyme Replacement Therapy' 16 *Therapeutics and Clinical Risk Management* 213.

59. Batten Disease Support and Research Association Australia, *Batten disease* (2020) accessed July 2021. <https://bdsraaustralia.org/learn/#:~:text=Approximately%201%20in%20100%2C%20000,diagnosed%20each%20year%20in%20Australia>.

60. Sara Mole et al, 'Genetics of the Neuronal Ceroid Lipofuscinoses (Batten disease)' (2015) 1852(10) *Biochimica et Biophysica Acta* 2237.

61. Canadian Agency for Drugs and Technologies in Health Common Drug Review, *Pharmacoeconomic Review Report Cerliponase Alfa (Brineura)* (2019).

62. National Institute for Health and Care Excellence, *Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2* (2019).

63. Ron Akehurt et al, *Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2* (2018).

64. Swinburne University of Technology, 'Major Depressive Disorder' available at <https://www.swinburne.edu.au/research/centres-groups-clinics/centre-for-mental-health/our-research/major-depressive-disorder/>.

65. Joachim Benitez et al, 'The clinical validity and utility of combinatorial pharmacogenomics: enhancing patient outcomes' (2015) 5 *Applied & translational genomics* 47.

66. Sheng-Min Wang et al, 'Addressing the side effects of contemporary antidepressant drugs: a comprehensive review' (2018) 54(2) *Chonnam medical journal* 101.

67. Chad A Bousman et al, 'Pharmacogenetic tests and depressive symptom remission: a meta-analysis of randomized controlled trials' (2019) 20(1) *Pharmacogenomics* 37.

68. 'About us' *Sonic Genetics* (2021) < https://www.sonicgenetics.com.au/about/>.

69. 'Pharmacogenomic (PGx) screen' *Sonic Genetics* (2021) <https://www.sonicgenetics.com.au/our-tests/all-tests/pharmacogenomic-screen/>.

70. Thomas M Polasek et al 'Pharmacogenomics in general practice:'The time has come'' (2019) 48(3) *Australian journal of general practice* 100.

71. Joel G Winner and Bryan Dechairo, 'Focus: Personalized Medicine: Combinatorial Versus Individual Gene Pharmacogenomic Testing in Mental Health: A Perspective on Context and Implications on Clinical Utility' (2015) 88(4) *Yale Journal of Biology and Medicine* 375.

72. John F Greden et al, 'Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: a large, patient-and rater-blinded, randomized, controlled study' (2019) 111 *Journal of psychiatric research* 59.

73. Julie-Anne Tanner et al 'Cost–effectiveness of combinatorial pharmacogenomic testing for depression from the Canadian public payer perspective' (2020) 21(8) *Pharmacogenomics* 521.

74. Erik J Groessl et al, 'Cost-effectiveness of a pharmacogenetic test to guide treatment for major depressive disorder' (2018) 24(8) *Journal of managed care & specialty pharmacy* 726.

75. Anthony D LaMontagne et al, 'Estimating the economic benefits of eliminating job strain as a risk factor for depression' (2011) *Occupational and Environmental Medicine* 68

76. Sara Evans-Lacko and Martin Knapp, 'Global patterns of workplace productivity for people with depression: absenteeism and presenteeism costs across eight diverse countries' (2016) 51(11) *Social psychiatry and psychiatric epidemiology* 1525.

77. National Institute of Health, *BRCA Gene Mutations: Cancer Risk and Genetic Testing* (2019) accessed June 2021. <https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet>.

78. NPS Medicinewise, *Olaparib* (2017) accessed June 2021. <https://www.nps.org.au/australian-prescriber/articles/olaparib>.

79. Jonathan Ledermann et al 'Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial' (2014) 15(8) *Lancet Oncology* 852.

80. Na Li et al 'Cost-Effectiveness Analysis of Olaparib Maintenance Treatment for Germline BRCA-Mutated Metastatic Pancreatic Cancer' (2021) 18(11) *Journal of the National Comprehensive Cancer Network* 1528.

81. Dan Su et al 'Cost-Effectiveness of Genomic Test-Directed Olaparib for Metastatic Castration-Resistant Prostate Cancer' (2021) 26(11) *Frontiers in Pharmacology* 610601.

82. 'Centre for Population Genomics' *Garvan Institute of Medical Research* (2021) < https://www.garvan.org.au/research/population-genomics>.

83. Mohammad Azimi et al, 'Carrier screening by next-generation sequencing: health benefits and cost effectiveness' (2016) 4(3) *Molecular genetics & genomic medicine* 292.

84. IVF Australia, 'IVF Treatment Costs' (2020) available at <https://www.ivf.com.au/ivf-cost/ivf-costs>.

85. Charles Denaro and Jennifer Martin, 'The challenge of costly drugs' (2016) 39(3) *Australian prescriber* 72.

86. 'Australian Burden of Disease Study: impact and causes of illness and death in Australia 2015' Australian Institute of Health and Welfare (13 June 2019) < https://www.aihw.gov.au/reports/burden-of-disease/burden-disease-study-illness-death-2015/data>.

87. 'Breast Cancer Stats' *National Breast Cancer Foundation* (2021) <https://nbcf.org.au/about-breast-cancer/breast-cancer-stats/>.

88. Gregory F Guzauskas et al, 'Cost-effectiveness of Population-Wide Genomic Screening for Hereditary Breast and Ovarian Cancer in the United States' (2020) 3(10) *JAMA network open* e2022874.

89. 'Breast Cancer' *Cancer Australia* (20 October 2020) available at <https://www.canceraustralia.gov.au/affected-cancer/cancer-types/breast-cancer/breast-cancer-australia-statistics>.

90. 'The Statistics' *Ovarian Cancer Australia* < https://www.ovariancancer.net.au/page/152/the-statistics>.

91. 'Medicare Benefits Schedule – Item 73296' Department of Health < http://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=73296&qt=item>.

92. David E Goldsbury, 'Health services costs for cancer care in Australia: Estimates from the 45 and Up Study' (2018) 13(7) *PLoS One* e0201552.

93. 'How much does a mastectomy cost' *Medibank* (2021) < https://www.medibank.com.au/health-support/hospital-assist/costs/mastectomy/>.

94. 'How much does a laprascopy cost' *Medibank* (2021) < https://www.medibank.com.au/health-support/hospital-assist/costs/laparoscopy/>.

95. Paul Gissen et al 'Investigating health-related quality of life in rare diseases: a case study in utility value determination for patients with CLN2 disease (neuronal ceroid lipofuscinosis type 2)' (2021) 16(217) *Orphanet Journal of Rare Diseases* 1.

96. Medicare Benefits Schedule – Item 11003 Department of Health <http://www9.health.gov.au/mbs/search.cfm?q=11003&Submit=&sopt=S>.

97. Medicare Benefits Schedule – Item 63425 Department of Health <http://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=63425&qt=item&criteria=63425%20>.

98. Medicare Benefits Schedule – Item 63425 Department of Health <http://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=65075&qt=item&criteria=65075>.

99. Medicare Benefits Schedule – Item 135 Department of Health <http://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=135&qt=item&criteria=135>.

100. Medicare Benefits Schedule – Item 44 Department of Health <http://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&qt=ItemID&q=44>.

101. Global Health Data Exchange 'GBD Results Tool' *Institute for Health Metrics and Evaluation* (2021) <http://ghdx.healthdata.org/gbd-results-tool>.

102. Erik J Groessl et al, 'Cost-effectiveness of a pharmacogenetic test to guide treatment for major depressive disorder' (2018) 24(8) *Journal of managed care & specialty pharmacy* 726.

103. The Pharmaceutical Benefits Scheme 'Browse by Body System' < https://www.pbs.gov.au/browse/body-system?depth=4&codes=n06ab#n06ab>.

104. National Hospital Cost Data Collection 'What is the cost of Australia's emergency care patients?' <https://www.ihpa.gov.au/sites/default/files/publications/round_22_nhcdc_infographics_emergency.pdf>.

105. Medicare Benefits Schedule – Item 2715 Department of Health < http://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=2715>.

106. Medicare Benefits Schedule – Item 10968 Department of Health < http://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=10968&qt=ItemID>.

107. Sara Evans-Lacko and Martin Knapp 'Global patterns of workplace productivity for people with depression: absenteeism and presenteeism costs across eight diverse countries' (2016) 51(11) *Social psychiatry and psychiatric epidemiology* 1525.

108. Fiona Cocker et al, 'Depression in working adults: Comparing the costs and health outcomes of working when ill' (2014) 9(9) *PLOS One* e105430.

109. Sara Evans-Lacko and Martin Knapp 'Global patterns of workplace productivity for people with depression: absenteeism and presenteeism costs across eight diverse countries' (2016) 51(11) *Social psychiatry and psychiatric epidemiology* 1525.

110. Fiona Cocker et al, 'Depression in working adults: Comparing the costs and health outcomes of working when ill' (2014) 9(9) *PLOS One* e105430.

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