Australian Cancer Genomics Landscape Assessment

Step 1, toward building an Australian Cancer Futures Framework – National Oncology Alliance

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NOA
NATIONAL ONCOLOGY ALLIANCE

rare cancers AUSTRALIA

Foreword

Genomic technology is creating new opportunities to extend the lives of cancer patients. Genomic sequencing has many applications and variations. It is currently used to screen for familial risk of developing certain cancers, molecular diagnosis, disease prognosis and to direct the best course of treatment. Its relatively early in its adoption so there is yet to be a co-ordinated national approach to its use.

The understanding of the complexity of cancers has evolved remarkably with advances in genomics. Cancers that were previously considered "common" are becoming rare through the discovery of multiple subtypes linked to the discovery of genetic mutations. Patients with lung cancer, a historically common cancer, were diagnosed as presenting with one of two possible cancer types, small-cell, or non-small cell lung cancer. Now we understand that there are over 30 mutations associated with lung cancers. Lung cancer is just one example of a group of cancers that have been historically classified by their tissue of origin rather than their molecular make-up.

The exciting prospect for cancer patients is that some of the genetic mutations are associated with molecularly targeted therapies, defined as personalised treatment. For those disease-related targets that do not have therapies available, there are many more in the development pipelines.

The rise in the discovery of pan tumours – multiple cancers that share the same disease targets – cannot be ignored. It creates complexities for the health system but provides an opportunity for patients with multiple rare cancer subtypes to be treated effectively with the same targeted therapy.

Next-generation sequencing (NGS) testing has reduced the cost and increased the speed of whole exome and whole-genome sequencing. This technology is being used in Australia within centres of excellence, but there is still much work to be done to understand the value and utility of the sequencing technology.

There are numerous genomics research initiatives underway in Australia which will ultimately inform the use and adoption of genomics in the long-term. In the shorter-term, genomic research provides patients with rare cancer sub-types with access to treatment options, where there were none, giving not only new hope for survival, but making this a reality.

NOA envisages a day when physicians and cancer patients will have access to genomic sequencing and comprehensive data analysis. Personalised treatment approaches will need guidelines, best practice standards, governance, and ethics around the use of tests, data interpretation, data storage and sharing. NOA seeks to support the existing work streams in delivering a National co-ordinated approach to long term integration of genomics into cancer care.

Dr Amanda Ruth, Head of Policy and Public Affairs, Rare Cancers Australia

"The best way to predict the future is to create it" Abraham Lincoln

Acknowledgement and Disclaimer

This report has been prepared by The National Oncology Alliance (NOA). NOA is an alliance of stakeholders comprised of patients, patients groups, clinicians, and industry, formed by Rare Cancers Australia to promote timely, affordable, and equitable access to the best care, emerging treatments and technologies to Australians who need them. In developing this report, NOA has worked closely with an expert consultancy, Health Technology Analysts, who have assisted in engaging all stakeholders, conducting research, and creating the report. We are also extremely grateful to the many other stakeholders who gave their time so willingly to help us in drafting this report and develop the recommendations herein.

About Rare Cancers Australia

Rare Cancers Australia Ltd (RCA) is a charity whose purpose is to improve awareness, support, and treatment of Australians with rare and less common (RLC) cancers. Every year there are over 52,000 diagnoses of RLC cancers and around 25,000 deaths.

As our understanding of cancer develops - more cancers are considered rare. There is very little patient support offered to these cancer patients. RCA works tirelessly to ensure that people with rare or less common cancers will never be forgotten or ignored again.

Contents

Glossary

aCGH	Array comparative genomic hybridisation
ALL	Acute lymphoblastic leukaemia
AML	Acute myeloid leukaemia
APML	Acute promyelocytic leukaemia
BP	Base pair
CGH	Comparative genomic hybridisation
CISH	Chromogenic in situ hybridisation
CNV	Copy number variation
CoE	Centre of excellence
CML	Chronic myeloid leukaemia
CT	Computed tomography
CUP	Cancer of unknown primary
DGE	Differential gene expressions
dMMR	Mismatch repair-deficient
DNA	Deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
FF	Fresh-frozen
FFPE	Formalin-fixed paraffin-embedded
FISH	Fluorescence *in situ* hybridisation
HTA	Health technology assessment
IHC	Immunohistochemistry
INGeNA	Industry Genomics Network Alliance
ISH	*In situ* hybridisation
Kb	Kilobase
LOH	Loss of heterozygosity
MBS	Medicare Benefits Schedule
MDT	Multidisciplinary team
MLPA	Multiplex ligation-dependent probe amplification
MMR	Mismatch repair
MoST	Molecular Screening & Therapeutics
MPS	Massively parallel sequencing
MRFF	Medical Research Futures Fund
mRNA	Messenger ribonucleic acid
MSAC	Medical Services Advisory Committee
MSH	MutS homolog
MSI	Microsatellite instability
MSI-H	Microsatellite instability-high
MTB	Molecular tumour board
NSCLC	Non-small cell lung cancer
NGS	Next-generation sequencing
NOA	National Oncology Alliance
OECD	Organisation for Economic Cooperation and Development
OOP	Out of pocket
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PCR	Polymerase chain reaction
PET	Positron emission tomography
PV	Polycythaemia vera
RCPA	Royal College of Pathologists of Australasia
RLC	Rare and less common
RNA	Ribonucleic acid
RT-PCR	Reverse transcription polymerase chain reaction
SNP	Single nucleotide polymorphism
TAT	Turnaround time
Tb	Terabyte
TKI	Tyrosine kinase inhibitor
TMB	Tumour mutational burden
TMB-H	Tumour mutational burden-high

Glossary of Genetic Variants

AKT	RAC-alpha serine/threonine-protein kinase
ALK	Anaplastic lymphoma kinase
ASXL1	Putative polycomb group protein
ATM	ATM serine/threonine kinase
BRAF	Proto-oncogene B-Raf
BRCA	Breast cancer gene
CALR	Calreticulin
CDKN2A	Cyclin-dependent kinase inhibitor 2A
CEBPA	CCAAT/enhancer-binding protein alpha
C-myc	MYC proto-oncogene, BHLH transcription factor
CSF3R	Colony-stimulating factor receptor
CTLA-4	Cytotoxic T lymphocyte antigen-4
DNMT3A	DNA (cytosine-5)-methyltransferase 3A
EGFR	Epidermal growth factor receptor
FLT3	fms-like tyrosine kinase 3
HER2	Human epidermal growth factor 2
IDH1	Isocitrate dehydrogenase 1
IDH2	Isocitrate dehydrogenase, mitochondrial
IKZF1	Ikaros family zinc finger protein 1
JAK2	Janus kinase 2
KIT	Proto-oncogene c-KIT
KRAS	Kirsten rat sarcoma viral oncogene
MET	Tyrosine protein-kinase Met
MGMT	O6-methylguanine DNA methyltransferase
mTOR	Mammalian target of rapamycin
MYD88	Myeloid differentiation primary response 88
N-myc	MYCN proto-oncogene
NPM1	Nucleophosmin 1
NRAS	Neuroblastoma RAS viral oncogene
NTRK	Neurotrophic tyrosine kinase
PALB2	Partner and localiser of BRCA2
PD-1	Programmed cell death protein 1
PDGFRA	Platelet-derived growth factor receptor A
PD-L1	Programmed death ligand 1
PIK3CA	Phosphatidylinositol 3-kinase
PTCH1	Patched-1 protein
PTEN	Phosphatase and tensin homolog
RAS	Rat sarcoma
RB1	Retinoblastoma protein gene
ROS1	C-ros oncogene 1
RUNX1	RUNX family transcription factor 1
SETBP1	SET binding protein 1
SF3B1	Splicing factor 3B subunit 1
SMO	Smoothened gene
SRSF2	Splicing factor, arginine/serine-rich 2
TET2	Tet methylcytosine dioxygenase 2
TP53	Tumour protein 53

1 Executive Summary

Rare Cancers Australia and the National Oncology Alliance are working towards improving the lives of cancer patients through innovative research and cutting-edge technologies. Genomics has increasingly become a major focus in cancer research and clinical care. Using genomics, clinicians and researchers can create personalised approaches to treatment using targeted anti-cancer drugs, leading to higher chances of success. This approach is known as precision medicine. Genomic testing, a key component of precision medicine, provides the molecular information clinicians need to determine the best course of treatment for each cancer patient.

The purpose of this report is to characterise the current landscape of cancer genomics in Australia and provide potential strategies for further integration of genomics into cancer care.

Cancer occurs when errors in the genetic code cause cells to replicate uncontrollably, invading surrounding tissue and eventually spreading to other parts of the body. Genomics is the study of the genetic code. Genomics is increasingly applied to cancer care by targeting specific genetic alterations with innovative anti-cancer drugs. Next-generation sequencing is a powerful genomic testing technology capable of rapidly sequencing large sections of the genome simultaneously. While it is currently used mostly in the research setting, it will become increasingly integrated into clinical care as costs decrease.

The status quo

Currently, a variety of conventional pathology techniques are used to diagnose cancer and determine the best course of treatment. Many molecular pathology tests analyse one gene or biomarker at a time, and some can analyse several at once. Tests that identify molecular alterations of interest in cancer are often funded through the Medicare Benefits Schedule (MBS) as a way of identifying eligible patients for the Pharmaceutical Benefits Schedule (PBS)-funded targeted treatments, such as small molecule inhibitors or monoclonal antibodies. These types of targeted therapies are increasingly available through the PBS. Current MBS-funded genetic and genomic testing is focused on tests that interrogate one to five molecular alterations. The narrow scope of these tests can sometimes lead patients down "testing odysseys" where multiple successive tests are conducted before pathologists and clinicians identify a useful variant or biomarker.

Pathology funding comes from a mix of state and federal sources. The MBS, the main source of federal funding, spent $14 million on cancer-related genetic and genomic tests in 2019. Many stakeholders argue pathology has historically been underfunded compared to pharmaceuticals, and currently there is no public funding for broader NGS testing in the clinical care of cancer.

The value of NGS

NGS can replace nearly all the conventional pathology tests by searching for many variants of interest simultaneously. Broad NGS tests (such as whole exome or whole genome sequencing) can also uncover variants of unknown significance. Given the wide scope of NGS technology, analysis and interpretation of test results are critical to realising the

technology's value and utility. Data analysis software can facilitate the analysis, however interpretation by clinicians and pathologists is still needed and may take more time depending on the size of the test. The interpretation process is still being refined at centres of excellence (CoEs) conducting genomics research across Australia. Clinicians believe NGS testing should be conducted at the beginning of the diagnostic journey, and that there could also be benefits associated with repeat testing after treatment failure given that the genomic profile of cancers can evolve in response to treatment. Stakeholders are also thinking about how various cancer patient populations would benefit from NGS testing. If broader funded genomic testing were rolled out in the current system, many patients would likely face a lack of access to funded treatment matched with their specific molecular alteration. This is a critical issue which currently prohibits further integration of genomic testing, especially large-scale panels, into the clinical landscape.

The international experience

Countries in Europe and Asia have begun funding genomic testing and creating national systems for genomics service delivery. Genomics England, which completed its pilot project (the 100,000 Genomes Project) in 2018, is a national program offering a range of NGS tests for most types of cancer. Data is collected with patient consent and stored in a national genomics library for research use. Japan has similarly created a national system where designated hospitals perform NGS testing and NGS data is stored as a national asset. South Korea partially funds NGS testing for solid tumours, however data collection is not yet centralised. These programs are intended to improve patient outcomes, collect data for research, and attract industry sponsors of clinical trials.

Current Australian initiatives

Australia is on the path to creating a national genomics system. Several national and state genomics research initiatives are underway with millions of dollars in funding. Current research is developing both evidence for the clinical effectiveness of genomic testing in cancer and other disease areas as well as testing the feasibility of implementation on a broader scale. For example, the MRFF-funded Genomics Health Futures Mission is conducting research on reproductive carrier screening (Mackenzie's Mission), proteomics big data analysis (ProCan), pathogen genomics, paediatric acute care, and bioinformatics. Australian Genomics has been defining key genomics implementation considerations, particularly around data management. States have invested in their own research programs as well. The federal government created the National Genomics Health Policy Framework and Implementation Plan for 2018 to 2021, which consists of guidance and implementation actions for policymakers on creating a person-centred approach to genomics, building workforce capabilities, cost-effectively financing genomics services, maximising quality of services, and managing data appropriately. These initiatives and frameworks are an important first step towards creating a national genomics system.

Evidence for NGS

There is a growing body of evidence demonstrating the value of NGS testing. Establishing the analytical and clinical validity of some NGS tests, especially large panels, is challenging given the number of potential variants that could be discovered. Researchers have begun to develop new guidelines on how to approach validation in these cases, however it remains a lengthy and labour-intensive process. Much of the research in recent years has focused on demonstrating clinical utility of NGS testing, with studies measuring feasibility and implementation outcomes as well as patient health outcomes. While much of the evidence comes from retrospective studies or non-randomised studies, stakeholders view the evidence as strong enough to justify creating a national genomics research program for cancer patients, especially those with limited treatment options. Ongoing clinical research studies are employing innovative trial designs called master protocols, which allow flexibility to enrol patients with a variety of cancer types and add or remove sub-studies trialling different therapies as needed. These designs

will facilitate easier development of evidence in a field where molecular subtyping of cancers has been creating smaller and smaller populations, reducing the feasibility of enrolling sufficient patient numbers in traditional randomised controlled trials.

Target populations for NGS

Many cancer patient populations have high unmet clinical need for the latest precision medicine technologies. In cancers with many known variants and available treatments, funded NGS testing would be more likely to have immediate clinical utility than in cancers that are less well-understood. In both cases, NGS testing could provide informative results regarding potential clinical trial enrolment and would produce valuable genomic data which could be leveraged in the research setting. Costs are still relatively high and turnaround time is long due to logistical hurdles and effort required for interpretation; however, sequencing is becoming more cost-efficient. Establishment of standardised processes will help increase efficiency and reduce costs further, all while sequencing costs are projected to continue declining. Eventually, NGS testing will become an affordable option in many cases.

Current gaps

Based on the current landscape of cancer genomics in Australia, there are gaps in the following areas to be addressed in the future:

- **Technology and process validation:** Validation for large NGS panels is still in development, and the heterogeneity in approaches to analysis and interpretation makes it difficult to compare the utility of NGS tests against each another using a consistent health technology assessment framework.
- **Sequencing capabilities:** Many laboratories have the capability to conduct some NGS tests, but these laboratories may not have the advanced instruments capable of running comprehensive panels or whole genomes. It may not be cost-effective to introduce such technologies in a wide array of laboratories given the high upfront costs.
- **Process capabilities:** There are challenges with biopsy sample quality, limited ability to conduct repeat biopsies, a lack of standardised process for determining what types of NGS tests patients should receive, and limited trained workforce for NGS analysis and interpretation, especially outside of CoEs.
- **Continuum of care:** Clear pathways from diagnostic test result to funded treatment options (PBS-listed drugs or clinical trials) should be developed; genetic counselling and broader care coordination between medical centres have also not yet been integrated into practice.
- **Data storage and management:** A key aspect of genomic testing is data storage and management. A national genomics data system which links with other health data would provide the most value to Australia. If executed with clear communication that builds public trust, this could also address concerns about private companies overseas obtaining genomic data from Australians without regulation.
- **Equity in the health system:** While funding for NGS testing would increase equity of access, the allocation of public funds must also be considered carefully given the currently limited options for funded treatment. The health system will also need to engage collaboratively with all stakeholders to avoid the system's built-in risks of inefficiency and inequity.

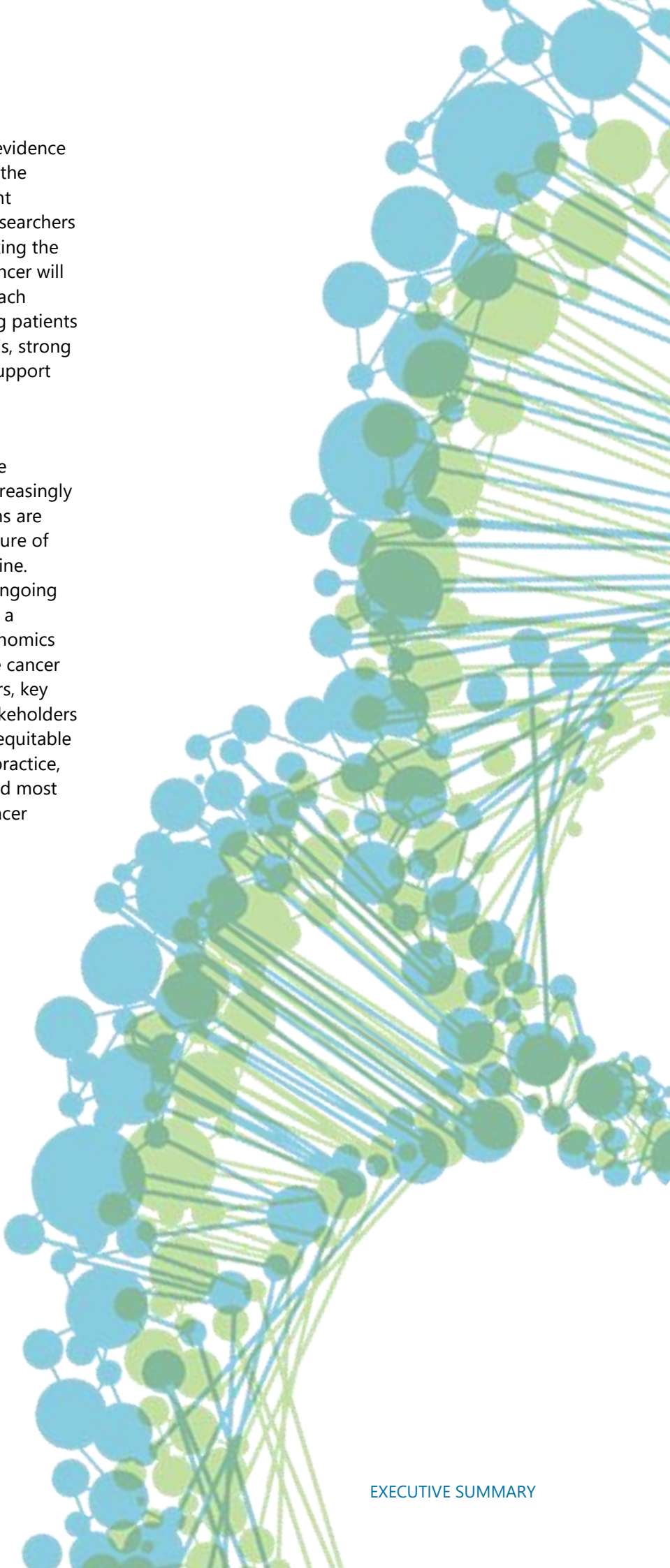
Future funding of NGS

Between 2020 and 2030, funding for NGS testing is likely to come increasingly from Medicare reimbursement, particularly as the cost of NGS decreases and the technology can be harnessed by laboratories in a cost-effective manner using existing MBS items. As research using NGS increases, funding may also partly come from government research funds such as the MRFF. Research funding has already been allocated to several programs across the country, which will continue to provide an important point of access to NGS testing for patients in the short-term. MBS funding is more likely to be allocated in the medium- to long-term, although there may be some instances in the nearer future where approval of pan-cancer drugs requiring broad NGS testing triggers funding for comprehensive

genomic profiling panels. As clinical evidence builds the case for reimbursement in the coming years, there are also important implementation considerations for researchers and policymakers to consider. Unlocking the full potential value of genomics in cancer will require a coordinated national approach including an infrastructure connecting patients with treatment options post-diagnosis, strong data management capabilities, and support services.

Conclusion

In the next decade, cancer care will be transformed as genomics enables increasingly personalised medicine. Health systems are beginning to adapt to the unique nature of NGS technology and precision medicine. Australia will be able to build on its ongoing genomics research initiatives to build a national infrastructure supporting genomics delivery and ultimately improving the cancer patient health outcomes. Policymakers, key opinion leaders, and other critical stakeholders will need to collaborate to create an equitable system that integrates research and practice, creates opportunities for research, and most importantly, improves the lives of cancer patients.



2 Introduction

2.1 Vision

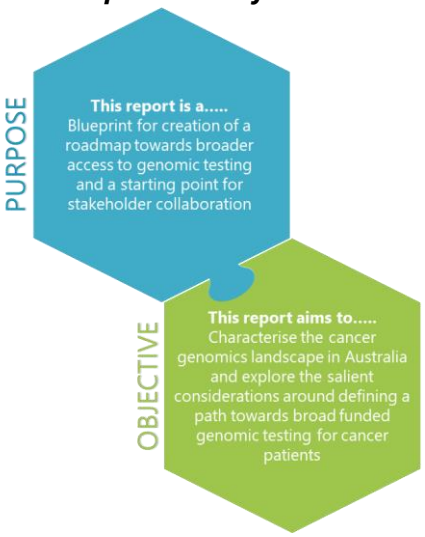
Recent advances in science and translation of discoveries into health technologies means that there has never been more hope for Australian cancer patients. Yet the benefits will only be realised if the health system keeps pace with innovation and is progressive enough to equitably deliver treatments and technologies to cancer patients. Rare Cancers Australia and the National Oncology Alliance (NOA) are working to shift policy to increase equitable access to the best cancer care and emerging cancer treatments and technologies. Through collaborative engagement with varied healthcare stakeholders, NOA is committed to ensuring that Australians living with cancer have access to a health system that provides them with the treatment, support, and care that they need and deserve. NOA exists to continue advocating for patients and working with the government to improve cancer patient survivorship. (1)

Genomic sequencing technology has enabled new frontiers of cancer research, drug discovery, and clinical care by offering the potential for precise and personalised approaches to cancer treatment. This is especially relevant for patients with rare cancers, who suffer from limited access to new targeted cancer treatments that offer hope for improved chances of survival. Genomics and precision medicine will become an increasingly critical component of cancer care in the future, as the focus shifts from treating tumours based on tissue of origin to treating tumours based on molecular profile. Genomic testing using next-generation sequencing technology is a key area of focus for NOA, as this technology can provide a molecular diagnosis for a patient's cancer, important prognostic information, and the opportunity to access precision medicines. Ultimately, it is hoped this will lead to greater longevity and improved quality of life for all cancer patients.

2.2 Objectives

This report seeks to characterise the cancer genomics landscape in Australia and explore the salient considerations around defining a path towards broad funded genomic testing for cancer patients. Diagnosis, treatment, and prediction of cancer is increasingly guided by genomics, as our understanding of cancer grows, and new technologies improve cancer survivorship. With cutting-edge research capabilities and a world-class equitable healthcare system, Australia is well-positioned to continue investing in the frontiers of genomics research and take bold steps towards fully integrating genomics into cancer care.

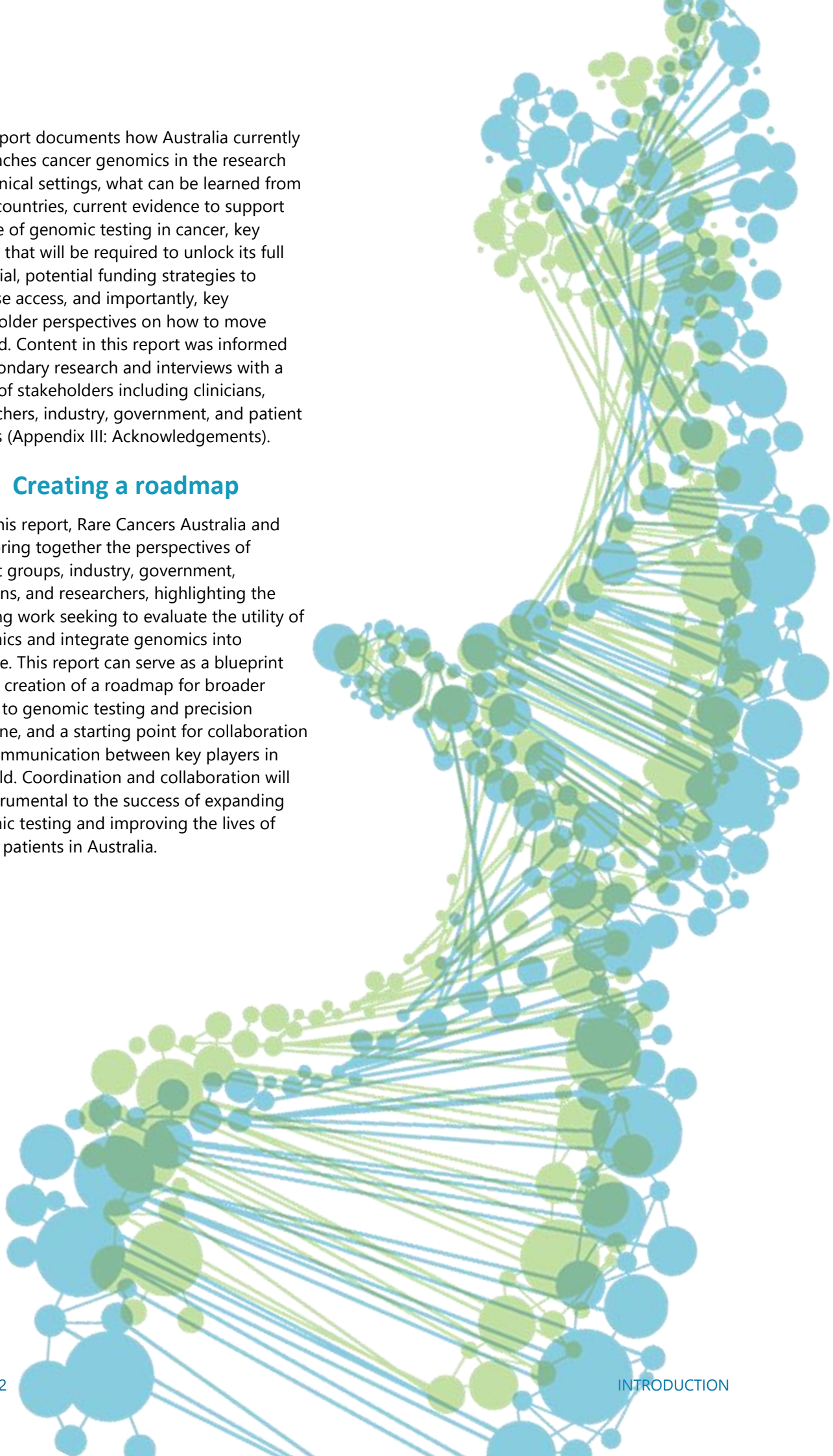
Figure 1. Purpose and objectives



This report documents how Australia currently approaches cancer genomics in the research and clinical settings, what can be learned from other countries, current evidence to support the use of genomic testing in cancer, key factors that will be required to unlock its full potential, potential funding strategies to increase access, and importantly, key stakeholder perspectives on how to move forward. Content in this report was informed by secondary research and interviews with a range of stakeholders including clinicians, researchers, industry, government, and patient groups (Appendix III: Acknowledgements).

2.3 Creating a roadmap

With this report, Rare Cancers Australia and NOA bring together the perspectives of patient groups, industry, government, clinicians, and researchers, highlighting the ongoing work seeking to evaluate the utility of genomics and integrate genomics into practice. This report can serve as a blueprint for the creation of a roadmap for broader access to genomic testing and precision medicine, and a starting point for collaboration and communication between key players in this field. Coordination and collaboration will be instrumental to the success of expanding genomic testing and improving the lives of cancer patients in Australia.



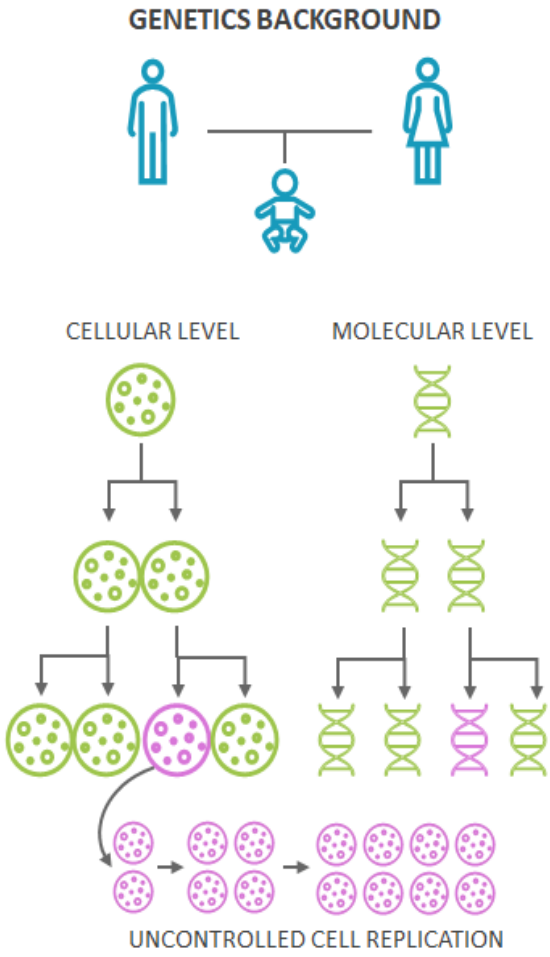
3 Genomics Background

3.1 What is cancer?

Understanding genomics and its relevance to cancer starts with an understanding of the genetic code. Each human being is derived from a blueprint, which we call our genetic code, or DNA. We inherit our genetic code from our parents – one copy from each parent – and the two come together to make us who we are (for example, our DNA determines our hair colour, eye colour, and can also influence our risk of developing diseases). Each cell in the body carries a copy of the genetic code. The genetic code tells the cell how to behave (for example, it tells hair cells to be hair cells and eye cells to be eye cells). Over the course of our lifetimes, most cells replicate and die continuously as part of normal growth and ageing. In each cell, the genetic code can sometimes accumulate errors as it is copied during cell replication. The errors that arise during replication are called mutations. Some mutations may cause cells to behave abnormally. Mutations can cause cells to become cancerous, meaning that they replicate in an uncontrolled manner. These abnormal cells can damage or invade surrounding tissues, or spread to other parts of the body, causing further damage. This is called cancer. (2)

The genome is the complete set of genes encoded in our genetic code, and genomics is the study of the genome. Genomic testing allows us to analyse the genetic code on a large scale and find mutations and structural patterns associated with cancer. (3)

Figure 2. Genetics background



Half of our genetic code is inherited from each parent to create a unique blueprint. The DNA inside a cell replicates when the cell divides into two cells. Mutations, or errors, may arise during the replication process and these may lead to uncontrolled cell replication.

3.2 Genomics in cancer diagnostics and treatment

Genomics has many applications in cancer. Genomic testing is used to understand gene mutations, patterns of mutations, and other alterations to the genetic code inside tumour tissue. Genomic testing typically refers to tests that look at larger sections of the genome, compared to genetic testing which is more focused on individual genes or groups of genes.

In research settings, genomic information can help identify new alterations such as mutations, fusions, rearrangements, patterns, or proteins (also called "targets") that researchers might attempt to target with novel drugs (Figure 3). Using genomic testing in research settings provides a wealth of genomic data which can be used to study cancers, especially when sample sizes are robust. Genomic testing is also used in clinical research to identify patients who are most likely to benefit from investigational drugs in clinical trials.

Genomic testing typically refers to tests that look at larger sections of the genome, compared to genetic testing which is more focused on individual genes or groups of genes

Figure 3. Types of genomic alterations

TYPE OF ALTERATION	DESCRIPTION	EXAMPLE	TYPICAL METHOD OF DETECTION
Point mutation	Single nucleotide substitution	EGFR L858R (lung cancer)	Sanger sequencing or targeted genotyping methods
Insertion/deletion	Nucleotides are inserted or deleted in exonic (coding) portions of the genome	HER2 exon 20 insertion (lung cancer)	Sanger sequencing or PCR-based sizing assays)
Gene amplification	Region of coding DNA acquires more than the normal two copies from each parent	HER2 gene amplification (breast cancer)	FISH
Fusion/rearrangement	Sections of DNA which are not normally adjacent become fused	ALK fusion (lung cancer	FISH (with limitations), RT-PCR
Gene deletion	Deletion of a gene	CDKN2A deletion (blood cancers)	FISH
Non-recurring variants	Unique to the individual and their tumour	N/A	NGS, microarray

Source: My Cancer Genome

Abbreviations: ALK, anaplastic lymphoma kinase; CDKN2A, cyclin-dependent kinase inhibitor 2A; DNA, deoxyribonucleic acid; EGFR, epidermal growth factor receptor; FISH, fluorescence *in situ* hybridisation; HER2, human epidermal growth factor 2; IHC, immunohistochemistry; N/A, not applicable; NGS, next-generation sequencing; PCR, polymerase chain reaction; RT-PCR, reverse transcription polymerase chain reaction

In clinical settings, genomic testing can provide a molecular diagnosis for a cancer. For example, a breast cancer patient's diagnosis can be further specified to indicate whether the patient is positive for the HER2 mutation. This kind of detail is useful in helping to understand prognosis and which treatments may be best suited for the patient. Some genomic alterations are also known to be associated with better or poorer prognosis, and this information can help patients plan their treatment and other life decisions. Often, genetic or genomic testing is used to identify patients who are most likely to benefit from targeted drugs. Targeted drugs, also called targeted therapies, are designed to work in patients who have a specific genetic alteration, therefore identifying the target is often a prerequisite for reimbursement of the drug by the government. For example, a breast cancer patient identified as HER2-positive will then be able to access trastuzumab through the Australian Pharmaceutical Benefits Scheme (PBS). Using molecular or genetic characteristics to inform cancer care is typically referred to as biomarker-based treatment, molecular-matched therapy, precision medicine, or personalised medicine. This terminology will be used throughout this report.

Patient groups consistently emphasise that cancer care is not only improved through access to new technologies, but through patient-centric approaches to treatment that consider patient goals and quality of life. The best approach for each patient should be determined based on a holistic assessment of clinical characteristics and patient priorities. Cancer care benefits immensely from innovative technologies and personalised treatments, however stakeholders argue that personalisation should extend beyond finding the treatment that works best with a tumour's molecular profile to include finding a solution that works best with the patient's goals.

3.3 Testing technology

Testing for genetic or genomic alterations can be performed using several pathology techniques. Typically, anatomical pathologists observe the tumour's histology under a microscope. Subsequently, molecular pathology tests can be conducted to identify genetic or genomic alterations or the presence of specific proteins. Conventional pathology techniques for genetic and genomic testing include *in situ* hybridisation (ISH), fluorescence *in situ* hybridisation (FISH), immunohistochemistry (IHC), mass spectrometry, polymerase chain reaction (PCR), single nucleotide polymorphism (SNP) microarrays, array comparative genomic hybridisation (aCGH), and multiplex ligation-dependent probe amplification (MLPA). Some techniques are best suited to identifying small target sections of DNA (e.g. PCR, Sanger sequencing), others detect specific proteins (e.g. mass spectrometry, IHC), and still others can study larger sections of the genome (e.g. SNP microarray, aCGH). Figure 4 outlines each technique.

Conventional pathology techniques for genetic and genomic testing include ISH, FISH, IHC, PCR, SNP microarrays, aCGH, and MLPA. Next-generation sequencing is a high-throughput method of sequencing many sections of genetic material simultaneously.

Figure 4. Conventional pathology techniques

***In situ* hybridisation (ISH)**	Locates positions of specific DNA segments on chromosomes by using known "probes" labelled with radioisotopes or fluorescent tags (fluorescence *in situ* hybridisation, or FISH) e.g.: ALK gene rearrangement.
Immunohistochemistry (IHC)	Uses antibodies for the detection of specific antigens in tissue sections. Important in detecting newly expressed or up-regulated tumour antigens in certain cancers e.g.: HER2 amplification.
Mass spectrometry	Analytical technique used to study proteins; used in cancer to detect tumours, monitor progression, and even predict tumour response e.g.: small hotspot panel.
Polymerase chain reaction (PCR)	Rapid method of amplifying a small segment of DNA to create quantities large enough for analysis. Multiple methods of analysis can be used once DNA is amplified e.g.: 1-4 genes (not as sensitive with more genes).
Sanger sequencing	Targeted technique using primers to seek out specific DNA regions. Used commonly with PCR-amplified DNA e.g.: point mutation, small deletion or duplication.
Single nucleotide polymorphism (SNP) microarrays	Uses DNA probes that derive from regions in the genome that show slight variations between individuals at the base-pair level. Less design bias than CGH e.g.: detecting loss of heterozygosity (LOH).
Comparative genomic hybridisation (CGH)	Compares fluorescently labelled sample genome with control; does not rely on specific target. Array comparative genomic hybridisation (aCGH) simultaneously analyses 100s-1000s of discrete regions in the genome.
Multiplex ligation-dependent probe amplification (MLPA)	Variation of PCR that permits amplification of multiple targets with one primer. Best applied to detect CNVs in specific regions. Can be methylation-specific e.g.: MGMT promoter methylation in glioblastoma.

Abbreviations: aCGH, array comparative genomic hybridisation; ALK, anaplastic lymphoma kinase; CGH, comparative genomic hybridization; CNV, copy number variation; DNA, deoxyribonucleic acid; FISH, fluorescence *in situ* hybridisation; HER2, human epidermal growth factor 2; IHC, immunohistochemistry; ISH, *in situ* hybridisation; LOH, loss of heterozygosity; MLPA, multiplex ligation-dependent probe amplification; MGMT, O6-methylguanine DNA methyltransferase; PCR, polymerase chain reaction; SNP, single nucleotide polymorphism

Massively parallel sequencing (MPS) technology, commonly known as next-generation sequencing (NGS), is a high-throughput method of sequencing many sections of genetic material simultaneously. NGS technology has advanced significantly since the early 2000s and the costs continue to decline. NGS is capable of analysing genes, exomes, genomes, transcriptomes (RNA), and DNA methylation. (4)

Genetic and genomic tests analyse solid or liquid samples of tissue. Solid tumour biopsy samples are often formalin-fixed paraffin-embedded (FFPE) or can be fresh-frozen (FF). For larger analyses such as whole genome sequencing (WGS), FFPE does not have high enough quality and fresh samples must be used. (5) Blood and bone marrow samples are usually used for patients with haematological malignancies. (6) Blood samples are increasingly being investigated as a less invasive method of obtaining testable samples from solid cancer patients. Circulating tumour cells, circulating tumour DNA, and exosomes can be analysed from these blood samples (also known as liquid biopsies). (7)

NGS technology is transformative for research, and as it becomes increasingly cost-effective, it is becoming more common in clinical practice. NGS is discussed in more detail in Section 5.

4 Current Landscape of Genetic & Genomic Testing in Cancer

4.1 Function of genetic and genomic cancer tests

Genetic and genomic testing can serve several functions in the oncology setting:

- **Screening:** for family members of patients with a known mutation or other patients thought to be at high risk for cancer. For example, BRCA1/2 screening for biological relatives of patients with breast or ovarian cancer (MBS item 73297).
- **Prognostic:** to further understand the nature of a patient's diagnosis, disease severity, and risk of recurrence. For example, OncotypeDx®, a 21-gene test for hormone receptor-positive cancer which provides prognostic information on chance of recurrence and likelihood of response to chemotherapy (not listed on MBS).
- **Diagnostic:** to confirm diagnosis of a disease suspected based on other laboratory and clinical evidence. For example, JAK2/MPL mutation test in patients with clinical and laboratory evidence of having polycythaemia vera (PV) (MBS item 73325).
- **Monitoring:** to monitor changes in a patient's condition after diagnosis. For example, detection of genetic polymorphisms in the thiopurine S-methyltransferase gene for prevention of dose-related toxicity during treatment with thiopurine drugs for leukaemia or lymphoma (MBS item 73327).
- **Companion diagnostic:** to identify whether a diagnosed patient has an alteration that will allow them to access an approved treatment. For example, an EGFR mutation test for patients with NSCLC for access to erlotinib, gefitinib, or afatinib under the PBS (MBS item 73337).

4.2 Access to targeted therapies

Small molecule inhibitors and monoclonal antibodies are both types of targeted therapy. Small molecule inhibitors block specific growth-related proteins inside cancer cells. Monoclonal antibodies, which are a type of immunotherapy, are synthetic versions of antibodies (immune system proteins) which interfere with growth or survival of cancer cells. (8) PBS-listed targeted therapies are listed in Appendix I: PBS-Listed Targeted Therapies.

Small molecule inhibitors and monoclonal antibodies are both types of targeted therapy.

Tyrosine kinase inhibitors (TKIs) are a common type of small molecule targeted drug. Some examples include EGFR-targeted drugs for

NSCLC such as gefitinib (Iressa®), erlotinib (Tarceva®), and crizotinib (Xalkori®), as well as drugs for Philadelphia chromosome-positive leukaemias such as imatinib (Glivec®), dasatinib (Sprycel®), and nilotinib (Tasigna®). Other types of small molecule drugs include mammalian target of rapamycin (mTOR) inhibitors such as everolimus (Afinitor®) for pancreatic neuroendocrine tumours and PARP inhibitors such as olaparib (Lynparza®) for ovarian cancer.

Checkpoint inhibitors are a type of monoclonal antibody that prevent the cancer cells from inhibiting the immune system, allowing the body's immune system to fight the cancer more effectively. They target the PD-1/PD-L1 or the CTLA-4 checkpoint pathways. (9) Immunohistochemistry is therefore a commonly used pathology technique to test for the PD-L1 protein prior to treatment with a checkpoint inhibitor. (10) Genomic signatures such as high tumour mutational burden (TMB) and microsatellite instability (MSI), which are characterised through NGS testing, can also predict a stronger response to checkpoint inhibitors given that highly immunogenic tumours are most responsive. (10) Recently, TMB-H[1] and MSI-H[2] solid tumours became eligible for treatment with pembrolizumab in the United States. Examples of PBS-reimbursed checkpoint inhibitors include pembrolizumab (Keytruda®), atezolizumab (Tecentriq®), nivolumab (Opdivo®), ipilimumab (Yervoy®), durvalumab (Imfinzi®), and avelumab (Bavencio®).

Genomic signatures can predict a stronger response to checkpoint inhibitors as highly immunogenic tumours are most responsive.

Other monoclonal antibodies target specific proteins or receptors. Examples include VEGF- or EGFR-targeted agents such as bevacizumab (Avastin®) for several solid tumours and cetuximab (Erbitux®) for RAS wild-type colorectal cancer.

[1] https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pembrolizumab-adults-and-children-tmb-h-solid-tumors

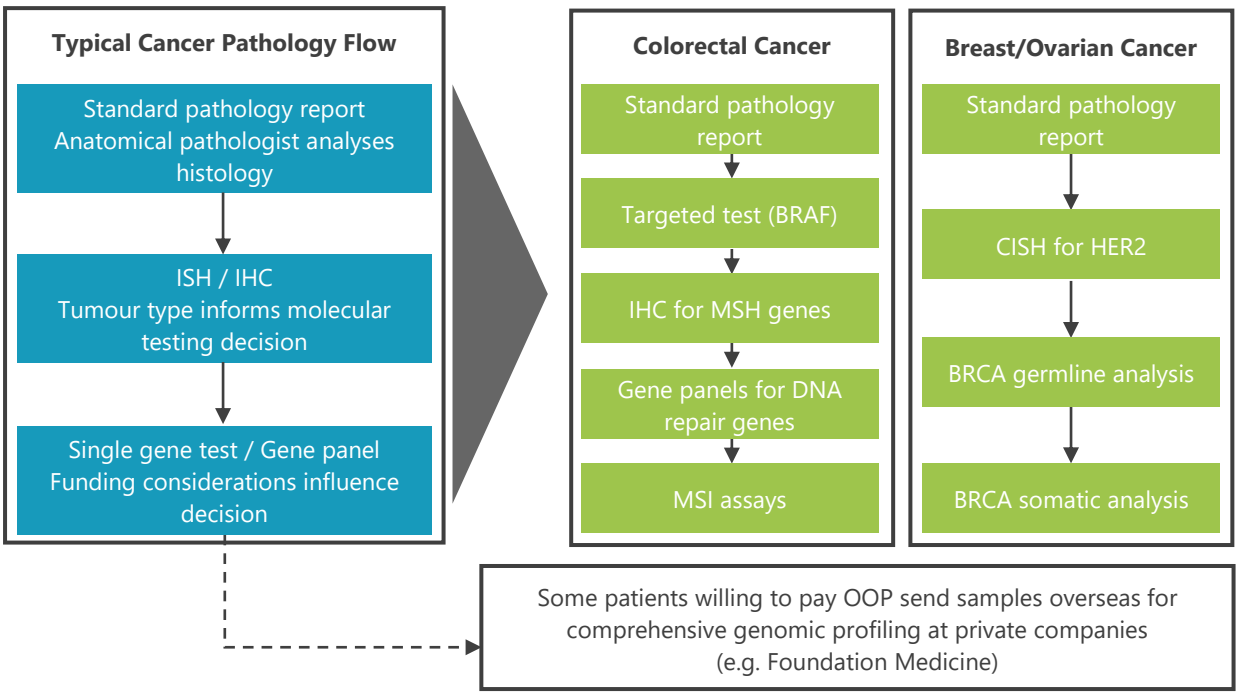
[2] https://www.fda.gov/news-events/press-announcements/fda-approves-first-cancer-treatment-any-solid-tumor-specific-genetic-feature

4.3 Clinical utilisation of genetic and genomic tests

4.3.1 Diagnostic journey

According to pathologists, utilisation of genetic and genomic testing in clinical practice is highly informed by MBS funding. Of the 46 cancer-related genetic or genomic testing items currently listed on the MBS, most are tests for single mutations or alterations and typically include no more than five variants.

Figure 5. Example cancer diagnostic pathways



Abbreviations: BRAF, proto-oncogene B-Raf; CISH, chromogenic *in situ* hybridisation; IHC, immunohistochemistry; ISH, *in situ* hybridisation, MSH, MutS homolog; MSI, microsatellite instability; OOP, out of pocket

As a result, there is minimal funding flexibility to run larger panels testing for multiple variants at once. Some patients may therefore find themselves on what some stakeholders have called "testing odysseys," which involve a series of single-gene or targeted tests (Figure 5). The cumulative costs of sequential testing can sometimes add up to over $1,000, in which case the cost of doing a targeted NGS panel would be the same or cheaper (pathologists estimate a panel for 3 to 4 genes would cost around $600). Costs of sequential testing compared to NGS testing are discussed further in Section 9.2.1. Furthermore, conducting a panel rather than sequential testing could be advantageous for patients who have limited biopsy tissue, which is a common problem. Pathologists acknowledge that there will likely always need to be some level of sequential analysis – for example, the standard histopathology report will continue to be an integral first step in the diagnostic process. However, pathologists and clinicians believe some of the downstream tests could be performed more efficiently.

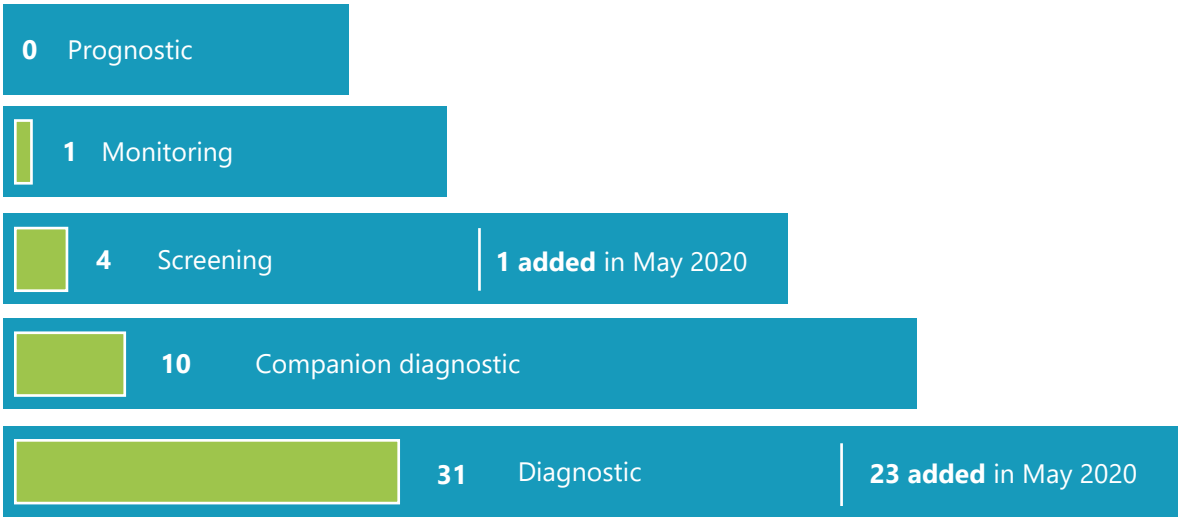
> The cumulative costs of sequential testing can sometimes add up to over $1,000, in which case a targeted NGS panel would be the same cost or cheaper.

4.3.2 Federally funded utilisation

The most common types of genetic and genomic tests listed on the MBS are diagnostic and companion diagnostic tests. In May 2020, 23 new diagnostic tests and one new screening test were added as part of a wave of Medical Services Advisory Committee (MSAC) approvals for group submissions covering various solid tumours and haematological cancers. The tests were grouped into three MSAC applications submitted by the Royal College of Pathologists of Australasia (RCPA):

1. Somatic tumour gene testing for diagnosis of diffuse large B-cell lymphoma, multiple myeloma, and subtypes of Non-Hodgkin's lymphoma (Application No. 1526)
2. Somatic tumour gene testing for diagnosis of gliomas, glioblastomas, and soft tissue and bone tumours
3. Somatic tumour gene testing for diagnosis of renal cell carcinoma, hydatidiform moles, granulosa cell ovarian tumour, salivary gland tumours, and secretory carcinoma of the breast

Figure 6. MBS-listed genetic/genomic cancer-related tests by function



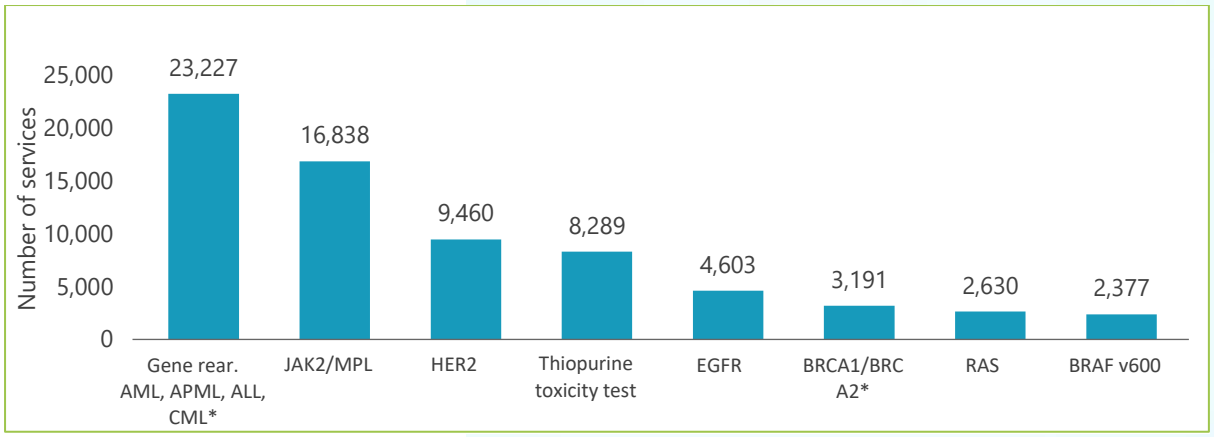
Source: MBS Services List

Based on MBS item reports, the genetic/genomic test with the highest utilisation is the gene rearrangement/mutation test for acute myeloid leukaemia (AML), acute promyelocytic leukaemia (APML), acute lymphoblastic leukaemia (ALL), and chronic myeloid leukaemia (CML) (MBS item numbers 73314 and 73315). In 2019, there were over 20,000 services for these two items, for which the fee is $230.95. Other mutations commonly tested include JAK2/MPL for PV, HER2 for breast cancer, EGFR for NSCLC, BRCA1/BRCA2 for breast or ovarian cancer, RAS for CRC, and BRAF v600 for melanoma (Figure 7).

Most somatic single-gene or rearrangement tests are reimbursed between $300 and $400. The recently listed sarcoma panels were organised into three fee tiers: $340 for one gene, $400 for two to three genes, and $800 for four to 21 genes. Germline tests for two to five gene rearrangements are listed at $1,200.

In 2019, there were over 20,000 services for gene rearrangement/ mutation testing for acute myeloid leukaemia (AML), acute promyelocytic leukaemia (APML), acute lymphoblastic leukaemia (ALL), and chronic myeloid leukaemia (CML).

Figure 7. Number of services for top eight genetic/genomic cancer-related tests funded by MBS (2019)



TUMOUR	MBS FEE	TOTAL BENEFIT
AML, APML, ALL, CML	$230.95	$4,547,999
PV	$74.50	$1,065,786
Breast	$315.40	$2,399,595
Leukaemia, lymphoma	$51.95	$364,940
NSCLC	$397.35	$1,498,400
Breast, ovarian	$1,200 (patient) $400 (relative)	$2,372,041
Colorectal	$362.60	$797,633
Melanoma	$230.95	$457,228

Source: MBS Item Reports

Abbreviations: ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; APML, acute promyelocytic leukaemia; BRAF v600, proto-oncogene B-Raf v600; BRCA1/BRCA2, breast cancer gene 1/breast cancer gene 2; CML, chronic myeloid leukaemia; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; JAK2, janus kinase 2; MBS, Medicare Benefit Schedule; MPL, myeloproliferative leukaemia; NSCLC, non-small cell lung cancer; PV, polycythaemia vera; RAS, rat sarcoma

*Combines two MBS items for the same service with slight differences in method of delivery or patient population – 73314 with 73315 for gene rearrangement in AML, APML, ALL, CML and 73296 with 73297 for BRCA1/BRCA2. Note: the BRCA1/BRCA2 test also optionally includes STK11, PTEN, CDH1, PALB2, and/or TP53.

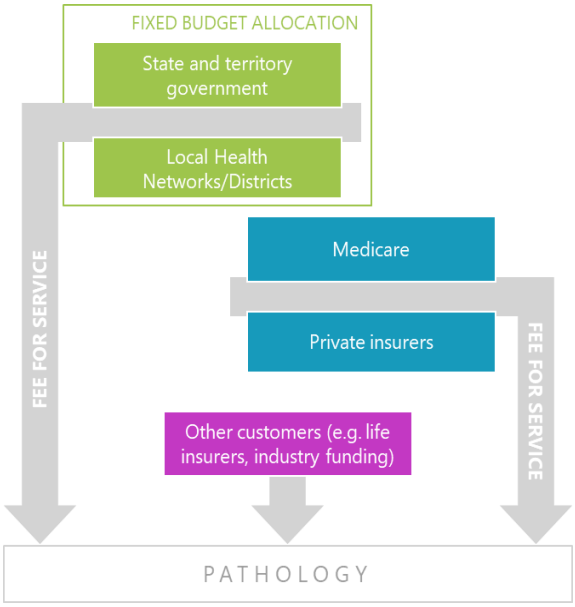
Note: MBS benefit paid was between 75% and 95% of the schedule fee.

4.4 Funding

4.4.1 Pathology funding structure

Pathology is funded through a mix of federal funding from the MBS and state funding from state hospitals. State and territory governments allocate funding to Local Health Networks (LHNs), which then distribute funding accordingly to hospitals within their networks. Hospitals generally have a fixed budget allocation for pathology (Figure 8).

Figure 8. Pathology funding structure



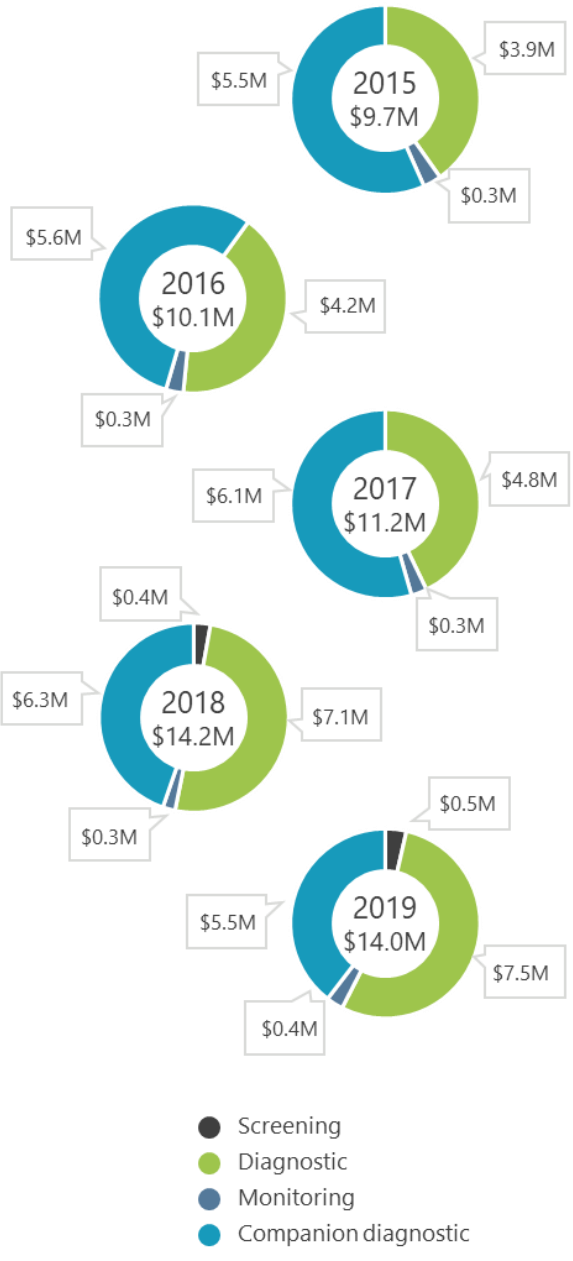
According to pathologists, laboratories typically charge hospitals for genetic and genomic tests on a fee-for-service basis. Federal Medicare funding is also fee-for-service according to the MBS item schedule fee. Despite the lower relative cost of testing compared to treatments, pathologists report that pathology has typically been underfunded compared to pharmaceuticals. Several pathologists suggested that there should be wider use of pathology to better target use of expensive pharmaceuticals.

4.4.2 Medicare spending on genetic and genomic testing

MBS spending on genetic and genomic testing increased by 24% between 2012 and 2016, with $43.5 million spent in 2016 (inclusive of both cancer and non-cancer tests). However, Medicare's coverage is limited compared to the number of tests available in Australia: there are over 80 genetic/genomic tests (46 of which are cancer-related) listed on the MBS, while there are approximately 1,700 types of tests being performed by laboratories across Australia. (11)

In the last five years, the majority of MBS spending on genetic and genomic tests was for diagnostic and companion diagnostic testing (Figure 9).

Figure 9. MBS benefit for cancer-related testing by test function ($, millions)



Source: MBS Item Reports

4.4.3 Limitations

Pathologists report that pathology services are largely limited by a lack of funding. The current approach to pathology is relatively narrow, in that the funded tests search for pre-specified variants of known significance. This approach often has the highest utility and lowest uncertainty because there are typically actionable steps clinicians and patients can take based on the test results. However, many clinicians and researchers argue that genetic and genomic testing should ideally seek to gain a deeper understanding of the cancer. Ultimately, they argue, a broader approach will help improve management of cancer for future patients as well as current patients.

While there is no MBS item for NGS testing in cancer, two MBS items for whole exome sequencing (WGS) were listed in May 2020 for children suspected of having monogenic conditions cause by germline variants. These panels have fees of $2,100 for singleton testing and $2,900 for trio testing (discussed further in Section 9.2). This may set a precedent for future large scale NGS tests to be listed for cancer indications.

5 Next-Generation Sequencing

5.1 What is next-generation sequencing?

NGS is high-throughput method of sequencing genetic material (DNA or RNA). Its ability to sequence many sections of genetic material at once has vastly decreased the time required for genomic sequencing and opened new possibilities for genomic research and clinical applications. As the cost of sequencing large sections of DNA and even whole genomes continues to decline, it has become increasingly feasible to use genomic information to guide approaches to research and clinical practice. The valuable applications of NGS technology in cancer are 1) identifying patients who are likely to benefit from existing or investigational targeted agents, 2) understanding prognostic information about the patient's cancer, and 3) identifying new potential targets for research (especially when sequencing large enough sections of DNA that incidental findings occur). When tests are used to determine patient eligibility for a corresponding therapy, the test is referred to as a companion diagnostic. The nature of this technology means that use of NGS testing, especially on larger sections of the genome, will lead to new discoveries and more research. Strong connections between clinical practice and research will be integral to the full realisation of the value of NGS. Section 1 discusses the value and utility of NGS in more detail.

Clinicians and researchers have explained that while cancer was historically categorised by tissue of origin, it is increasingly common to define a cancer in molecular terms as well. Most targeted therapies are indicated for a specific tissue-variant combination, as described in Section 4.2. However, the first pan-cancer tissue-agnostic therapies have been approved overseas. For example, pembrolizumab (Keytruda®) was approved by the United States Food and Drug Administration (FDA) in 2017[3] for patients with tumours characterised as microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR). Larotrectinib and entrectinib were also FDA-approved in 2018 and 2019 for advanced solid tumours with NTRK fusions[4]. In June 2020[5], the FDA also approved pembrolizumab for unresectable or metastatic solid tumours with high TMB. As molecular insights about cancer continue to direct treatment and research, NGS will likely become an increasingly important part of the diagnostic journey for cancer patients as it helps provide a more detailed diagnosis and inform treatment selection or clinical trial eligibility.

[3] https://www.fda.gov/news-events/press-announcements/fda-approves-first-cancer-treatment-any-solid-tumor-specific-genetic-feature

[4] https://www.cancer.gov/news-events/cancer-currents-blog/2019/fda-entrectinib-ntrk-fusion

[5] https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pembrolizumab-adults-and-children-tmb-h-solid-tumors

5.2 Hardware and panels

NGS capabilities exist in many laboratories across Australia. Two industry players in the genomic sequencing field are an American company called Illumina and a Chinese company called BGI. Illumina and BGI manufacture both sequencing hardware as well as proprietary assays. According to an industry stakeholder, Illumina's biggest instrument (called NovoSeq) costs approximately $1 million and has a maximum output of 6000Gb. It is the only Illumina sequencer that can conduct human WGS and it can run over 64 samples at once. The NextSeq instruments are the next-largest, costing $350,000 - $400,000, with a maximum output of 120Gb – 300Gb. Illumina also offers the iSeq, MiniSeq, and MiSeq sequencers, which can all sequence targeted gene panels, conduct targeted gene expression analyses, and conduct small RNA analyses. (12)

NGS can be used in a variety of ways – from hotspot panels targeting a small subset of genes, to large comprehensive panels targeting hundreds of genes, all the way up to whole genome analyses. The term "panel" refers to a group of genes analysed in one test. A hotspot panel may contain approximately five to 50 genes, while a comprehensive panel contains hundreds. Laboratories and private companies design panels by selecting genes relevant to cancer treatment and care. Table 1 lists several examples of tests which use NGS technology.

Table 1. Types of tests using NGS

Test	Genetic material	Number of genes/ base pairs	Purpose
Hotspot panel	DNA	5 to 50 genes	Targeted panels consist of well-known common driver mutations. They are often used to understand which targeted therapies, if any, a patient would be eligible to use.
Comprehensive genomic profiling (CGP) panel	DNA +/- RNA	300 to 500 genes	Comprehensive panels contain genes known to be involved in cancers. These panels provide information not only on mutations, but also structural issues such as TMB, microsatellite instability (MSI), and/or loss of heterozygosity (LOH). (13, 14)
Whole exome sequencing (WES)	DNA	Whole exome (1% of genome)	The exome, which is the protein-coding region of the genome, is thought to contain most disease-causing mutations. WES can be considered an efficient method of genomic testing given that it targets the sections that have a higher probability of containing pathogenic mutations. (15)
Whole genome sequencing (WGS)	DNA	Whole genome	As the most comprehensive form of DNA sequencing, WGS can detect single nucleotide variants, insertions/deletions, copy number changes, and large structural variants across the entire genome. This is currently used mostly in research settings. (16)
RNA sequencing (RNAseq)	RNA	Short-read: 100-300 bp Long-read: >1000 bp (length of full mRNA)	RNAseq is a catch-all term for various approaches to RNA sequencing, such as differential gene expression (DGE) or detection of fusions. (17)
Methylation analysis	DNA	1000 base pairs to whole genome	Methylation analyses can characterise DNA methylation at single bp resolution to provide epigenetic information. (18)

Abbreviations: bp, base pair; CGP, comprehensive genomic profiling; DNA, deoxyribonucleic acid; LOH, loss of heterozygosity; mRNA, messenger ribonucleic acid; MSI, microsatellite instability, RNA, ribonucleic acid; TMB, tumour mutational burden; WES, whole exome sequencing; WGS, whole genome sequencing

5.3 Use of NGS panels in practice

Most laboratories in Australia use NGS technology for smaller hotspot panels given that larger analyses are not yet reimbursed by state or Medicare pathology funding, according to genomic sequencing industry stakeholders and pathologists at RCPA. For example, MBS item 73296 for germline BRCA1/BRCA2 +/- STK11, PTEN, CDH1, PALB2, and/or TP53 in patients with breast or ovarian cancer has a rebate of $1,200, which is adequate to cover the costs of NGS and interpretation.

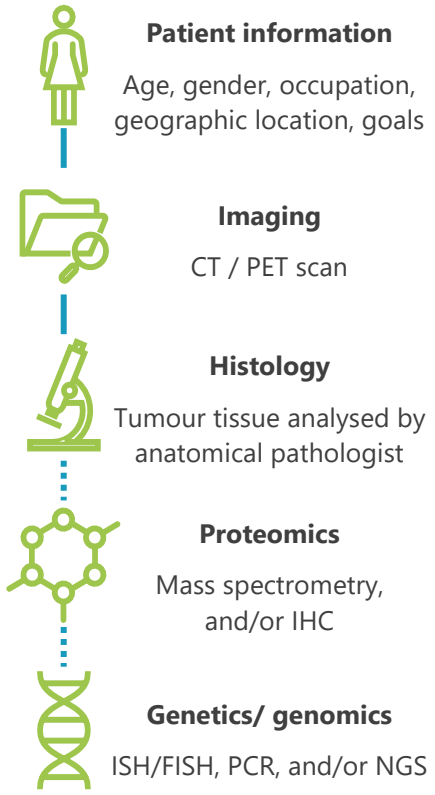
Comprehensive genomic profiling (CGP) and other large-scale genome analyses are usually only offered in the clinical research setting or when patients are willing to pay out-of-pocket. Only a few centres of excellence (CoEs) in Australia currently offer comprehensive NGS tests as part of research; these include among others the Peter MacCallum Cancer Centre, the Garvan Institute of Medical Research and the Monash Cancer Centre. Section 9.4 further details the current research landscape in Australia.

Clinicians and patient groups report that some patients pay out-of-pocket (OOP) for CGP performed by companies such as Foundation Medicine, Inc., which was acquired by Roche in 2018[6]. Most patients cannot afford the OOP costs, presenting an equity issue (Section 11), and those who can afford access may spend several thousand dollars to send their samples to Foundation Medicine's laboratory in the United States for testing. Foundation Medicine then provides a report which patients' clinicians can interpret and use to inform treatment, however identifying an actionable result is not guaranteed.

5.4 What does NGS replace?

Despite the presence of existing NGS capabilities in Australia, pathologists and clinicians from leading institutions have reported that sequential testing using conventional techniques is common in the clinical setting. Throughout the diagnostic flow outlined in Figure 10, clinicians and pathologists gather more information at each stage and must decide at each step whether to order subsequent tests. These decisions, according to a pathologist from a leading academic institution, are often based on costs and reimbursement. There is therefore an unmet need around streamlining the diagnostic process by allowing pathologists and clinicians to make testing decisions based on the clinical information available rather than cost concerns.

Figure 10. High-level oncology diagnostic flow. This flow represents a common path, however there is variation depending on the clinician, pathologist, and nature of the cancer. Testing after histological analysis may not always be necessary



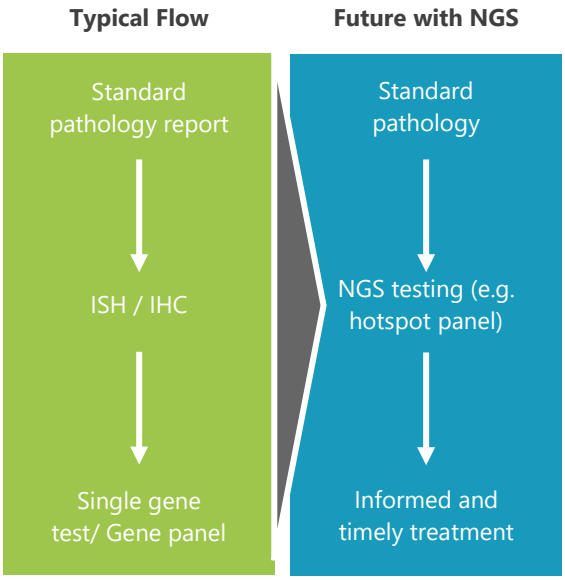
Abbreviations: CT, computed tomography; FISH, fluorescence *in situ* hybridisation; IHC, immunohistochemistry; ISH, *in situ* hybridisation; Mb, megabase; NGS, next-generation sequencing PCR, polymerase chain reaction; PET, positron emission tomography

[6] https://www.roche.com/media/releases/med-cor-2018-06-19.htm

Depending on the type of assay used, further use of NGS in clinical practice could supplement or replace one or more steps in the diagnostic journey of cancer patients after the standard histopathology report:

- Hotspot panels containing multiple genes of interest can replace sequential single-gene testing.
- CGP can replace single-gene tests, gene panels, somatic analyses, and MSI assays. CGP would also provide information about TMB.
- WES and WGS could replace single-gene tests, gene panels, somatic analyses, MSI assays, and germline analyses. WES and WGS would provide information about TMB and a wealth of additional information on structural variants.

Figure 11. Potential impact of NGS on diagnostic flow



In addition to streamlining the diagnostic process, the utility of NGS testing is especially high when clinicians are unsure of the cancer's driver mutation, as NGS testing enables testing for many potential alterations at once. This is especially relevant for patients with rarer cancers or patients facing non-curative treatments. In these situations, NGS can supplement existing tests to provide a last-line option, with results linking to off-label therapies or clinical trials. This is discussed further in Section 1.

5.5 Analysis and interpretation

Analysis and interpretation of the test results are key elements of the NGS testing process. The larger the panel, the more information is uncovered, and the more potential uncertainty if findings of unknown significance are discovered. This element of NGS is top of mind for experts in the field, who are working to establish processes and methods for how to manage such large amounts of information and derive clinically meaningful insights.

The labour for analysis and interpretation depends on the scope of the test. Hotspot panels and even CGP panels can have automated outputs. Foundation Medicine, Illumina, and BGI provide automatically generated reports on the test findings for CGP panels. The reports indicate which variants were discovered, the level of relevance of each, and may contain information on relevant treatments or clinical trials. Some oncologists view these reports as sufficient to support clinical decision-making, while others believe further interpretation among experts is necessary. Software programs which can assist with the bioinformatics and interpretation process are discussed further in Section 8.3.

The analysis of raw outputs by bioinformaticians is also an area of debate, with one expert describing the increasing need for bespoke data analyses rather than automated reports as the scope of the panel increases. There are two stages of bioinformatics involved the analysis of NGS testing outputs. Genome bioinformatics entails decoding the raw genomic data to identify and annotate genetic variants. At this stage, bioinformaticians do not make any conclusions about the significance of individual variants. The findings are translated into interpretable results in the next step, which is called clinical bioinformatics.

Multidisciplinary molecular tumour boards (MTBs) bring together specialists to interpret the outputs of comprehensive panels and

larger exome- or genome-wide analyses. MTBs, organised by major cancer centres, also help facilitate continuous learning in the field. While this approach may be considered best practice by some stakeholders, it is not considered sustainable for all patients given the large amount of time required from experts and the current lack of structural funding or reimbursement for these activities. Clinicians ultimately make time to participate in MTBs to improve their practice and the field, however this is likely unsustainable. This fledgling infrastructure requires adequate funding to become a part of standard care. There are MBS item numbers[7] for multidisciplinary case conferences, however they do not seem suited to MTBs, which are 60- to 90-minute meetings to which dozens of participants may be invited. Most stakeholders consulted during this research emphasised that a genomic test alone will not deliver the desired results. Interpretation of the test output, even if part of that process is automated, is critical to unlocking its value. The larger the panel, the greater the value of an MTB's interpretation. In cases where the case complexity may not justify conducting an MTB, some pathologists and researchers assert that it would be reasonable to use a multidisciplinary team (MDT).

5.6 The timing of NGS

The timing of NGS-based genomic testing in the diagnostic and treatment journey is a key area for continued discussion. There appears to be consensus among clinicians, researchers, pathologists, and patient groups that conducting genomic testing using NGS as early as possible after diagnosis is ideal to best inform treatment decisions. Not only would this help clinicians select the treatments that are most likely to yield the best outcomes, they would also be able to avoid treatments that are unlikely to be beneficial (or could even be harmful).

Given that the genetic makeup of cancer often evolves over time and in response to treatments, many stakeholders believe re-testing would be valuable for some patients after treatment failure to help reformulate the treatment strategy. While this would provide clinical value, clinicians acknowledge that the logistics would be complicated: obtaining new biopsies from patients is invasive and often impractical, more time is required for new analyses to be conducted, and costs are higher. With these considerations in mind, the priority for clinicians would be to at least conduct a genomic test as soon as possible after diagnosis to inform the treatment plan from the start of the journey.

5.7 Use of NGS in different cancer groups

The approach to NGS-based genomic testing must also consider the type of cancer and the patient's individual characteristics. Two natural groups of cancers with distinct considerations around NGS testing are solid cancers and haematological cancers. Many targetable alterations have been identified in common solid cancers such as non-small cell lung cancer (NSCLC), colorectal cancer (CRC), and breast cancer, and reimbursed treatments are available for those alterations through the PBS. In terms of diagnostic journey, patients with such cancers can usually be effectively managed using panel testing to identify which alteration is present and to select the appropriate treatment. Some stakeholders believe that the need for broader and more comprehensive testing is therefore less urgent in the common solid cancers. In haematological cancer, there are fewer targeted therapies available. According to a haematological cancer patient advocacy and research organisation, the genetic underpinnings of blood cancer are extremely important to understand because there are no solid biopsies as there are with solid cancers.

There is also debate about what kind of testing is best suited for adult patients compared to paediatric patients. ZERO Childhood Cancer's PRISM trial leverages WGS results to tailor treatment plans for paediatric cancer patients, while Omico's Molecular Screening &

[7] MBS items 871 and 872

Therapeutics (MoST) trial for adult cancers uses a CGP panel. Mutation rates in paediatric cancers are significantly lower than in adult cancers, and the types of mutations are often different. WGS is therefore a particularly useful option for the paediatric population. (19) These two research programs are discussed further in Section 9.4.

Cutting across the solid, haematological, adult, and paediatric cancers are the rare and less common cancers (RLCs). Clinicians' and researchers' feedback indicate that NGS-based genomic testing using large panels is most needed in this population. These cancers are the most poorly understood, and comprehensive genomic testing could enable repurposing of treatments, placement in clinical trials, and a better understanding of the cancer. However, access to funded treatment for these patients after conducting the test is likely to be limited given the currently available PBS drugs. Lack of access to funded treatment for many patients is a critical issue which currently prohibits further integration of genomic testing, especially large-scale panels. Characterising the cancer's molecular profile has low utility in the clinical setting if that information fails to lead to treatment.

Lack of access to funded treatment for many patients is a critical issue which currently prohibits further integration of genomic testing, especially large-scale panels.

6 Cancer Genomics Overseas

In the next five years, genomic data from over 60 million patients is expected to be generated worldwide. (20) Across the EU member states, 63% have policies on genomics, and 83% of those with policies have developed specific guidelines. Thirteen EU countries plan to cooperate in genomic data and knowledge sharing. (11) Countries around the world have been working towards embedding genomics into cancer care. Australia may benefit from considering examples from overseas, where some countries have begun to provide funded access to NGS tests including targeted gene panels, CGP, WES, and WGS for certain cancer patient populations.

The Global Alliance for Genomics and Health (GA4GH) is an international policy-framing organisation seeking to set technical standards and enable responsible genomic data sharing. GA4GH has partner organisations in many countries, including Australian Genomics in Australia.

Beyond government-funded genomics research initiatives, government reimbursement of NGS testing varies widely between countries and depends on the type of cancer. In the United States, reimbursement also depends on the patient's insurance carrier. An NGS test for EGFR, ALK, ROS1, BRAF, MET, HER2, RET, and NTRK1 in metastatic NSCLC was assumed by one study to be reimbursed at US $627.50 (AU $873.03) by Medicare (the U.S. government-provided health insurance for people over age 65) and at US $2,860 (AU $3,979.05) by commercial insurance plans. England, South Korea, and Japan have taken significant steps to provide reimbursed access to NGS testing for cancer patients. These three countries are profiled below.

Table 2. Reimbursement of NGS overseas

Country	Type of health system	Type	Reimbursement criteria
England	Primary national public health service	NGS panels and WGS	Specific criteria: WGS indicated for 134 cancer indications across neurological, sarcoma, haematological, and paediatric solid tumours; multi-target NGS panel indicated for 171 indications.
Japan	Mandatory universal health coverage (Employees' Health Insurance or National Health Insurance)	Comprehensive genomic profiling	Solid tumours or metastatic cancers where there is no SOC or conventional treatment is completed (or almost completed). Reimbursement is lower when test is used as companion diagnostic.
Korea	Mandatory universal health coverage (similar to Japan)	NGS gene panel	Partial coverage for all solid cancers (10 most common at first, then expanded to all).

Sources: Commonwealth Fund, Genomics England, Korea Biomedical Review, GenomeWeb

Abbreviations: NGS, next-generation sequencing; SOC, standard of care; WGS, whole genome sequencing

6.1 England

Genomics England is a company set up and owned by the Department of Health and Social Care in England. Its partners are the NHS, Health Education England, and Public Health England. The company's first project was the 100,000 Genomes Project, which aimed to sequence 100,000 genomes by 2018. After that goal was accomplished, Genomics England established the National Genomic Research Library. The Library builds on the infrastructure developed by Genomics England for the 100,000 Genomes Project and provides a national standardised genomic research resource. Genomics England's next goal is to sequence five million genomes in five years, adding to this ongoing and expanding resource.

Within the program, the NHS Genomic Medicine Service (NHS GMS) is the main source of recruitment, sample collection, and data acquisition. The NHS GMS consists of:

1) **NHS Genomic Medicine Centres (GMCs)**, which were established as part of the 100,000 Genomes Project infrastructure. NHS GMCs are centres sponsored by the NHS which identify and enrol participants. Each GMC includes several NHS Trusts and hospitals.
2) **NHS Genomic Laboratory Hubs (GLHs)** which will work as part of a national genomic testing service. The provisions and reimbursement criteria in this service are determined by the National Genomic Test Directory that outlines the testing strategies and technology to be employed for rare and inherited disease, cancer, and other defined conditions.

The reimbursement criteria described by the National Genomic Test Directory encompass 191 cancer indications and 970 tests. Key highlights include:

- **WGS** is approved for 134 indications across neurological tumours, sarcomas, haematological tumours, and paediatric solid tumours.
- **Panels** (gene rearrangement test using NGS or multi-target NGS panel) are approved for 171 indications and can cover one gene up to a long list of genes. This coverage spans haematological tumours, neurological tumours, sarcomas, and adult and paediatric solid tumours.
- **FISH** is the method specified for 456 different tests across solid tumours, neurological tumours, sarcomas, haematological tumours.

Patients in the NHS GMS will be asked if they want to donate their blood, saliva, tissue, sequencing data, and health data for research. To create the opportunity for expansion to include other kinds of 'omics, Genomics England is also seeking to collect other types of samples including:

- Serum and plasma for proteomics and metabolomics.
- Cell-free serum for circulating tumour DNA and to assess tumour recurrence.
- Germline RNA for transcriptomics.
- Lymphocyte DNA for epigenetics.
- Tumour for RNA expression profiles, tumour epigenetics and proteomics.

Genomics England stores data in a secure, monitored infrastructure where it is analysed, and important findings can be transmitted to clinicians. With patient consent, data is used for research.

Funding for Genomics England comes from the Department of Health and Social Care along with Genomics England Clinical Interpretation Partnership (GeCIP) funders. (21)

The system built by Genomics England is an example of an integrated system providing access to testing in clinical settings and harnessing the data obtained from that utilisation for research purposes, however the problem of systematically providing access to matched therapies has still not been solved.

6.2 South Korea

South Korea has approved panel tests for solid cancers and some haematological cancers (Table 3). South Korea began granting partial reimbursement coverage for NGS gene panel tests for the ten most common types of cancer in 2017, and since expanded its criteria to include all solid cancers. (22) However, the level of reimbursement for NGS testing depends on the number of genes or cumulative gene length analysed and whether the condition is hereditary. Level II tests have a higher price than Level I tests (Table 4). Re-testing may occur for non-hereditary conditions one time in the case of recurrence or treatment failure. Patients with progressed, metastatic, and recurrent cancers typically have a 50% co-pay, while other patients may be charged co-payments of up to 90%. Aside from some level of coverage from Korea's National Health Insurance Service, 68% of the population have supplementary or complementary health insurance. Some genetic tests for cancer are covered by these private health insurers. (23)

Table 3. Approved cancer tests in South Korea

Type of cancer	Required genes
Solid cancer	HER2, EGFR, ALK, KRAS, NRAS, BRAF, BRCA1, BRCA2, KIT, PDGFRA, IDH1IDH2, MYC (Cmyc), N-myc (MYCN)
Plasma cell tumour	NRAS, KRAS, TP53
Acute myeloid leukaemia	CEBPA, FLT3, JAK2, KIT, NPM1, RUNX1, TP53, IDH1, IDH2
Acute lymphocytic leukaemia	TP53, RB1, JAK2, NRAS, IKZF1
Myelodysplastic syndrome, myeloproliferative tumours	ASXL1, CALR, CSF3R, DNMT3A, JAK2, MPL, RUNX1, SETBP1, SF3B1, SRSF2, TET2
Malignant lymphoma	MYD88, BRAF, TP53

Source: OECD

Note: see Glossary of Genetic Variants for gene acronym definitions.

Table 4. NGS testing levels and test frequency permitted

	Hereditary	Non-hereditary
Level I	The number of genes is 2 to 30, or the gene length is 150 kb or less	The number of genes is 5 to 50 or the gene length is 150 kb or less
Level II	If the gene length exceeds 150kb or more than 31 genes, it is recognised only for hereditary retinitis pigmentosa, hereditary hearing loss, and Charcot maritus disease	The number of genes is over 51 or the gene length is over 150 kb
Frequency	1 time per disease	1 time at diagnosis However, in case of recurrence and treatment failure only one additional authorisation

Source: OECD

Abbreviations: kb, kilobase, NGS, next-generation sequencing

South Korea's bioinformatics system is seen as one of the most advanced in the world, according to the Organisation for Economic Cooperation and Development (OECD). Approximately 80% of South Korea's datasets cover at least 80% of the population. More than 90% of datasets share the same unique patient IDs, and more than 70% of datasets are regularly linked for research, statistics, or monitoring. The National Biobank of Korea is a network of biobanks with biospecimens and health records, however it is not yet linked with the nation's public health records. (23)

Despite this strong foundation, there is not yet a national database to integrate NGS data with clinical, prescription, and outcome data. Currently, pathology departments at hospitals store genomic data locally. (22) Korean hospitals have accumulated 7,000 cases of NGS data per year since reimbursement of NGS for solid cancers, which many view as an opportunity for research. (22)

6.3 Japan

By 2019, Japan began reimbursing two CGP tests for patients with solid tumours: FoundationOne®CDx Cancer Genomic Profile consisting of 324 genes, and Sysmex's OncoGuide™ NCC Oncopanel system. (24) Eligible groups include patients with solid tumours or metastatic cancers for which there is no standard of care (SOC) or conventional treatment is completed. In the latter case, the test would be considered a companion diagnostic. In early 2020, Japan also approved the FoundationOne® CDx test as a companion diagnostic for entrectinib (Roche's Rozlytrek). This allows clinicians to use the test to detect ROS1 fusion genes in patients with locally advanced or metastatic NSCLC. (24) There are two steps for reimbursement: ¥80,000 (AU $1,052) for administration of the test, and ¥480,000 (AU $6,313) when results are explained to the patient. Reimbursement for the test when used as a companion diagnostic is lower. (25)

Noticing the value lost in South Korea's program due to the lack of national genomic data systems, Japan aimed to establish a strong data infrastructure to obtain the most value out of NGS testing. NGS data is a national asset in Japan, which is the approach that some Korean experts would like to see happen in their own country. (22) As part of the condition for reimbursement, anonymised genomic data and treatment history information are gathered into a National Cancer Centre database. The data is intended to be shared with research institutions and companies to increase drug development, however this is concerning to some patients and their families who fear that the data may be used against them. (26) Part of Japan's objective in funding NGS testing is to help create a hub for research and drug development.

The genomic testing delivery structure is tiered, consisting of core hospitals, hub hospitals, and liaison hospitals. Throughout the system, over 170 medical institutions were designated to perform NGS testing. Japan has also funded a database called Medical Genomics Japan Variant Database (MGeND), which documents genomic variation data in the Japanese population. The types of variants included consist of single nucleotide variants (SNVs), insertions/deletions (indels), and others.

As in Australia and elsewhere, a major challenge is access to drugs. Patients must pay OOP to access off-label drugs. Compassionate use through the Patient-Requested Therapy System must be initiated by the patient through a request to the government, and it is administratively burdensome for physicians and therefore has not been widely adopted. (27)

It is expected that 10,000 to 20,000 of the 1 million Japanese people diagnosed with cancer each year with receive a test. (26) Managing patient expectations and finding new solutions for treatment access will be key areas of focus in the future.

7 Ongoing Genomics Initiatives and Frameworks

Various organisations across Australia are engaged in ongoing genomics research and collaboration initiatives (Table 5). Some are funded by federal research funds such as the Medical Research Future Fund (MRFF), others are funded by academic institutions or state governments. The MRFF awarded $500 million over 10 years to the Genomics Health Futures Mission and $67 million in collaboration with the Minderoo Foundation to the ZERO Childhood Cancers Program run by the Children's Cancer Institute. The MoST trial run by Omico has also received $50 million of federal research funding. Besides projects that seek to build the clinical evidence base for genomics-guided cancer care, Australian Genomics is also conducting implementation research and piloting models for integration of genomics into healthcare using $25 million of federal research funding. New South Wales, Victoria, and Queensland have each committed $25 million towards their respective state-specific research initiatives – the Sydney Genomics Collaborative, Melbourne Genomics Health Alliance, and Queensland Genomics.

The federal government has also outlined a National Health Genomics Policy Framework and Implementation Plan with guidance for policymakers at all levels of the health system (Table 6). The implementation plan focuses on high-level actions that will help translate the framework into outcomes. Stakeholder engagement and clear governance arrangements are key success factors. The planned actions in the Implementation Plan fall into five categories: person-centred approach, workforce, financing, services, and data. As the Implementation Plan focuses on 2018-2021, each category contains multiple actions with time frames for completion between 12 and 24 months. Some actions are intended to be ongoing. For example, identifying and collating people's views on ethical, legal, and social issues around genomics is one of the actions intended to be completed in the short-term (12 to 18 months), but also planned to continue in an ongoing manner. The importance of proper infrastructure and processes are discussed further in Section 12.2.

Table 5. Genomics initiatives in Australia

Initiative	Type	Organisation	Time frame	Description
Genomics Health Futures Mission	Federal government-affiliated	MRFF	2019-2029	• $500 million over 10 years (started 2019) dedicated to saving or transforming the lives of >200,000 Australians through genomic research aimed to deliver better testing, diagnosis, and treatment • Early funding priorities include reproductive carrier screening (Mackenzie's Mission), proteomics big data analysis (ProCan), pathogen genomics, paediatric acute care, bioinformatics, and others • Long-term goal is to embed genomics into clinical practice and health policy
Omico	Private non-profit	Omico (formerly Australian Genomics Cancer Medicine Centre)	Started 2018	• National genomic clinical trials program for advanced and incurable cancers • Brings together Australia's major cancer centres, leading research institutes, federal and state governments, industry partners and patients
InGeNA	Industry	InGeNA	Started 2020	• An independent industry alliance to inform and develop genomics policy and to work collaboratively with research, government, and service providers across the genomics and health sectors • Topics of interest include access and reimbursement, development of the digital infrastructure and principles to underpin genomics, workforce planning and skills development, consent, and consumer-centricity
ZERO Childhood Cancer	Private non-profit	Children's Cancer Institute and The Kid's Cancer Centre at Sydney Children's Hospital Randwick	Started 2015	• Personalised medicine program for children with high-risk or relapsed cancer • Involves multiple types of complex testing (WGS, targeted panels, residual disease testing), the results of which are reviewed by expert multidisciplinary tumour boards to decide on a treatment strategy • Awarded $67 million in funding from the MRFF in April 2020 to expand the program after conducting a pilot study and national clinical trial
Australian Genomics	Private non-profit	Murdoch Children's Research Institute	Started 2016	• Collaborative national research partnership which received $25 million of funding from NHMRC to demonstrate the value and practical strategies of implementing genomic medicine in the Australian healthcare system • Administers several MRFF-funded projects totalling $34 million including the Australian Reproductive Genetic Carrier Screening Project 'Mackenzie's Mission'

Initiative	Type	Organisation	Time frame	Description
Sydney Genomics Collaborative	Private non-profit and state government	Garvan Institute and NSW government	Started 2014	• $24 million investment by NSW government over 4 years to boost genomic research in diseases with a genetic component, including inherited disorders and cancer • Uses Illumina's HiSeq X Ten technology • Includes a Medical Genome Reference Bank containing ~4,000 whole genome sequences, NSW Genomics Collaborative Grants for researchers to undertake WGS, and the Genomic Cancer Medicine Program
Queensland Genomics	State government	University of Queensland and Queensland government	2017-2021	• $25 million investment in clinical and capability-building projects • Focused on breast cancer, melanoma, myeloid cancers, lung cancer, infectious disease, rare disease, epilepsy, and diabetes
Melbourne Genomics Health Alliance	State government	Victorian government and ten leading hospitals	2016-2020	• $25 million from Victorian government and $10 million from partners • 11 clinical projects are investigating the use of genomic testing in areas including immune disorders, genetic heart conditions, neurological disease, deafness, and advanced lymphoma and solid cancers
South Australian Genomics Health Alliance	State government	8 academic and hospital partners in South Australia	Not specified	• SA Genomics Health Alliance is in the early stages of development and planning to engage in work on strategy for genomics implementation, pilot projects in specific clinical areas, developing infrastructure, building a state-wide genomics registry linking genomic data with electronic health records
Bioplatforms Australia	Private non-profit	Bioplatforms Australia	2018-2023	• Non-profit which received $111 million in funding from the National Collaborative Research Infrastructure Strategy to provide 'omics sequencing technology for life sciences research • In 2019, Bioplatforms Australia supported 3,040 users, its 15 node facilities engaged more than 15,000 research contracts, and supported over 200 science and industry collaborators • Leads the Australian BioCommons, a national bioinformatics infrastructure capability with multiple national partners

Abbreviations: ACT, Australian Capital Territory; InGeNa, Industry Genomics Network Alliance; MRFF, Medical Research Futures Fund; NHMRC, National Health and Medical Research Council; NSW, New South Wales; SA, South Australia; WGS, whole genome sequencing

Table 6. Frameworks and strategies

Name	Organisation	Time frame	Description
National Health Genomics Policy Framework and Implementation Plan	Australian Health Ministers' Advisory Council	2018-2021	• A tool for decision-makers and policymakers at the federal, state, and health service level to provide guidance for developing and implementing genomic-related policies, strategies, actions, and services • Implementation plan for five strategic priorities: person-centred approach, workforce, financing, services, and data
NSW Health Genomics Strategy and Implementation Plan	NSW government	2018-2020	• Lays out the vision for NSW Health to become recognised as a leader in the development and use of genomic technologies in healthcare and public health, and a preferred partner for industry in (gen)omics research, education and training, with effective translation into clinical practice and public health initiatives • Identifies six key implementation recommendations around governance, service delivery, community engagement, and others • NSW Health was actively involved in the National Health Genomics Policy Framework
NCIG Strategic Plan	NCIG	2017-2021	• Under Indigenous Governance, NCIG conducts research and other activities to build and maintain a genome resource for the research community • The NCIG Collection is based on material donated for research purposes in the second half of the 20th Century by approximately 7,000 Aboriginal and Torres Strait Islander peoples at 43 localities • NCIG's objectives are to care for the collection with high governance standards, maximise the value of the collection through research, cultivate partnerships to advance indigenous genomics, and seek sustainable funding to secure the future of the centre

Abbreviations: NCIG, National Centre for Indigenous Genomics; NSW, New South Wales

8 Future Landscape of Cancer Genomics

A combination of new tests, pan-cancer drugs, improved processes, and digital solutions in the next decade will continue to rapidly improve genomics capabilities and impact on patients' lives. With further integration of genomics, molecular approaches to diagnosis and treatment of cancer will continue to develop and enable increasingly personalised care and better outcomes. A genomics-based approach to cancer requires not only tests and treatments, but validated processes and resources to facilitate logistics and derive value from data as part of a collaborative and integrated system. The future landscape of cancer genomics will focus on developing all three aspects: tests, treatments, and process.

8.1 Tests

While substantial attention has been paid to diagnostic and companion diagnostic genomics test, monitoring for residual disease and prognostic testing are also being studied. Some monitoring and prognostic tests have already been approved overseas.

clonoSEQ® is an NGS-based assay used to detect measurable residual disease (MRD) in B-cell lymphoid cancers using blood or bone marrow samples. MRD can provide insights on patients' responses to treatment, however with standard MRD testing procedures disease can often go undetected and lead to relapse. Standard MRD testing is costly, labour-intensive, and unstandardised. clonoSEQ is designed to precisely identify unique cancer DNA sequences and quantify MRD with deep sensitivity. With sufficient sample quantity, clonoSEQ can detect and routinely identify the presence of one cancer cell among one million healthy cells. (28) The assay is FDA-cleared[8] for multiple myeloma, B-cell acute lymphoblastic leukaemia (ALL; assess from bone marrow), and chronic lymphocytic leukaemia (CLL; assessed from bone marrow or blood), and has is incorporated in clinical trials at CoEs worldwide. However, it has not yet been approved for use in Australia.

Another test developed in the blood cancer space is MMProfiler™, a 92-gene risk identification test using microarray technology for multiple myeloma. Given that multiple myeloma is a heterogeneous disease with a complicated treatment paradigm, MMProfiler uses SKY92, a prognostic biomarker (or "signature") to understand prognosis and risk level. The test works by evaluating gene expression for each of the 92 included genes using RNA from bone marrow samples. This test can identify newly diagnosed multiple myeloma (NDMM) patients with high risk disease who demonstrate significantly shorter survival with standard of care. (29) Risk stratification in multiple myeloma is recommended by the American Society of Hematology (ASH), the European Hematology Association (EHA), the Medical and Scientific Advisory Group (MSAG), Myeloma Australia and others. MMProfiler has been studied in over 4,000 patients and has been approved for diagnostic purposes in the U.S. and Europe. Results from the UK Medical Research council MM XI trial demonstrated that SKY92 high-risk

[8] https://www.cancernetwork.com/view/fda-clears-clonoseq-assay-to-evaluate-mrd-in-patients-with-cll

patients derived no survival benefit from the use of the high-cost immunomodulatory agent lenalidomide. (30) Clinical studies conducted by the Myeloma Research Group at The Alfred Hospital in Melbourne have incorporated MMProfiler over the last three years.

Single cell genomics and other types of 'omics including proteomics, transcriptomics, and metabolomics will also become more prominent as advances in research are made. Illumina has developed single cell sequencing capabilities, citing benefits over bulk-sequencing including detecting specific cell populations in the tumour microenvironment, decoding sequences of individual cells, understanding epigenetic heterogeneity in cancer progression, and constructing somatic variant evolution.

While MBS-funded tests are mostly single-gene tests or small panels, MSAC has begun to address the unique considerations associated with NGS testing in its new 2020 draft guidelines. The draft guidelines propose new classifications for genomic tests to account for the wide range of panel sizes:

- Monogenic testing – limited mutation testing or whole gene testing
- Small gene panel – assaying 2 to ≤10 genes
- Medium gene panel – assaying 11 to ≤200 genes
- Large gene panel – assaying >200 genes, but remaining sub-exome
- Non-targeted – WES or WGS

The guidelines also address challenges with selecting a reference standard and outlines specific measures to include when demonstrating test reliability. MSAC will likely continue to issue new guidance as the genomics field evolves.

8.2 Treatments

New pan-cancer drugs will continue to enter the market in the future, increasing the demand for access to genomic testing. Thus far, the indications of approved pan-cancer drugs have not necessitated NGS testing as relevant variants can be found using conventional pathology techniques, or by using smaller NGS panels if laboratories choose to do so. However, drugs such as larotrectinib for cancers with NTRK gene fusions have entered the reimbursement process in Australia. Overexpression of TRK proteins can be detected using IHC as a surrogate for the presence of an NTRK gene fusion, although FISH or NGS testing using RNA should be used to confirm the result. (31) Pembrolizumab has been approved in other countries for TMB-H, a pan-tumour signature that can only be detected by analysing at least 1Mb of genetic material using an NGS test. The entry of these therapies increases the urgency for a national solution to provide access to NGS testing (Section 1).

8.3 Process

Refining processes for tissue sampling, testing, and analysis will enable higher quality and more efficient testing.

Obtaining high quality tissue samples as close to the time of testing as possible is currently a challenge. Solid tissue biopsy procedures are invasive for patients and difficult to repeat. The tissue quality is also not always high enough and preserving the sample can cause damage to the genetic material. FFPE samples are the bedrock of cancer pathology, and while they are suitable for targeted panels, they are not sufficient for larger analyses like WGS. Programs like ZERO Childhood Cancer are developing processes for national acquisition, safe transport, and analysis of fresh samples suitable for comprehensive analyses. Sample quality is particularly important for RNA sequencing, which is used to assess important biomarkers such as gene expression, fusions, and allelic imbalance. While solid tissue biopsies are still the gold standard for tumour sampling in solid cancers, the potential to use liquid biopsies more broadly as an alternative is being investigated.

Liquid biopsy for broader panels can be challenging because there is not sufficient material available from a blood sample to test for as many genes as one could with a solid biopsy. One industry stakeholder familiar with sequencing technology estimated that a liquid biopsy sample could be used to analyse 100

genes as opposed to 300 or more genes with a solid biopsy. There is also currently less standardisation for use of liquid samples. However, there are several advantages which are driving researchers to find methods of overcoming these hurdles:

- Less invasive and easily repeated, which is valuable given that there are significant challenges with obtaining enough tissue from solid biopsies and there is value in repeated testing over time
- Can reveal tumour heterogeneity, offering a more comprehensive view of the cancer
- Can be used for close monitoring to assess drug response and resistance
- Process is simpler and results can be delivered quickly (32)

As discussed in Section 5.5, bioinformatics is a key element of the process that has been partially automated, but where experts are continuing to learn and develop the field. Analysis of a CGP panel can be largely automated (this is how Illumina and Foundation Medicine create the reports discussed in Section 5.5), but analysis of WGS outputs takes more time and is not yet a standardised process. For example, bioinformaticians are currently figuring out the best ways to distinguish between noise and mutations and how to reduce false positives. Dynamic Read Analysis for GENomics (DRAGEN®) and BaseSpace®, Illumina's informatics tools, try to address these challenges. The DRAGEN pipeline includes user-friendly data analysis tools, and BaseSpace Sequence Hub is the web-based platform through which DRAGEN can be accessed (DRAGEN can alternatively be accessed directly on the NextSeq sequencer systems sold by Illumina). DRAGEN offers several analysis tools for DNA and RNA analysis of mutational profiling outputs, and a somatic DNA analysis tool for WGS. BaseSpace also provides resources to simplify the workflow, including library preparation and planning, sample management, run set-up and chemistry validation, data monitoring, and data transfer to computing and analysis modules. Over time, bioinformatics tools will continue to develop more robust capabilities.

Analysis of a CGP panel can be largely automated (this is how Illumina and Foundation Medicine create the reports discussed in Section 5.5), but analysis of WGS outputs takes more time and is not yet a standardised process.

As previously discussed, access to treatment through clinical trials is a critical avenue by which patients gain access to innovative treatments. A digital solution is being developed by Omico to track ongoing precision medicine clinical trials and facilitate matching of patients with genomic test results to appropriate trials. This will be an important tool to help bridge the gap between obtaining a test result and gaining access to treatment.

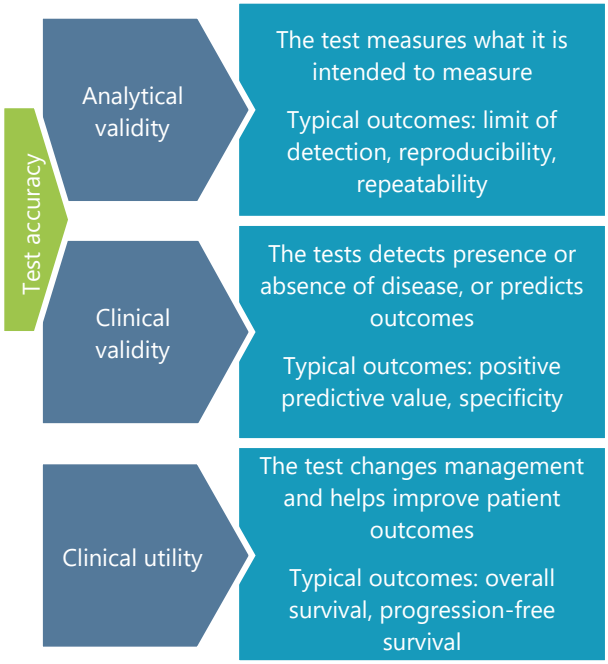
9 Summary of Evidence

9.1 Clinical evidence

According to the Australasian Genomic Technologies Association, there are three components of validation for a genomic test: analytical validity, clinical validity, and clinical utility. (33) Analytical validity means that the test measures what it is intended to measure. Clinical validity means that the measurement has clinical implications – such as detecting presence of disease or predicting future patient outcomes. Clinical utility means that knowing the test result can lead to improved patient outcomes – for example, by informing treatment decisions (Figure 12). These concepts are widely used in *in vitro* test development. MSAC's new draft guidelines (mentioned above in Section 8.1) combine analytical validity and clinical validity under the term "test accuracy." Test accuracy therefore covers detection of the biomarker and the disease state, while clinical utility covers management and outcomes. There are unique challenges to validating NGS-based tests discussed in Section 9.1.1, especially larger panels, whole exomes, and genomes.

Given that pan-tumour Pharmaceutical Benefits Advisory Committee (PBAC) and MSAC applications are becoming more common, MSAC recently published a discussion paper providing guidance on evidentiary requirements for pan-tumour applications. (34) MSAC's priority is to ensure that that new tests are able to identify appropriate biomarkers and inform patient management. The accuracy of the test is considered when weighing potential harms of receiving an incorrect test result with the potential benefits of targeted therapy informed by the test results.

Figure 12. Components of test validation



Source: Australasian Genomic Technologies Association: Live Webinar

The 2020 discussion paper recommended the following key pieces of information to be included in pan-tumour testing applications:

- **Population:** relevance of the test to target population including prevalence of target biomarker(s) at relevant disease stages, including possibility of changes in prevalence
- **Comparator:** identification of other relevant biomarkers and the reference standard, comparative data against reference standard
- **Analytical validity:** test accuracy and reproducibility across tumour types
- **Clinical validity:** positive predictive value (PPV) and negative predictive value (NPV) across tumour types

- **Clinical utility:** expected benefits of pan-tumour treatment for the target patient populations

The paper also outlined several potential strategies MSAC and PBAC could take to mitigate risk, including:

- Requiring consideration of other viable treatments before a pan-tumour treatment, or triaging patients based on biomarker prevalence rate and/or level of evidence supporting efficacy in each tumour type
- Sequential testing could be used for tumour types with low biomarker prevalence to minimise false positives

It is also noted that re-biopsies may be needed if prevalence of the biomarker changes during the course of the disease, which would have cost, safety, and uptake implications.

Importantly, available evidence to support pan-tumour testing applications is often non-randomised and/or single arm. Acknowledging this challenge, MSAC suggests using the most common cancer or cancers covered by the test as a reference case to demonstrate the effect of biomarker-based treatment compared to SOC. Historical prognostic data from subgroup cohorts representing different test results could also be used as benchmarks against which to compare single arm trial results. (34)

Evidence on pan-tumour testing is often non-randomised and single arm; the most common cancer and historical prognostic data from subgroup cohorts representing different test results could be used as benchmarks against which to compare single arm trial results.

The guidance provided in this paper is most appropriate for pan-tumour applications seeking to test for one or a small number of pre-defined variants, such as dMMR. Further reflection will be required to consider evidentiary requirements for assays such as WGS, which is known as "hypothesis-free testing" – meaning that it is not known which variants might be discovered before the test is conducted. Hypothesis-free testing hinders the ability to provide the biomarker-specific information outlined above. However, there are innovative approaches to demonstrating validity and utility, such as the ZERO Childhood Cancers program. ZERO tracks a number of biomarker-agnostic outcomes, including percentage of patients with targetable alterations, percentage of patients receiving MTB-recommended therapy, and response to treatment (Section 9.4). Furthermore, ZERO has demonstrated that whole genome sequencing and RNA sequencing are highly complementary – that using both platforms identifies changes often missed by either approach, and that either platform is able to identify atypical forms of well-known clinically important variants missed by targeted approaches.

9.1.1 Analytical and clinical validity

The need for uniform validation standards and guidelines became clear as use of NGS testing increased. (35) In 2017, the Association for Molecular Pathology and College of American Pathologists issued guidelines for the validation of NGS-based oncology panels. (36) The National Pathology Accreditation Advisory Council in Australia also published requirements for medical genome testing using NGS. (37) Experts explain that validating comprehensive panels or WGS assays is difficult because each individual variant cannot feasibly be tested in the way that they would be for small panels or single-gene tests. The Peter MacCallum Cancer Centre has conducted validation studies on Illumina's TruSight Oncology 500 CGP panel by grouping variants into classes. Validating the panel was reportedly a labour-intensive process requiring over 1,000 hours of work and 18 runs on Illumina's NextSeq500 instrument. There is still further validation work to be done beyond

these analyses. (33) The ongoing nationwide NCI-MATCH trial in the United States has also demonstrated high reproducibility of complex NGS assays in an analytic validation study intended to serve as a template for other investigators. (38)

Clinical validity of NGS testing is supported by real-world utilisation of the technology. The analytic accuracy and high-throughput capability of NGS have been established, and many laboratories have adopted the technique as a gold standard for diagnosis of hereditary diseases. (39) NGS can also be cost-effective compared to other methods, based on anecdotal evidence from stakeholders (Section 4.3.1) and published literature (Section 9.2.1). For example, MSAC listed two new item numbers for whole genome and whole exome NGS in suspected childhood monogenic disorders (Section 12.1.3). Beyond hereditary conditions, somatic tumour testing using large NGS panels is increasingly being incorporated into SOC in other countries such as the United States. This represents a shift away from single-gene testing or smaller targeted panels. (40)

9.1.2 Clinical utility

Evidence of the clinical utility of NGS is increasingly showing that the technology is feasible to implement into the healthcare system and that it leads to improved patient outcomes. Demonstrating improved patient outcomes because of NGS testing has been the focus of research in recent years.

Table 7 summarises evidence on the feasibility of NGS testing, including turnaround times, proportion of patients with identified actionable alterations, and proportion of patients receiving matched treatment. Achieving a clinically relevant turnaround time has been a challenge in several studies, however studies like the Individualised Molecular Pancreatic Cancer Therapy (IMPaCT) Trial have reported on these issues and provided guidance for future best practices. Other studies such as TARGET have already demonstrated feasibility of clinically relevant turnaround times, suggesting that this issue will continue to be addressed as research progresses. These considerations are discussed further in Section 11.

Based on the current evidence and stakeholder perspectives, logistical feasibility issues will be addressed as infrastructure improves, and the proportion of patients found to have actionable alterations is sufficient to warrant NGS testing. The Know Your Tumour study in pancreatic cancer found actionable alterations in 26% of samples, and Wheler and colleagues reported finding actionable alterations in 317 out of 339 sequenced samples from refractory cancers in 2016. (41, 42) Thus far, the MoST trial has delivered treatment recommendations for 883 (64%) out of 1,387 patients who received an MTB report. The main hurdle to maximising utility of NGS testing is obtaining funded access to matched treatments for patients with actionable alterations. In the TARGET and IMPACT clinical trials, only 11% - 38% of patients received matched therapy. (43, 44) In a U.S. study conducted by Pennell and colleagues, an NGS hotspot panel identified 40% more patients with variations that were not associated with FDA-approved therapies (compared to conventional techniques, either non-NGS panel testing, single-gene testing, or a combination). (45) While these patients could have the opportunity to participate in clinical trials based on such test results, this would not be guaranteed. In the MoST study, there were 370 treatment recommendations[9] for a MoST sub-study; 629 were for a funded or unfunded drug, and 235 were for existing clinical trials outside of MoST. (46)

The main hurdle to maximising utility of NGS testing is obtaining access to matched treatments for patients with actionable alterations.

[9] Patients could receive more than one recommendation; the total number of recommendations was 1,234.

Table 7. Evidence on validity and feasibility

Study	Sample size	Tumour types	Reported outcomes
Chantrill 2015 (IMPaCT)	93 patients considered for molecular screening	Metastatic pancreatic cancer	• 74 screened • 22 eligible candidates for treatment identified (eligibility defined as: HER2 amplification, DNA damage repair defects (e.g. BRCA1/2, PALB2, ATM), or KRAS wild-type) • 0 treated thus far (discussed further in Section 12.1.2)
Pennell 2019	Hypothetical model of U.S. health plans covering 1 million lives each	Metastatic NSCLC	• NGS hotspot panel and non-NGS hotspot panel had same TAT and time-to-result • NGS hotspot panel identified 40% more patients with variations with no FDA-approved therapies
Pishvaian 2020 (Know Your Tumour)	189 (46 matched, 143 unmatched); 488 no actionable alterations	Pancreatic	• 26% of samples found to have actionable mutations
Rothwell 2019 (TARGET)	First 100 patients of TARGET program	Advanced; mostly colorectal, breast NSCLC, CUP	• With 2.5% VAF: actionable mutations identified in 41 out of 100 patients • 11 of 41 received matched therapy • ctDNA showed good concordance with matched tumour • TAT was clinical acceptable for MTB review
Sicklick 2019 (I-PREDICT)	83 (73 matched, 10 unmatched)	Refractory after median 2 lines prior therapy; mostly gastrointestinal, gynaecological, breast, and CNS	• Median characterised genomic alterations per tumour: 5 (range 1-20) • Median time from consent to treatment: <1 month
Tsimberidou 2019 (IMPACT)	3,487 successfully profiled	Lethal/ refractory advanced cancer; mostly gastrointestinal, gynaecological, breast, melanoma, and lung	• 1,307 (37.5%) had at least one alteration and received therapy
Wheler 2016	500 enrolled, 339 successfully profiled	Refractory after median 4 lines prior therapy; mostly ovarian (18%), breast (16%), sarcoma (13%), and renal (7%)	• 317 out of 339 (93.5%) had at least one potentially actionable alteration
Yu 2018	57 patients expected to have activating mutations	Advanced NSCLC	• NGS: 54 out of 57 identified • Single-gene testing: 35 out of 57 identified

Abbreviations: ATM, ATM serine/threonine kinase; BRCA, breast cancer gene; CNS, central nervous system; ctDNA, circulating tumour DNA; CUP, cancer of unknown primary; DNA, deoxyribonucleic acid; FDA, Food and Drug Administration; HER2, human epidermal growth factor 2; KRAS, Kirsten rat sarcoma viral oncogene; MTB, Molecular Tumour Board; NGS, next-generation sequencing; NRAS, neuroblastoma RAS viral oncogene; NSCLC, non-small cell lung cancer; PALB2, partner and localiser of BRCA2; TAT, turnaround time; VAF, variant allele frequency

A key component of the current body of evidence is a group of studies which have investigated the improvement in patient outcomes when molecularly matched or personalised therapies are used compared to SOC. Matched or personalised therapies are selected based on genomic testing results characterising the tumour's molecular profile. Key results are outlined in Table 8.

While current evidence is mostly retrospective and non-randomised, leaders in the field believe it provides strong justification to create a national genomics research program for patients who have limited or no treatment options. Participating in a precision medicine trial which provides the opportunity for matched or personalised therapy is associated with improvements in response rate and progression-free survival. A meta-analysis of 112 trials (57 randomised and 55 non-randomised; n = 38,104) which led to FDA approval of anti-cancer agents found that trials which used personalised approaches to treatment had higher relative response rates and longer PFS than trials that did not use personalised approaches. (47) Furthermore, much of the evidence summarised in Table 8 shows improved survival for advanced, lung, and pancreatic cancer patients treated with matched therapy. Singal and colleagues (48) also present results suggesting there is higher efficacy of immunotherapy in NSCLC patients with high TMB compared to those with low TMB. There have also been several studies conducted in multiple tumour types (for example, breast, gastrointestinal, brain, and colorectal) which show improved patient outcomes on matched therapy. A more detailed table of evidence is included in Appendix II: Clinical Evidence.

Evidence is being generated at a rapid pace, and countries around the world are seeking to integrate genomics into their health systems based on the current evidence (discussed further in Section 0). For example, ASCO and the National Comprehensive Cancer Network (NCCN) have recommended the use of hotspot panels and CGP for some cancer types such as NSCLC. (49) While most stakeholders do not believe the evidence is strong enough to justify MBS funding of large NGS panels for all cancer patients under the current system, they are enthusiastic about the growing body of evidence and encourage government funding towards research. This would not only advance the field but also provide innovative treatment options for patients with limited options in the shorter term.

Conducting a test that searches for variants for which there is no funded treatment is seen by some stakeholders as having limited utility in clinical settings.

Some stakeholders do not believe there is utility in using CGP outside of clinical research. In common cancers for which many known variants have been identified and for which drugs have been produced to target those variants, some clinicians and pathologists say that using a panel of 10-20 genes would be sufficient to determine which variant patients have and which treatment should be selected. This perspective centres around the idea that the utility of genomic testing depends on access to treatment. While the evidence may show that patients have strong responses, progression-free survival, and overall survival on matched therapy after CGP testing, patients in real-world clinical settings are likely to face greater challenges accessing treatment. Conducting a test that searches for variants for which there is no funded treatment is therefore seen by some stakeholders as having limited utility in clinical settings. From a government funding perspective, this is a significant barrier to increasing access to NGS testing (funding considerations are discussed further in Section 12).

Table 8. Summary of evidence comparing matched or personalised therapy informed by genomic testing vs SOC

Patient population	Study	Study type	Reported outcomes
All cancers	Schwaederle 2015	Meta-analysis	• RR: 31% vs 10.5% • PFS: 5.9 vs 2.7 months • OS: 13.7 vs 8.9 months
	Schwaederle 2016b	Meta-analysis	• RR: 30.6% vs 4.9% • PFS: 5.7 vs 2.7 months
All cancers with no treatment options (targeted vs IO)	Van der Velden 2019	NRSI	• ORR: 34% (both arms)
Advanced/ metastatic cancers	Haslem 2018	Retrospective study	• OS: 51.7 vs 25.8 weeks
	Nadauld 2015	Retrospective study	• PFS: 22.9 vs 12 weeks
	Tsimberidou 2017 (IMPACT)	Retrospective study	Responders vs non-responders: • FFS: Matched – 7.6 vs 4.3 months; unmatched – 6.6 vs 4.1 months • OS: Matched – 23.4 vs 8.5 months; unmatched – 15.2 vs 7.5 months
	Tsimberidou 2019 (IMPACT)	Retrospective study	• ORR: 16.4% vs 5.4% • ORR & stable disease ≥ 6 months: 35.3% vs 20.3% • PFS: 4.0 vs 2.8 months • OS: 9.3 vs 7.3 months • 3-year survival: 15% vs 7% • 10-year survival: 6% vs 1%
Refractory cancers	Rodon 2019 (WINTHER)	NRSI	• Stable disease ≥ 6 months, partial remission, or complete remission: 26.2% (arm A: 23.2%, arm B: 31.6%) • PFS ratio (PFS2/PFS1) of >1.5: 22.4% (arm A: 20.3%; arm B: 26.3%) • PFS ratio (PFS2/PFS1) of >1.3: 25% • Fewer previous therapies, better performance status, and higher matching score correlated with longer PFS
	Sicklick 2019 (I-PREDICT)	NRSI	• Higher matching score was a predictor of higher disease control, longer PFS, and OS • PFS: 6.5 vs 3.1 months • OS: not reached vs 10.2 months

Patient population	Study	Study type	Reported outcomes
	Wheler 2016	NRSI	• Higher matching scores were independently associated with greater frequency of SD ≥ 6 months/PR/CR: 22% (high scores) vs 9% (low scores)
High utility indications (CRC, melanoma, lung, ovarian)	Tsimberidou 2012	NRSI	• ORR: 27% vs 5% • TTF: 5.2 vs 2.2 months • OS: 13.4 vs 9 months
Lung	Aisner 2016 (lung adenocarcinoma)	NRSI	• OS: 2.8 vs 1.5 years
	Kris 2014 (lung)	NRSI	• OS: 3.5 vs 2.4 years
	Kostenko 2016 (NSCLC)	NRSI / Single arm	OS: • EGFR+: 55 vs 22 months • ALK+ (next-gen ALK inhibitor after crizotinib failure vs crizotinib): 35 vs 23 months • BRAF+: 23 months, HER2+: 25 months, ROS1+: not reached
	Singal 2019 (NSCLC)	Retrospective study	OS: • Targeted vs non-targeted: 18.6 vs 11.4 months • IO with TMB-H vs TMB-L: 16.8 vs 8.5 months
Pancreatic	Pishvaian 2020 (Know Your Tumour)	Retrospective study	• OS: 2.58 (matched) vs 1.51 (unmatched) vs 1.32 (no actionable alteration) years

Abbreviations: ALK, anaplastic lymphoma kinase; BRAF, proto-oncogene B-Raf; CR, complete response; EGFR, epidermal growth factor receptor; FFS, failure-free survival; HER2, human epidermal growth factor receptor 2; IO, immunotherapy; NRSI, non-randomised study of the effects of interventions; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; ROS1, c-ros oncogene 1; RR, response rate; SD, stable disease; SOC, standard of care; TMB-H, tumour mutational burden-high; TMB-L, tumour mutational burden-low; TTF, time to treatment failure

9.2 Economic evidence

9.2.1 Healthcare budget impact and cost-effectiveness

Economic evidence of the value of NGS is more limited than clinical evidence, however there are several examples of studies assessing budget impact or cost-effectiveness of NGS testing. Many of the studies conducted are from the United States. While diagnostic and treatment costs differ between the United States and Australia, the analyses provide indicative evidence which future Australian research can build upon.

Several United States studies analysed budget impact and costs of NGS testing in lung cancer. A 2018 paper modelled the hypothetical budget impact to U.S. payers of NGS testing compared to single-gene testing in advanced NSCLC. Assuming all patients who would receive genetic testing used NGS, test-related costs to the payer decreased by US $24,651 over five years due to avoided sequential testing. However, treatment costs increased by US $432,554 over 5 years given that more actionable alterations were identified, and more patients were given targeted therapies. However, the authors noted that the increase in first line treatment and pre-progression costs is somewhat offset by savings in second line and later given better patient outcomes. The costs were also higher compared to other studies because the authors used higher drugs cost assumptions and higher clinical trial enrolment rates. Given that the hypothetical health plan included 1 million patients, the budget impact was US $0.0072 per member per month, which the authors describe as minimally additive. (50)

A 2015 analysis used claims data to analyse the costs of NGS testing in 28,011 newly diagnosed lung cancer patients in the United States. The total cost of sequential single-gene testing was $3,763 (KRAS: $464, EGFR: $696, ALK: $1,070, ROS1: $1,127, BRAF: $406), while the cost of NGS testing was $2,860. While the prevalence of NGS testing is still low (NGS was used to test for BRAF in only 6.6% of cases), this analysis demonstrates that NGS testing may be more cost-effective than sequential testing. (51)

Another study modelled the economic impact of NGS testing compared to single-gene testing in NSCLC, finding savings to the U.S.'s Medicare (which covers people over age 65) of US $1,393,678 for over 2,000 lung cancer patients compared to exclusionary testing (exclusionary testing consisted of sequential single-gene testing starting with KRAS, the most common alteration). (45)

In another American study, researchers conducted a retrospective analysis comparing metastatic cancer patients who received genomic testing and targeted therapy with historical controls who received SOC or best supportive care. Average weekly cost per patient over a 1.5 year period was US $2,720 in the NGS group, compared with $3,453 in the historical control group. (52) While this study had a smaller sample size of 44 patients, it demonstrates lower costs associated with downstream effects of NGS testing. A 2015 study also found that using NGS testing of 34 cancer-associated genes rather than single-gene testing to inform treatment selection in metastatic melanoma created savings of US $8,943 $1,393,678 and increased per-patient QALYs by 0.0174. (53)

An Italian analysis found that NGS testing in metastatic NSCLC and CRC almost always produced cost savings compared to SOC (which involved testing using conventional pathology techniques such as PCR, IHC, FISH, mass spectrometry, etc.). (54)

Obtaining a molecular profile before proceeding with treatment that may cost tens of thousands of dollars per year could be a wise financial decision.

In Australia, the recently listed MBS items for whole exome or genome sequencing in children suspected of having monogenic disorders were approved with fees of $2,100 for singleton testing and $2,900 for trio testing. Singleton testing involves testing only the patient's DNA, whereas trio testing entails sequencing the DNA of the patient and their two biological parents. This approach can lead to higher diagnostic yield than singleton testing in some cases, therefore the two MBS item numbers provide clinicians and families with the option for either. MSAC agreed that there would be cost savings due to reduction in the "diagnostic odyssey," however it was difficult to quantify the savings. MSAC recommended post-implementation monitoring to track uptake and costs. (55) One of the studies cited in the Public Summary Document, Stark 2017, prospectively assessed the cost-effectiveness of using WES as a first line diagnostic in infants with suspected monogenic disorders in Australia. The research found that early use of WES more than tripled the diagnostic yield for only one-third of the cost per diagnosis compared to SOC. The savings per additional diagnosis when WES replaced most other tests was $2,182. (56)

The cost of NGS testing is often much lower than cost of targeted therapies, therefore many clinicians and pathologists have argued that obtaining a molecular profile before proceeding with treatment that may cost tens of thousands of dollars per year would be a wise financial decision for the government. The MBS currently addresses this to a certain extent by funding single-gene tests or small panels of several genes, as described in Section 4.3, however pathologists and clinicians believe that those tests do not provide a complete enough picture to make the most informed treatment decisions.

9.3 Value to society

Beyond providing value to current patients, NGS testing has value to society. Data collected through a public genomics program could be a source of revenue and an incentive for industry to conduct trials and research in Australia. The data, which will grow over time, can be used to make new discoveries and direct future research, ultimately improving cancer care at a faster rate for future patients.

Cancer diagnoses have a large impact on many aspects of patients' and family members' lives. A cancer diagnosis can cause substantial distress in the whole family system, especially if the patient is a child dependent on the care of their parents. Children may experience a sequence of stress periods, beginning from the initial diagnosis of cancer and continuing throughout medical treatment to recovery. An effective cancer diagnosis and treatment system would have an even broader impact than decreasing cancer recurrence and mortality. Positive impacts of early and accurate diagnosis of cancer through NGS include:

- Improvements in patient mental health, as uncertainty associated with a cancer diagnosis is known to cause depression in patients
- Improvements in partners' and families' mental health, as accurate diagnosis and targeted treatments would reduce the mortality risk and give families more time to cope with the diagnosis and plan for the future
- Reduction in financial impact through early detection of cancer, as not only is the cost of treatment much lower in early stages, but patients can also continue to work and support their families if they access effective treatment in time
- Reduced emotional and caregiving burden for caregivers, as better outcomes due to NGS testing could prevent the decrease in labour productivity associated with informal caregiving and minimise health expenses.

A cancer diagnosis has a large impact on many aspects of patients and their family members

These benefits have substantial social value and could lead to significant social return on investment, and even financial return in the long-term.

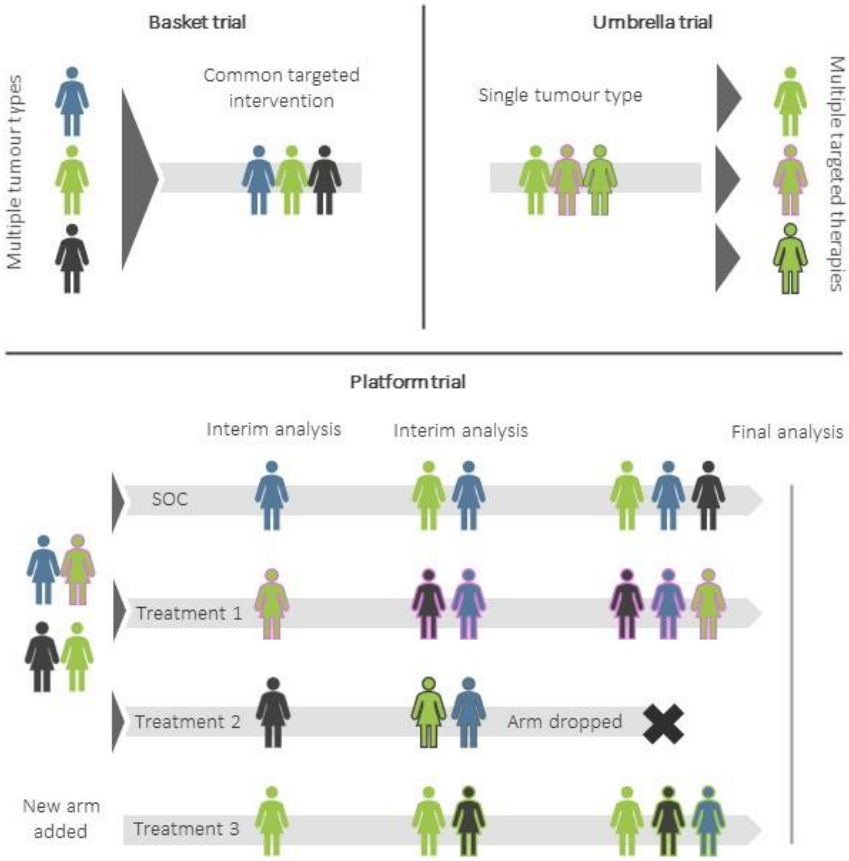
9.4 Ongoing research

As discussed in Section 9.1, there are unique challenges associated with building evidence in precision medicine. Tumour-agnostic tests and therapies do not necessarily fit neatly into the established Australian health technology assessment (HTA) processes. However, several Australian and international research programs have been working to adapt trial designs and research approaches to suit newer genomic technologies.

These trials use master protocols, which are frameworks designed to test multiple hypotheses. Master protocols often include several sub-studies which operate like standard clinical trials. The three main types of master protocol that researchers use in genomics are basket trials, umbrella trials, and platform trials (Figure 13).

- **Basket trials:** the same targeted therapy is evaluated in patients with cancers from different tissues of origin but with a common molecular alteration. For example, a BRCA1/BRCA2 trial was conducted with the PARP inhibitor olaparib, which led to FDA approval of the drug for women with BRCA1/BRCA2-associated ovarian cancer and provided initial proof of efficacy in prostate and pancreatic cancers. (57)
- **Umbrella trials:** multiple targeted interventions are evaluated in patients with the same tumour type (same tissue of origin) who are split into subgroups based on molecular alteration.
- **Platform trials:** several interventions are assessed compared to a common control group, and the protocol has built-in flexibility to allow addition or removal of sub-studies. Also referred to as multi-arm, multi-stage design (MAMS) trials. For example, the MoST trial recruits patients with advanced cancer and recommends a sub-study based on molecular testing results. The protocol allows for creation of new sub-studies where applicable.

Figure 13. Master protocol trial designs



Source: Park 2019

Molecular Screening & Therapeutics Trial (Omico)

The MoST trial has a platform design and covers three broad populations: advanced or metastatic solid cancers, lung cancer (subprogram ASPIRATION), and advanced blood cancer (subprogram MoST-LLy). The trial has been ongoing since 2016 and has screened 1,673 patients as of the end of 2019. Several sub-studies are recruiting or in follow-up, two are in start-up, and one is closed for analysis. 3 new sub-studies were planned to open in Q4 2019, and other new concepts are in development. Actionable alterations identified through CGP in the MoST trial fall into three categories: alterations aligned with a MoST sub-study, alterations for which there is an existing funded or unfunded drug, and/or alterations for which there is a suitable clinical trial outside of MoST. (46)

Table 9. MoST sub-studies

Study	Status	Description
Palbociclib	In close-out	Single arm, open-label, signal seeking, phase Ib/IIa trial of the CDK4/6 inhibitor palbociclib in patients with tumours with amplified Dtype cyclins or CDK4 or inactivation of CDKN2A.
Durvalumab and tremelimumab	Patients on treatment and in follow-up	Study to assess the clinical activity of durvalumab and tremelimumab in patients grouped post-hoc based on tumour expression of PD-L1, TIL, and MTB.
Olaparib and durvalumab	Patients on treatment and in follow-up	Olaparib is a PARP inhibitor, which targets cancers with defects in HR DNA repair (BRCA1/BRCA2 mutations). Durvalumab blocks the PD-1/PD-L1 pathway relieving PD-L1 mediated suppression of T-cells activation.
Vismodegib	Now recruiting	Vismodegib in patients with tumours harbouring PTCH1 or SMO mutations.
Larotrectinib	In start-up	CNS or non-CNS patients harbouring NTRK1-2+ expressions.
TDM1 (Kadcyla)	In start-up	
Tremelimumab	In development	

Source: Australian Genomic Medicine Centre Annual Report 2019

Abbreviations: BRCA1/BRCA2, breast cancer gene 1/2; CDK4, cyclin-dependent kinase 4; CDKN2A, cyclin-dependent kinase inhibitor 2A; CNS, central nervous system; HR, homologous recombination; MTB, Molecular Tumour Board; NTRK, neurotrophic-tropomyosin receptor kinase; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PTCH1, patched-1 protein; SMO, smoothened gene; TIL, tumour infiltrating lymphocytes

Note: there are three additional concepts in the clinical sub-study protocol development phase and four proposals for concepts in the pipeline.

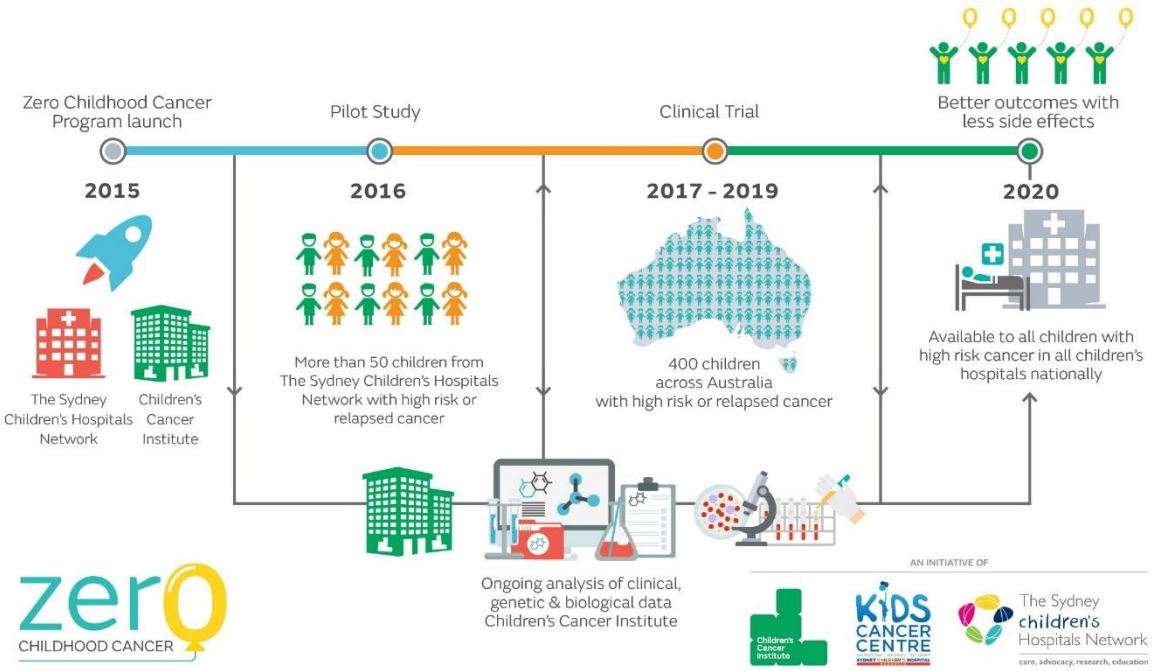
ZERO Childhood Cancer (Children's Cancer Institute)

The ZERO Childhood Cancer Program aims to deliver Australia's first personalised medicine program to assess the feasibility of precision medicine to identify targeted therapeutic agents for patients with high-risk paediatric cancers. The 2016 pilot study (TARGET) set up and tested the systems needed to conduct a national clinical trial, and in 2017 the national PRISM trial was launched to serve children with high-risk and relapsed cancer with less than 30% chance of survival. With new funding from the MRFF and Minderoo Foundation, the PRISM trial will be expanded over the next three years to eventually be open to all children with cancer.

Figure 14. ZERO Childhood Cancer Program

ZERO recently reported that among the first 247 patients, 93.7% of patients had at least one germline or somatic aberration and 71% of patients had targetable findings. Targetable findings are those which can be actioned through use of existing or investigational drugs. Of the 134 patients who have received MTB recommendations, 43 (32%) have received the recommended therapy. Response data is available for 35 patients: 4 (11%) had complete response, 7 (20%) had a partial response, 14 (40%) had stable disease, and 10 (29%) had progression. According to ZERO, these promising results reinforce the value of the program's complementary sequencing strategy, which involves WGS (somatic and germline), RNASeq, and methylation sequencing. These techniques mostly analyse different types of alterations, giving a fuller picture of the molecular drivers of the cancer. The approach can be tailored based on the patient and the quality of the sample. (58)

Figure 15. Zero Childhood Cancer Program Journey



NCI-MATCH (National Cancer Institute - USA)

The National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH) trial has been ongoing since 2015 at 1,100 sites across the United States and Puerto Rico. Like the MoST trial, NCI-MATCH has a platform design which allows multiple sub-studies for each molecular alteration of interest to run in parallel (Table 10). Over time, some sub-studies are closed, and new ones added. Typically, sub-studies enrol 35 patients, although 70 may be enrolled for the sub-studies investigating more common molecular alterations. Patients with advanced solid tumours, lymphomas, or myeloma may be eligible for MATCH either after treatment failure on SOC or if there is no SOC. The study aims for 25% of enrolled patients to have rare or less common cancers. Thus far, 60% have cancers other than colon, rectal, breast, NSCLC, and prostate.

Genomic sequencing to identify molecular alterations must be performed by designated commercial labs. Once enrolled, therapies available to participants are either existing FDA-approved drugs, or investigational treatments that have already shown some effectiveness in the patient population of interest.

NCI-MATCH seeks to evaluate the clinical utility of these treatments by measuring objective response rate, progression-free survival, time to progression, and adverse events.

The trial covers the costs of treatment within its sub-studies, however patients and/or their insurance carriers are responsible for testing costs, any procedures, or other medicines. (59)

Table 10. NCI-MATCH active sub-studies

Arm	Targeted Genetic Change	Drug(s)
A	EGFR mutation	Afatinib
C2	MET ex 14 sk	Crizotinib
E	EGFR T790M	AZD9291
L	mTOR mutation	TAK-228 (formerly MLN0128)
T	SMO/PTCH1 mutation	Vismodegib
V	cKIT mutation	Sunitinib
Z1E	NTRK fusions	Larotrectinib (LOXO-101)
Z1G	PTEN loss without PIK3CA mutation	Copanlisib
Z1H	PTEN (deleterious) seq result and PTEN exp	Copanlisib
Z1K	AKT mutation	Ipatasertib
Z1L	Non-V600 BRAF mutation	Ulixertinib (BVD-523)

Source: National Cancer Institute

Note: Refer to Glossary of Genetic Variants for gene acronym definitions.

CUPISCO (Roche)

CUPISCO is a Roche Foundation Medicine randomised clinical trial in patients with cancer of unknown primary (CUP) and poor prognosis. It aims to evaluate the efficacy and safety of biomarker-based therapy compared to standard platinum chemotherapy. A number of TKIs and monoclonal antibodies are included as investigational therapies (Table 11). CGP is used to test samples for molecular alterations. The trial is being conducted across 37 countries. (60, 61)

In 2019, researchers reported results from preliminary testing of 303 CUP patients at ESMO. Based on CGP results, 32% could have been treated by targeted therapies. (62)

Table 11. Therapies included in CUPISCO

Investigational		Control
Tyrosine kinase inhibitors	Monoclonal antibodies	Chemotherapy
Alectinib, vismodegib, ipatasertib, olaparib, erlotinib, vemurafenib, cobimetinib, entrectinib	Bevacizumab, trastuzumab SC, pertuzumab, atezolizumab	Carboplatin, paclitaxel, cisplatin, gemcitabine

Source: ClinicalTrials.gov

Targeted Agent and Profiling Utilisation Registry (TAPUR) Study (ASCO)

Sponsored by ASCO, TAPUR is a non-randomised clinical trial evaluating the efficacy and safety of FDA-approved drugs for treatment of advanced cancers with potentially actionable molecular alterations. The therapies used in the study are contributed by pharmaceutical companies. TAPUR aims to benefit all stakeholders by providing better outcomes for patients, assistance in delivering genomics-based medicine to physicians (including providing MTB interpretation where applicable), and new insights on new uses of existing drugs to the cancer community and drug manufacturers. Treatments are provided at no cost to participants.

A central focus of TAPUR is collecting and tracking data. Types of data collected in this study include clinical outcomes, real-world prescribing practices, and oncologists' choice of genomic profiling tests. (63)

Drug Rediscovery Protocol (DRUP) Trial (Netherlands Cancer Institute)

DRUP is a prospective non-randomised clinical trial seeking to expand the use of anti-cancer drugs by studying efficacy and safety of therapies being used in cancers outside of their approved indications. Eligible patients have exhausted standard therapies and have potentially actionable molecular alterations for which there are no approved therapies available. Tumour types included are advanced solid cancer, multiple myeloma, or B-cell non-Hodgkin's lymphoma. DRUP leverages an MTB to interpret genomic profiling findings and recommend treatments. Similar to CUPISCO, there are a number of therapies available in the trial through collaboration with pharmaceutical companies (Table 12). (64)

In 2019, researchers reported results for 215 treated patients. Of the treated patients, 34% had clinical benefit, which was defined as complete or partial response or stable disease beyond 16 weeks. Targeted therapy was administered to 136 patients, and immunotherapy was administered to 79 patients. A cohort of patients with MSI-H tumours who received nivolumab had a clinical benefit rate of 63%. Conversely, colorectal cancer patients with low TMB did not respond

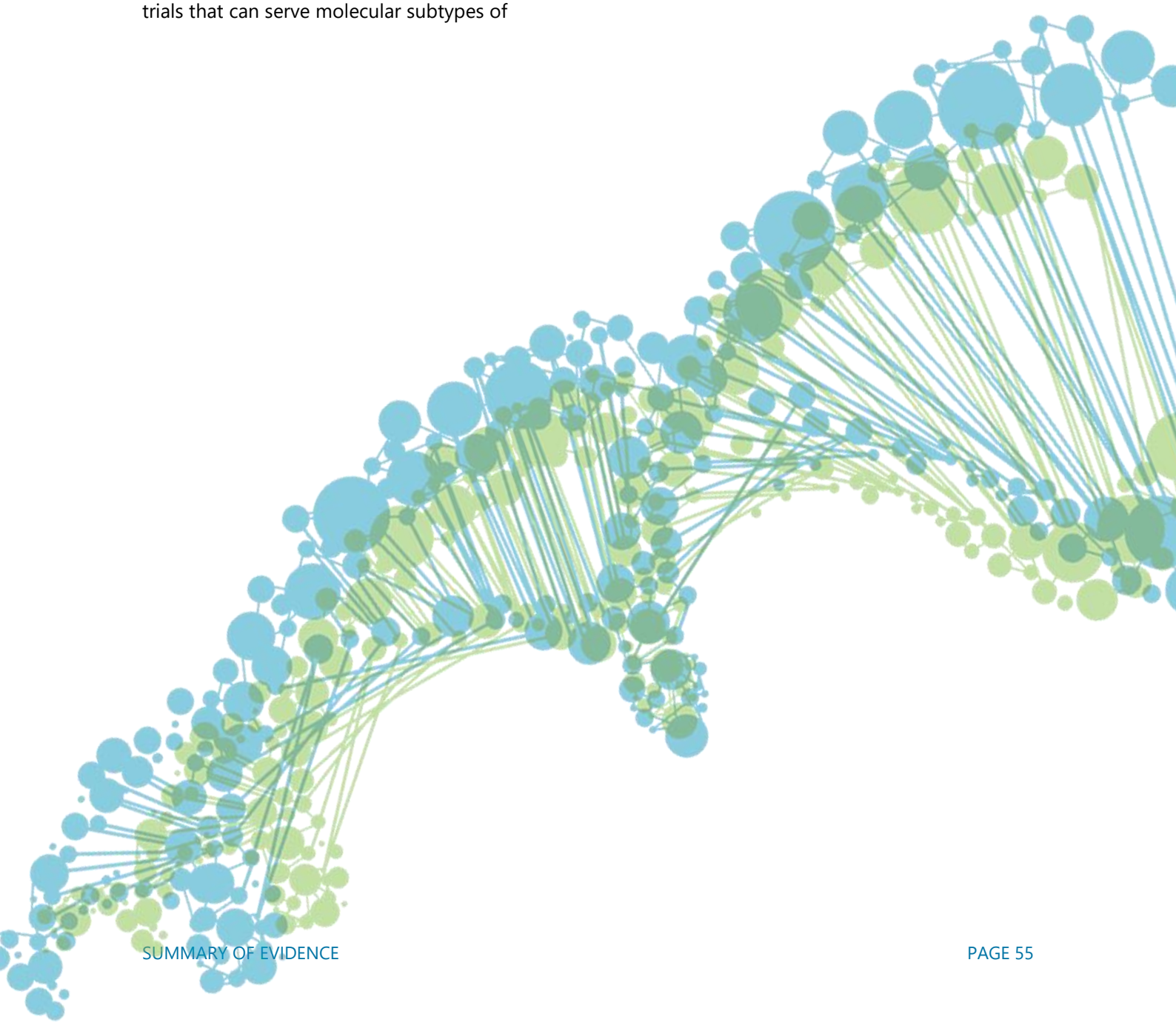
as well to immunotherapy. These insights help discover new uses for cancer drugs and accelerate access to patients. The data collected through this trial will be publicly available. (65)

Table 12. Therapies included in DRUP

Investigational	
Tyrosine kinase inhibitors	Monoclonal antibodies
Olaparib, dabrafenib, nilotinib, trametinib, erlotinib, vemurafenib + cobimetinib, vismodegib, regorafenib, afatinib, dabrafenib + trametinib, ribociclib, lenvatinib, rucaparib, axitinib, palbociclib, crizotinib, sunitinib, cabozantinib, brigatinib, abemaciclib, alectinib	Panitumumab, trastuzumab + pertuzumab, nivolumab, pembrolizumab, durvalumab, atezolizumab + bevacizumab

Source: ClinicalTrials.gov

Clinical trials continue to be an important way for patients to access genomic testing and investigational treatments. Innovative trial designs have made it easier to launch clinical trials that can serve molecular subtypes of cancer and RLC cancers. The trials outlined in this section are only a snapshot of all the cancer genomics research being conducted worldwide.



10 Key Patient Populations and Costs

10.1 High unmet need patient groups

While the process of determining the clinical benefit of NGS for cancer patient populations is still underway in the research setting, stakeholders have begun to form opinions based on their experiences and current evidence on how different patient groups would benefit. Table 13 outlines the patient populations identified by stakeholders, stakeholder rationales for why NGS testing would be beneficial, and incidence statistics sourced from the Australian Institute of Health and Welfare (AIHW) where possible.

Since NGS testing – especially larger comprehensive panels – seems to improve the chance of finding alterations, some stakeholders argue that all patients would benefit from receiving a test. The disadvantage of that approach currently, others argue, is that many patients would have identified alterations for which there are no treatment options available, or for which the treatment options are too costly. This creates clear ethical concerns and reinforces the importance of establishing systems that connect patients with treatment options based on their genomic test results (Section 11). Following this logic, some stakeholders argue that there are "high utility" indications for which NGS testing would, in many cases, lead to funded targeted treatments. These are the relatively well-understood cancers such as NSCLC, CRC, melanoma, and breast cancer with multiple known actionable variants. Many stakeholders believe that these cancer patients have a higher chance of extracting immediate clinical utility from an NGS test, while patients with less well-understood cancers may be less likely to find an immediate pathway to treatment due to lack of available treatment options for alterations present in those cancers. However, in both cases the test results would provide valuable information that could potentially be used to inform treatment in the future. If collected and studied systematically, the genomic data produced by those tests would help improve researchers' understanding of the cancer and increase the likelihood of creating new treatment pathways in the future.

There is therefore a rationale for NGS testing from two perspectives: on one hand, testing patients who are more likely to have actionable alterations means that the test is likely to have immediate clinical utility. On the other hand, testing patients with lower chances of having actionable alterations (and often, for RLC cancers, fewer treatment options in the first place) needs to be done so that clinicians and researchers can gain a better understanding of those cancers. Conducting the test in the latter group could also lead to immediate clinical benefit to the patient if an appropriate drug or clinical trial is available. The value in providing NGS testing to patients is, in theory, not only to inform short-term clinical decision-making but to learn more about cancer. This requires better integration of clinical practice and research that allows the value of genomic data in research to be translated into the clinical world. The current healthcare system does not yet sufficiently facilitate that connection (Section 1).

The patient populations identified below are presented to illustrate how stakeholders are considering the benefits of NGS testing for high unmet need patients and to benchmark those considerations against patient incidence numbers.

Table 13. Cancer patient groups with high unmet need for NGS testing

Patient group	Rationale	Incidence
All cancers	Some patients may gain an immediate treatment decision or clinical trial placement, while others will not. However, there is still value for those who do not because the data can be revisited when new treatments become available, and the data will also contribute to the larger understanding of cancer.	145,483
Solid tumours	Many solid cancers can have poor prognosis and have known variants or signatures that can be addressed with targeted therapy.	128,162
Patients eligible for 2L treatment	Approximately ~60% of all patients. They have high unmet need given fewer treatment options available, and the cancer has likely not progressed enough to preclude efficacy of further treatment.	~87,000[a]
High utility indications	Indications with many known mutations and signatures (meaning there is a higher likelihood of finding an actionable alteration through testing).	Total: 64,807 Lung: 12,817 CRC: 16,398 Melanoma: 16,221 Breast: 19,371
Rare or less common cancers	RLCs have fewer treatment options and are more poorly understood. Genomic testing would help characterise the cancer and open the potential for repurposing an existing treatment if an actionable alteration is discovered.	46,070
All cancers with no treatment options	Includes patients for whom: • Treatment options have been exhausted. • There are no suitable treatment options from diagnosis. • Performance status is ≤2 (potential to benefit from treatment).	~24,000[b]
Patients under 50	Relatively young, healthy (more likely to respond to treatment), and more likely to have germline mutations than patients over 50. **Patients who fail 1L** are a possible subcategory.	18,521
Blood cancers	Blood cancers are a smaller group of cancers for which understanding genetic underpinnings is especially important given that biopsies and scans are not options in the diagnostic pathway.	17,321
Advanced/metastatic cancers (Stage III or IV)	Due to poorer prognosis, higher urgency to find a suitable treatment. **High utility indications** (e.g. NSCLC, CRC) or **patients who fail 1L** are potential subcategories.	17,204 1L failure: 10,000[a]
Non-small cell lung cancer (NSCLC)	NSCLC has around ten drug targets and over 30 drugs. Funding genomic testing for this indication would help demonstrate the test's clinical value.	8,075 Advanced: 5,652
Patients under 25	Young cancer patients are less likely to have cancer due to environmental factors and more likely to have germline mutations. Identifying these helps inform prognosis and treatment.	1,806

Source: AIHW
Abbreviations: 1L, first line therapy; 2L, second line therapy; CRC, colorectal cancer; NSCLC, non-small cell lung cancer

a. Estimates based on AIHW data and rates of 1L treatment failure and 2L treatment from various tumour types

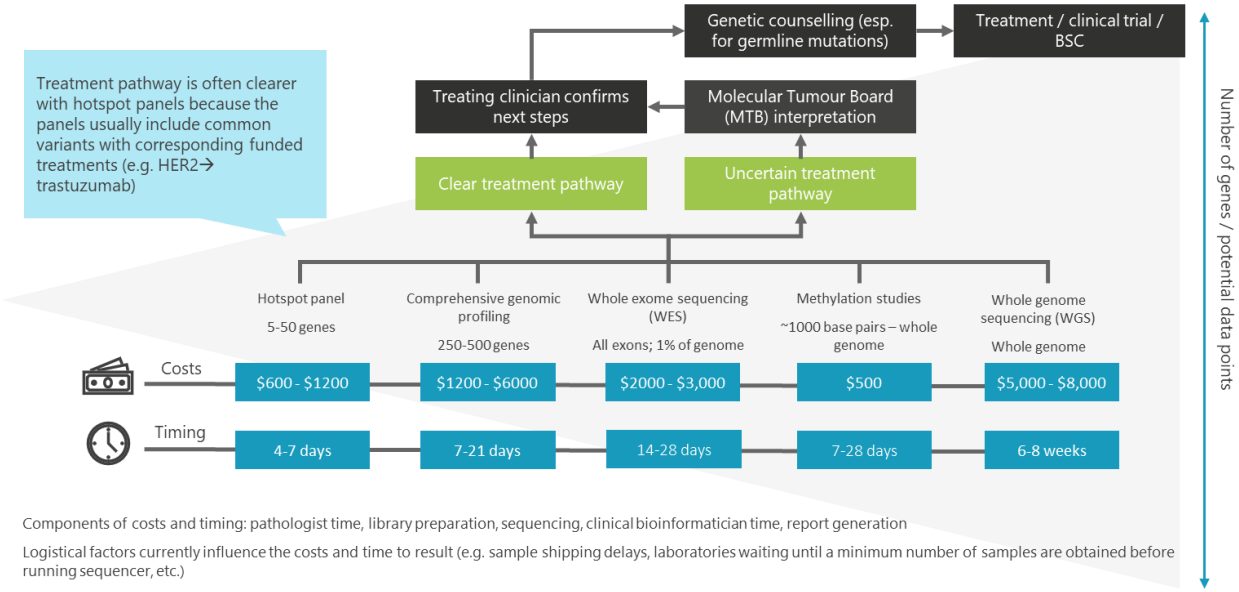
b. Estimate by leading stakeholder: ~48,000 cancer patients die each year; we can assume approximately 50% have performance status ≤2. This is a rough estimate given that there is limited data on performance status; additionally, there are other considerations besides performance status that factor into treatment decisions.

10.1.1 Preliminary cost assumptions

Costs of NGS testing have been declining over time and will continue to decline in the future. (11) Testing, analysis, and interpretation costs are directly correlated with panel size. Costs include sequencing, report generation, pathologists' time, bioinformaticians' time, and clinician bioinformatician time (

Figure 16). NGS hotspot panels can cost laboratories and providers several hundred dollars, comprehensive panels can cost over $2,000, and WGS costs over $5,000. The increased costs with large panels are in part due to the amount of genetic material being analysed and the labour required for analysis and interpretation. As automated analysis and interpretation capabilities improve (Section 8.3), costs are likely to become lower. Currently, however, analysis and interpretation are costly and time-consuming for whole exome and genome sequencing. In addition to testing costs, other costs associated with interpretation, counselling, and patient services should be considered when projecting the costs of future funded access to NGS testing.

Figure 16. Costs and turnaround time for NGS-based tests



Abbreviations: BSC, best supportive care; HER2, human epidermal growth factor receptor 2; NGS, next-generation sequencing; WES, whole exome sequencing; WGS, whole genome sequencing

Note: Cost and timing figures were estimated by expert stakeholders.

11 Current Gaps

Healthcare costs are becoming an increasing share of Australia's GDP (10.3% in 2015-2016 versus 8.68% in 2005-2006). Burns and colleagues (11) argue that reform is required to create a sustainable public health system, and Australia's priorities in the genomics field should be:

- Investing in a robust monitoring and evaluation system.
- Ensuring that appropriate sequencing and data infrastructure is available to support demand.
- Improving reimbursement/funding streams for multidisciplinary teams.
- Assessing cost-effectiveness of population-based genomic screening programs.

These priorities align with feedback from stakeholders interviewed for this report.

A key central issue for the continued uptake of NGS in Australia is solidifying the connection between the results of NGS and access to clinical trials or funded therapies. If this is not solved, patients may be forced to pay OOP to access off-label or non-reimbursed therapies causing financial hardship. Additionally, there is some scepticism around the feasibility and utility of rolling out broader NGS capabilities for clinical delivery. While many laboratories have the capability to conduct some NGS tests, there are cost-effectiveness considerations to be considered when determining the utility of ubiquitous large-scale NGS testing capabilities.

The current gaps hindering integration of NGS testing into cancer care are:

1) **Technology and process validation:** As discussed in Section 9.1, the validation process for large NGS panels is still in development, and will likely continue to evolve as new applications of NGS are invented. Despite some common practices, analytics and interpretation capabilities are also not currently standardised; research centres and companies develop their own methods. This heterogeneity makes it difficult to compare the utility of NGS tests against each another and use a consistent framework in assessing the technology.
2) **Sequencing capabilities:** while many laboratories have the capability to conduct some NGS tests, these laboratories may not have the advanced instruments capable of running comprehensive panels or whole genomes (discussed in Section 5.2), and it may not be cost-effective to introduce such technologies in a wide array of laboratories given the high upfront costs. It is also more cost-effective to run as many samples as possible together simultaneously, therefore each laboratory considering obtaining larger scale capabilities should have a high enough volume of samples to justify the costs. (12)
3) **Process capabilities:**
   a. ***Clinical:*** biopsy samples are not always high enough quality to conduct genomic analyses. Different levels of sample quality are required for DNA versus RNA, and it

may not always be clear which type of genetic material is best suited for the patient's testing needs. Patients may not be well enough to undergo biopsy procedure. There are also not standard approaches for patient stratification to determine which patients require which types of NGS tests.

   b. ***Analysis and interpretation:*** workforce and interpretation capabilities outside of large CoEs are not robust enough to cope with processing comprehensive genomic panels or larger assays. RCPA pathologists report that genomics is a "highly specialised area" and the "bottleneck" is in interpretation and providing reports, despite some companies providing standardised reports as outputs of CGP panels. As mentioned above, the best method of analysis and interpretation for each patient is not always clear. Many clinicians, pathologists, and researchers are cautious to advocate for funded genomic testing without highlighting the interpretation and analysis required to maximise the utility of the technology (Section 5.5).

4) **Continuum of care:** genetic counselling and broader care coordination have not yet integrated genomics into practice.
   a. ***Connecting diagnostics and treatment:*** critical to the success of a genomics-guided health system will be a strong connection between NGS testing results and either approved treatments or clinical trials.
   b. ***Genetic counselling:*** stakeholders recommend that the existing genetic counselling workforce be trained to provide guidance to patients on how to manage genomic testing results, especially results that do not create a clear actionable treatment pathway. There is also higher need for counselling after germline analyses compared to somatic, as germline results have implications for the patient's family and the potential for future genetic diseases.
   c. ***Care coordination:*** care coordination between local medical centres and CoEs is especially important for patients travelling from regional areas for testing or treatment in major metropolitan locations. If NGS testing capabilities continue to be concentrated at CoEs, systems should be developed to facilitate participation of patients from regional and rural parts of the country. Genetic counselling, patient groups argue, should be a part of care coordination between a patient's healthcare providers.

5) **Data storage and management:**
   a. ***National data system:*** A key aspect of integrating genomics into cancer care will be creating suitable systems for data storage and management. Currently, most genomic data generated in Australia is stored within pathology laboratory or hospital firewalls. According to RCPA, there exist some platforms where data can be uploaded into a cloud for processing and subsequently be re-downloaded by the laboratory. However, these are not widely used because laboratories are cautious about data security and must comply with Australian Privacy principles. To inform integration of genomics into Australia's digital health system, Australian Genomics introduced its National Approach to Data Federation program. The program aims to create a shared, scalable, cloud-based standardised genomic database compliant with international standards. This approach would help avoid fragmentation and create opportunities for use of genomic data in research.
   b. ***Private sector:*** there are currently concerns about genomic data leaving Australia, which occurs voluntarily when patients send samples overseas for testing. While turning to private companies fills a current unmet need in the healthcare system, many stakeholders fear that excessive private sector involvement without regulation will result in fragmentation and limited access to data. Industry has a large interest in using genomic data to create new products and services. One industry stakeholder reported that by analysing

large amounts of genomic data, companies have begun to identify and patent molecular signatures to create their own tests or to generate a commercial return whenever a laboratory elects to search for that patented signature.

c. ***Privacy:*** collecting genomic data on a national scale and using it for research purposes will likely create privacy concerns. My Health Record is an example of a public health effort to increase efficiency and improve care through nationwide digitisation of patient health records, however people continue to distrust the program despite the benefits it would provide to consumers. The lesson from My Health Record is that promoting participation in the program is not enough, there also needs to be clear communication and patient consent throughout the process so that consumers are comfortable with how their data is being used. (66)

6) **Equity in the health system:**

a. ***Reimbursement:*** there is currently no reimbursement for large NGS panels and their interpretation, nor would there be funded access to matched treatment for many patients if they were to receive a test. Access to testing is currently dependent on ability and Willingness to pay OOP, and access to clinical trials is dependent on where patients are treated. However, there is not yet sufficient evidence to justify broader MBS funding of NGS testing.

b. ***Prioritisation of public funds:*** given the lack of clear connection between NGS test results and access to funded treatments, some patient groups warn that attempting to roll out NGS testing pre-emptively could distract from other worthwhile endeavours such as cancer care coordination, using up funds that could otherwise be used in different areas of cancer care.

c. ***Risks of inefficiency and siloes:*** Given that states are the providers of diagnostic services and the responsibility for funding is split between federal and state governments, there are risks of duplication, inefficiency, siloes, and inequities of access in the Australian health system. For example, Australian Genomics found that there are varying levels of genomics expertise, capacity, and investment depending on the state, indicating that each state provides its own standard of genomics services. (20)

12 Funding and Implementation Strategies

12.1.1 Funding

Between 2020 and 2030, funding for NGS testing is likely to come increasingly from Medicare reimbursement, particularly as the cost of NGS decreases and the technology can be harnessed by laboratories in a cost-effective manner using existing MBS items. As research using NGS increases, funding will also partly come from government research funds such as the MRFF.

12.1.2 Short-term: research

Research has a dual purpose in cancer genomics: 1) to provide patients with access to novel innovative health technologies, and 2) to build an evidence base intended to support future MSAC applications for genomic testing. To achieve both goals, it will continue to be critical to fund cancer genomics through research, and for the many research groups across Australia to collaborate as they have been through networks such as Australian Genomics. Effective and transparent communication will both support efficient clinical trial enrolment (thereby maximising patient benefit from innovative technologies) and provide a forum for continuous refinement of the value propositions in development for applications to MSAC to list new MBS items in the future. Funded research also provides an opportunity to trial solutions for many of the gaps identified in Section 11, such as finding a way to link patients to clinical trials in a seamless and equitable way.

Based on the evidence summarised in Section 1 and the perspective of genomics researchers, there is a substantial and compelling foundation of evidence to support use of NGS testing to inform biomarker-based approaches to therapy. Thus far, most studies have focused on demonstrating the value of biomarker-based approaches to treatment in advanced cancers, lung cancer, and several other tumour types including colorectal, brain, and breast cancers. Given the nature of the intervention and the target patient population, the studies conducted to date have been non-randomised studies of the effects of interventions (NRSIs), many of which are retrospective studies. Despite the non-randomised nature of the current evidence, leaders in the field view it as compelling justification to scale up national genomics research to both provide better access to patients and continue to build evidence.

> Leaders in the field view the current evidence as compelling justification to scale up national genomics research.

Researchers expect that prospective randomised controlled trials for biomarker-based treatment approaches will be conducted in the future. However, leaders in the field argue that it is more important to create flexible and scalable trial designs than to strictly abide by traditional trial design standards. For example, a phase II randomised trial assessing personalised treatment based on specific tumour characteristics in pancreatic cancer against SOC was designed in 2010 (the IMPaCT trial). Patients with one of three

potential molecular profiles were eligible to received targeted treatment: 1) HER2 amplification, 2) DNA damage repair defects (e.g. BRCA1/2, PALB2, ATM), or 3) KRAS wild-type. IMPaCT faced challenges with sample collection logistics and achieving clinically relevant turnaround times (TAT), which is especially important in diseases like pancreatic cancer with poor prognosis. Between 2013 and 2015, 93 patients were referred to be considered for molecular screening, and 72 patients' samples were successfully sequenced. Of the 72 sequenced samples, 22 samples were found to have one of the three types of molecular targets eligible for targeted treatment within the trial's protocol: 14 KRAS wild-type signatures, five cases of HER2 amplification, two mutations in BRCA2, and 1 ATM mutation. However, by 2015 IMPaCT had not successfully treated any patients for the following reasons: death before results were obtained (n = 6), worsening condition beyond an Eastern Cooperative Oncology Group (ECOG) Performance Status of 2 (n = 3), starting chemotherapy before results obtained (n = 4), becoming ineligible due to other diagnosis or condition (n = 4), refusing randomisation or withdrawing after randomisation to SOC (n = 2), undergoing successful resection without disease recurrence (n = 3). (67) The problems in this study were slow turnaround time, restrictive randomised design, and limited alterations eligible for targeted therapy.

The challenges faced in trials such as IMPaCT can be addressed by improving logistics and using flexible trial designs. Achieving clinically relevant turnaround times can be limited by delays in acquiring archival FFPE samples from pathology laboratories, time required for re-biopsies if original samples do not yield high quality DNA, and confirmatory molecular testing (which took 1-28 days in the IMPaCT trial). Median time from consent to returned result was 21.5 days, which was also consistent with at least three other studies. (67) Stakeholders involved in ZERO Childhood Cancers have reported that turnaround times for WGS, RNASeq, and methylation analyses have been decreasing from 12 weeks to 6 to 8 weeks. (19) Turnaround time for a Foundation Medicine CGP panel is 14 days, suggesting that turnaround in the clinical setting might be faster than in clinical trials. Logistical challenges and interpretation are the main cause of longer turnaround times in both research and clinical settings. As discussed in Section a, the sequencing and bioinformatics analysis can be done within one or two days. However, the time needed for shipping samples in some cases and allowing time for interpretation can increase the turnaround time by weeks. Anticipating potential logistical hurdles and incorporating plans to manage those issues into research protocols will support both the success of future trials and demonstration of feasibility that will translate to the clinical setting in the future.

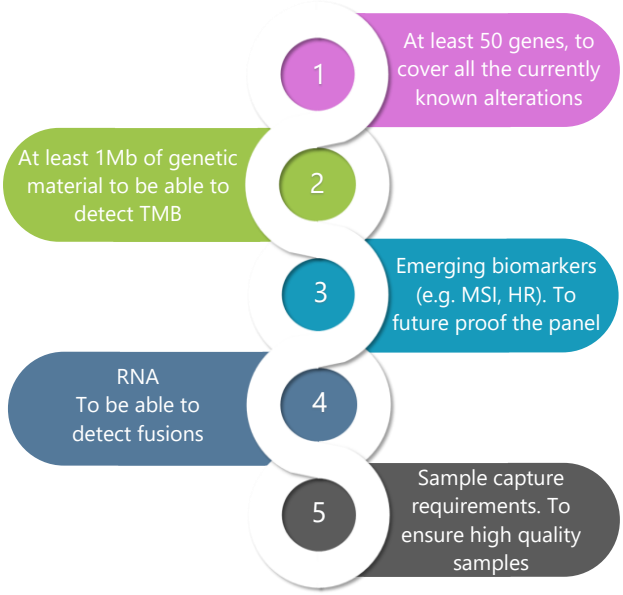
Improving logistical capabilities and using flexible trial designs will help address some of the hurdles faced in precision medicine research.

Another issue faced by cancer genomics trials is low enrolment. A platform trial design would allow for new treatment arms to be added depending on sequencing results, expanding the pool of eligible patients and the potential number of treatments investigated in the trial. (68) The IMPaCT trial used an umbrella design, which had three investigational treatment arms for different molecular profiles within the same histological cancer type (pancreatic cancer). However, the investigational treatment arms were limited to the three pre-specified categories. Using a platform design would allow new treatment arms to be added based on alterations discovered during sequencing, and perhaps would have allowed a higher proportion of the 72 patients whose samples were successfully sequenced to be eligible for targeted therapy in the IMPaCT trial. This would have also allowed the trial to generate evidence on a higher number of existing or investigational therapies, obtaining results that could support future funded access to those therapies in the studied pancreatic cancer

subtypes. If possible, protocols ideally should take prognostic considerations into account if turnaround times are a potential hurdle, as the IMPaCT trial did by amending the protocol to allow patients to begin chemotherapy while waiting for the sequencing results. Finally, the In addition to continuing to study the efficacy of personalised medicine guided by NGS testing, there has not yet been research conducted to compare the utility of the various CGP assays manufactured by companies such as Illumina, Foundation Medicine, BGI, ThermoFisher, and others. Industry stakeholders report that the large panels of hundreds of genes usually contain the same key genes and can be customised as the manufacturer sees fit. Based on current knowledge in the field, leading stakeholders reported that CGP panels should have the following features (Figure 17):

- At least 50 genes to cover all the known alterations
- At least 1Mb to be able to detect TMB
- Emerging biomarkers such as MSI and homologous recombination
- RNA to be able to detect fusions
- Requirements for method of sample capture to preserve quality

Figure 17. Ideal elements of a CGP panel



Abbreviations: HR, homologous recombination; Mb, megabase; MSI, microsatellite instability; RNA, ribonucleic acid; TMB, tumour mutational burden

As the evidence base supporting NGS testing grows and clinicians, researchers, and patients value of a randomised trial design should be weighed against the potential enrolment hurdles it creates (e.g. patients unwilling to be randomised to the SOC treatment, increased need to enrol higher numbers of patients).

become increasingly enthusiastic about genomics, the federal government and state governments have taken steps to prioritise genomics research funding. As described in Section 1, the federal government has awarded over $600 million to research projects, and state governments have also contributed several million dollars each to state-based initiatives.

Given Australia's relatively small population and cancer incidence of nearly 150,000 patients, there are advantages to establishing a nationally coordinated approach to genomics research. Such an approach would help ensure that patients are matched with appropriate clinical trials as quickly as possible, trials with master protocols can be conducted on a large enough scale to capture adequate sample sizes, and a foundation for integration of genomics into clinical practice is consistently and rigorously established nationwide.

12.1.3 Medium- to long-term: reimbursement

Obtaining sustainable and broad funding from the MBS can likely be considered in the medium- to long-term time frame. However, the arrival of tumour-agnostic therapies (as discussed in Section 8.2) increases the need for a solution in the short- to medium-term to allow access to these drugs via the PBS. Pembrolizumab for TMB-H will potentially be the first application in Australia which specifically requires access to NGS to identify eligible patients. This could be considered as part of a broader application to widen access to NGS and link patients to tumour agnostic therapies.

The HTA process followed by MSAC requires strong clinical and technical evidence (covering analytical/clinical validity and clinical utility) and clear demonstration of cost-effectiveness. Several examples of successful and unsuccessful applications in recent years help illustrate this point. In May 2020, the MBS

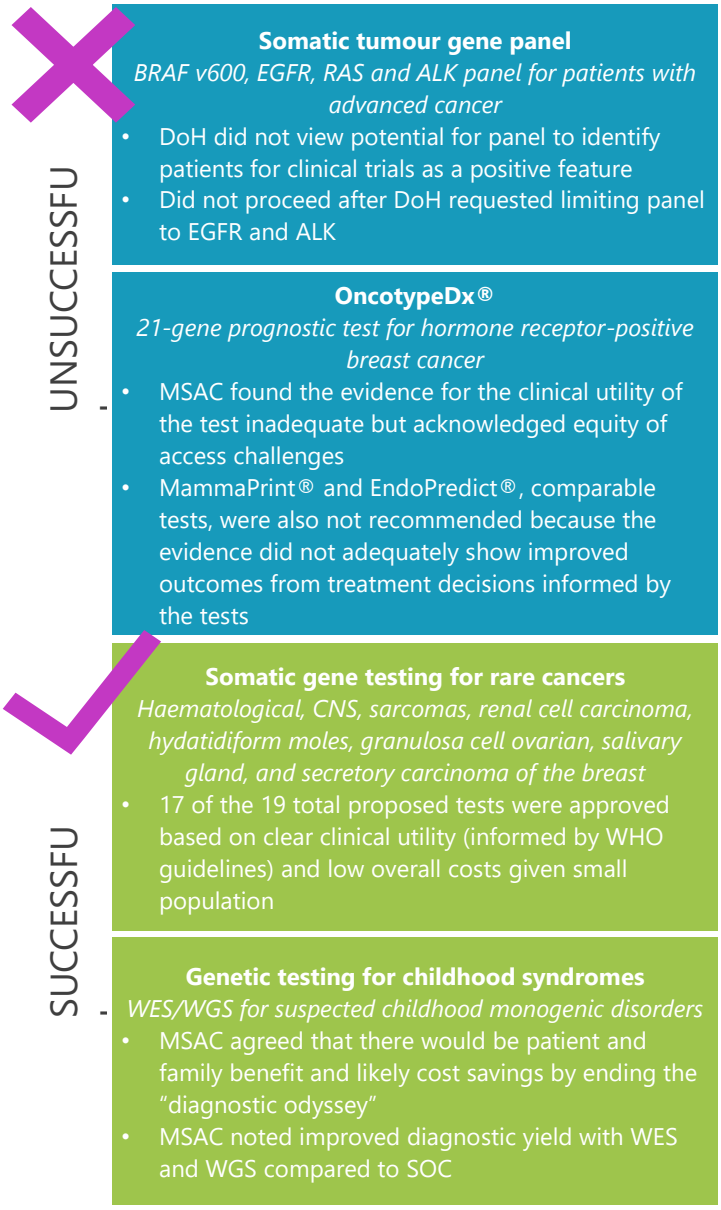
listed nearly two dozen new genetic testing items, including:

1) Several somatic gene tests for rare cancers were grouped into three MSAC applications and submitted by RCPA. After being considered together by MSAC, 17 of the 19 tests were listed on the MBS for diagnostic purposes (with no linkage to access to medications). MSAC noted that nearly all of the tests were recommended by World Health Organisation (WHO) guidelines, providing support for the tests' validity. Further, the patient populations were well-defined and relatively small, therefore the tests would not create large budget impact.
2) WES and WGS testing for childhood conditions were also approved in the same round of recommendations. MSAC noted that the diagnostic yield was higher with WES compared to SOC, and even higher with WGS. There would be a significant patient and family benefit by making the path to diagnosis easier and ending the "diagnostic odyssey" faced by many families.

Besides the recent wave of successes, there have also been notable unsuccessful applications for new genetic and genomic tests in recent years:

1) OncoType DX®, a 21-gene prognostic test for hormone receptor-positive breast cancer, was submitted to MSAC six times. The test proposed to provide information on which patients have higher chance of recurrence and higher likelihood of benefiting from chemotherapy; such results would ideally help prevent unnecessary use of chemotherapy in patients who are unlikely to benefit. Ultimately, the six applications were rejected because MSAC found the evidence for the clinical utility of the test inadequate: the patient population proposed did not exactly align with the evidence base, the cost comparator was not appropriate in the first submission, the requested price was considered too high, and there was uncertainty around predicted savings to the PBS through reduced use of chemotherapy. (69) (70).
2) In 2017, RCPA submitted an MSAC application (Application No. 1495) for a somatic tumour gene panel which would test for clinically relevant alterations in at least three genes in patients with advanced cancer. The proposed MBS item required that BRAFv600, EGFR, RAS or ALK be included on the panel, and that at least one of the genes be "used to determine whether requirements for a targeted therapy listed on the PBS are fulfilled." RCPA also highlighted to MSAC that the panel would confer research benefits by identifying variants in patients' tumours that could lead to their enrolment in clinical trials. RCPA indicated that sequential testing could be avoided by using the panel, and that this approach would lead to better patient outcomes by informing optimal treatment selection. The testing techniques proposed were ISH, PCR, and NGS, although the submission noted that others could be used as well. The estimated cost per test was $600. (71) According to RCPA, the potential for the panel to help identify patients for clinical trials was not viewed as a favourable feature of the value proposition by the Department of Health. The Department advised that the application should prioritise funding tests that would connect patients with funded PBS treatments and requested that the panel be limited to ALK and EGFR. Given that this did not offer the same clinical utility and would require one DNA analysis and one RNA analysis, RCPA did not proceed with the application.

Figure 18. Recent MSAC applications for genetic and genomic tests



Abbreviations: ALK, anaplastic lymphoma kinase; BRAF, proto-oncogene B-Raf; DoH, Department of Health; EGFR, epidermal growth factor receptor; MSAC, Medical Services Advisory Committee; RAS, rat sarcoma; SOC, standard of care; WES, whole exome sequencing; WHO, World Health Organisation; WGS, whole genome sequencing

As illustrated by these examples, MSAC's process weighs the clinical and economic benefits of equitable funded access to a service with the opportunity costs of funding the service. Given that funds are limited, the benefits of public funding for a medical service must be justified through robust clinical evidence. Successful applications have clearly defined patient populations, and it is likely easier to obtain approval if the proposed population is relatively small with low overall budget impact implications (with a low risk of leakage). Patient groups and clinicians highlighted that inequitable clinical access to NGS testing, especially for large panels, is an issue in the absence of MBS funding, as only patients who can afford to pay thousands of dollars OOP are able to receive the tests. In its decision-making, MSAC is conscious of equity of access the proposed service, however the allocation of finite funds across all potential medical services must also be executed in an equitable manner. Beyond evidence, support from relevant stakeholders will also be an important factor in the success of future MSAC submissions.

MSAC's process weighs the clinical benefits of equitable funded access to a service with the opportunity costs of funding the service.

The MSAC process guards against the risks of spending public funds on unjustified services, however many stakeholders believe that the current process is too lengthy, and reform will be required to keep pace with rapid innovation in genomics. For example, stakeholders would like to explore the possibility for creating more flexibility around the requirements for randomised control trial evidence given that patient populations are becoming smaller with more molecular classifications and randomisation in precision medicine trials can be challenging. There will also need to be strategies around how to create MBS items that avoid obsolescence for a reasonable amount of time to avoid the need for multiple successive submissions, and how to quicken the approval process to give access to patients more rapidly.

While MBS item numbers would enable better equity of access and further integration of genomics into clinical practice, many stakeholders believe the infrastructure systems around the test are equally important to achieve it. These considerations are discussed in Section 12.2.

12.2 Implementation

Implementation of genomics into clinical practice will continue to be a gradual process, and that process should take into account infrastructure, data management, ethics, and equity considerations. Clinical trials such as MoST, which use CGP to inform treatment for cancer patients, are generating evidence on the utility of such panels which may be used in the future for an MSAC submission. The cost to a laboratory of running a CGP panel is approximately $2,000, according to experts. While creating an MBS item reimbursed at $2,000 would provide a stronger financial incentive to laboratories compared with existing genetic and genomic test items, stakeholders doubt that a high MBS fee alone will be enough to support creation of the relevant genomics infrastructure and delivery system. Most stakeholders believe there should be a deliberate national effort to build an integrated data and monitoring infrastructure as well as a coordinated genomics delivery system. A national program's advantages would include larger datasets for analysis and research, seamless data sharing, increased efficiency, and greater equity of access. Within a national program, each state's unique capabilities and expertise should be leveraged strategically to avoid duplication and maximise efficiency. For example, a CoE in Victoria specialised in a specific area of genomics could be the nationwide leader on that field of study rather than requiring all states to develop their own expertise. State engagement will also be critical to development of robust datasets including not only genomic data but other health data. Given that states are typically the providers of clinical care, state provider systems will be an important source of health data. Workforce training and reimbursement of support services are also important components of the infrastructure that would benefit from national coordination. Stakeholders emphasised that state-based initiatives would not be equipped to provide nationwide equity of access, therefore a federal approach would be favourable.

12.2.1 Infrastructure

According to key stakeholders with public health and clinical expertise, delivery of genomics services should operate through a centralised model with satellites that emphasise seamless coordination of care and patient well-being. Testing resources would be concentrated at large CoEs, to maximise efficient use of sequencing technology and bioinformatics expertise. Strong satellite networks with regional hospitals would work with the CoEs to coordinate care and allow patients to be home and continue to have access to services. Patient groups such as the Australasian Leukaemia & Lymphoma Group (ALLG), which conducts clinical trials and maintains a repository of genomics data, and CanTeen, which also runs clinical trials with industry partners, are enthusiastic about expanding access to genomics testing for their constituents and may be well-poised to serve as a foundation for care coordination between medical centres.

Another key element in the infrastructure design is an adequate workforce. The genomics workforce involves oncologists, lab scientists, clinical pathologists, bioinformaticians, clinical geneticists, genetic counsellors, and non-genetics healthcare professionals, who must know how to:

- Determine when to order genomics tests.
- Interpret test results to inform clinical decision-making.
- Counsel patients on genetic conditions and genomic tests.
- Obtain informed consent.
- Ensure understanding and appropriate action following test result or procedure. (11)

As discussed in Section 11, members of RCPA believe a larger genomics workforce will be needed to expand capacity. Associated services such as multidisciplinary teams, MTB, and genetic counselling would need to be funded and integrated as appropriate. Through a centralised approach, training and knowledge sharing would be consistent and streamlined.

Linking NGS testing results with treatments at a system level will also be a critical part of the genomics infrastructure. This would include creating pathways for patients to obtain approved drugs or be enrolled in clinical trials. Given that access to treatments is critical to realising the value of genomic testing, part of a national genomics infrastructure could address this by creating a living database of Australian clinical trials that clinicians could easily access to find investigational treatment options for patients based on their genomic test results. The program could also collect real-world evidence on the use of funded therapies in molecular subtypes of cancer to build further evidence.

12.2.2 Data

While the costs of sequencing have been declining, informatics capacity for computation and storage has become a bottleneck. WGS creates an especially large challenge not only because large amount of data generated is more complex to analyse, but it requires more storage space. In the UK, for example, data from 1,700 whole genomes occupies 200 Tb of storage. New developments in cloud computing technology have begun to help facilitate the collection, use and sharing of large datasets less expensively. Increasing data storage and sharing capabilities will soon enable much wider implementation of genomics. (11)

Many stakeholders imagine a national database of genomic data (like those in England or Japan) would create significant opportunities for researchers and enhance clinical care by connecting with broader patient health data. With the government or perhaps a government-nominated independent body as a shepherd of the database, access could be provided to private sector organisations seeking to conduct research. This would also help attract research and development funding and clinical trials to Australia. Industry and academic stakeholders alike view this as a positive opportunity that would be a major improvement over the current situation, where some patients send samples overseas for testing and Australia loses the opportunity to document and store the genomic outputs of those tests.

> Creation of a living database of Australian clinical trials could facilitate patients' access to treatment while collecting real-world evidence on the use of funded therapies in molecular subtypes of cancer.

12.2.3 Ethics

A national database of genomic data involves ethical and privacy considerations. Patients would have to understand and consent to the use of their anonymised genomic data for research. A rigorous method of protecting misuse of genomic data would need to be defined and clearly communicated to patients. The learnings from Japan's approach (Section 1.1) are that patients will have legitimate concerns about privacy and misuse of data. While granting access to funded drugs after patients have provided consent to use their genomic data may be effective, a more sustainable approach to establishing trust and willingness to participate will likely be through proactive communication and responsible independent management.

> A national database of genomic data connected with broader patient health data would create significant opportunities for researchers and enhance clinical care.

Support services also require an ethics consideration. Conducting genomic testing, especially germline testing, will inevitably lead

to unfavourable or unexpected results that have implications for patients and potentially their families. Genetic counselling and mental health services should be part of the care coordination process to ensure that patients are supported when confronting difficult decisions.

12.2.4 Analogues

Several stakeholders drew parallels between the potential path to integration for NGS testing and the normalisation of medical services which are now common, but once were considered novel and sometimes met with resistance:

- **Magnetic resonance imaging (MRI):** when MRI was first introduced, there were concerns that healthcare providers would be unfamiliar with the technology and unsure of how to make use of it. Eventually, radiologists created a subspecialty of expertise around the technology.
- **Colorectal cancer screening:** while evidence showed that screening for people over age 50 reduced colorectal cancer mortality, it has been a challenge to convince patients to follow the screening recommendations. A 2018 analysis of the National Bowel Cancer Screening Program (NBCSP) by AIHW found that people not invited to screen in the program had a 13% higher risk of mortality due to bowel cancer compared to invitees. The program also helps save the government money in downstream healthcare costs. While healthcare professionals still would like to see participation rates increase, stakeholders view this as an example of clear efficacy and cost-saving evidence driving integration of the service into standard practice. (72)
- **Positron emission tomography (PET) scans for lymphoma monitoring:** in the early 2000s, ALLG conducted clinical trials to show that yearly PET scans helped in monitoring progression of certain types of lymphoma. Conscious that the scans were costly, ALLG presented clinical trial data to MSAC and showed that the scans would prevent high downstream costs by allowing clinicians to find the disease and start treatment at the right time.

These examples suggest that while the workforce relevant to genomics is more limited today than it will be in the future, it is likely to be malleable and responsive to the entry of new technologies, and that compelling clinical and cost-effectiveness evidence are critical to receiving MSAC approval and becoming standard practice.

Next Steps

Genomics will undoubtedly guide the future of cancer care both in Australia and around the world. With this report, we hope to describe the current landscape, highlight key considerations for the path forward, and inspire future collaborations that aim to advance Australia's genomics capabilities in cancer diagnostics, treatment, and management. The findings of this report demonstrate that there is a considerable opportunity to create a world leading cancer genomics architecture in Australia, that harnesses the existing expertise and infrastructure already in place and builds on overseas experience.

NOA's Australian Cancer Futures Framework is a vehicle to bring together a dedicated task force including a broad range of expert stakeholders across the entire cancer community to drive the reforms necessary to deliver a national approach to genomic testing for cancer patients. The foundation established by this report demonstrates that the rollout of integrated cancer genomics testing should start in the research setting, before ultimately becoming a part of established clinical practice. This will require cross-stakeholder collaboration between clinicians, researchers, industry, patient groups, and government. Rare Cancers Australia and NOA are excited to continue supporting this opportunity for Australian leadership in genomics and the critical work that will improve the lives of cancer patients and their families.

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Appendix I: PBS-Listed Targeted Therapies

Table 14. PBS-listed monoclonal antibodies with oncologic indications

Type	Class	Description	PBS-listed treatments	PBS-listed oncologic indications
Monoclonal antibodies	Checkpoint inhibitors	Prevent cancer cells from inhibiting the immune system by targeting PD-1/PD-L1 or CTLA-4 checkpoint pathways	Pembrolizumab	EGFR and ALK negative NSCLC, PD-L1+ NSCLC, melanoma, urothelial carcinoma, Hodgkin lymphoma
			Atezolizumab	EGFR+ or ALK+ NSCLC, SCLC
			Nivolumab	Melanoma, NSCLC, RCC, HNSCC
			Ipilimumab	RCC, melanoma
			Durvalumab	NSCLC
			Avelumab	MCC
	Anti-VEGF	Target VEGF receptor to reduce blood supply to a tumour to slow or stop growth	Bevacizumab	CRC, NSCLC, glioblastoma, epithelial ovarian / fallopian tube, peritoneal, cervical
	HER2-targeted agents	Destroy or limit growth of HER2+ cancer cells, which grow uncontrollably	Trastuzumab/ trastuzumab emtansine	HER2+ breast, HER2+ gastric
			Pertuzumab	HER2+ breast
	Anti-CD20	Target CD20 protein found on some B-cell leukaemias and NHLs	Rituximab	CD20+ B-cell NHL, CD20+ CLL, CD20+ ALL
			Obinutuzumab	CD20+ CLL, FL
	Anti-EGFR	Target EGFR protein to downregulate signalling pathways that promote cancer growth	Cetuximab	Wild-type RAS CRC, HNSCC
			Panitumumab	Wild-type RAS CRC
	Bi-specific T-cell engager (BiTE)	Direct T-cells to bind CD19 protein on surface of B-cells in leukaemias or lymphomas	Blinatumomab	ALL, MRD of Pre-B-cell ALL
	Antibody drug conjugates	Combine monoclonal antibodies with small molecule cytotoxic agents	Brentuximab vedotin	CD30+ Hodgkin lymphoma, CD30+ cutaneous T-cell lymphoma, CD30+ systemic anaplastic large cell lymphoma
			Inotuzumab ozogamicin	CD22+ ALL

Source: Cancer Council, PBS.gov.au, International Journal of Cancer Research and Treatment

Abbreviations: ALL, acute lymphoblastic leukaemia; ALK, anaplastic lymphoma kinase; CLL, chronic lymphocytic leukaemia; CML, chronic myelogenous leukaemia; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; FL, follicular lymphoma; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma, MCC, Merkel cell carcinoma; MRD, minimal residual disease; NHL, non-Hodgkin's lymphoma; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; SCLC, small cell lung cancer; VEGF, vascular endothelial growth factor

Table 15. PBS-listed small molecule inhibitors

Type	Class	Description	PBS-listed treatments	PBS-listed oncologic indications
SMALL MOLECULE INHIBITORS	Tyrosine kinase inhibitors (TKIs)	Block tyrosine kinases from sending growth signals to cancer cells	Imatinib	CML, Ph+ ALL, CEL, KIT+ GIST, DFSP
			Dasatinib	Ph+ CML, CML, Ph+ ALL
			Nilotinib	Ph+ CML
			Ponatinib	CML, T315I+ CML, T315I+ ALL, Ph+ ALL
			Midostaurin	FLT3+ AML
			Gefitinib	EGFR+ NSCLC
			Erlotinib	EGFR+ NSCLC
			Afatinib	EGFR+ NSCLC
			Osimertinib	EGFR T790+ NSCLC
			Crizotinib	ALK+ or ROS1+ NSCLC
			Alectinib	ALK+ NSCLC
			Brigatinib	ALK+ NSCLC
			Ceritinib	ALK+ NSCLC
			Lorlatinib	ALK+ NSCLC
			Entrectinib	ROS1+ NSCLC
			Lapatinib	HER2+ breast
			Abemaciclib	HR+ breast
			Palbociclib	HR+ breast
			Ribociclib	HR+ breast
			Dabrafenib	BRAF V600+ melanoma
			Vemurafenib	BRAF V600+ melanoma
			Trametinib	BRAF V600+ melanoma
			Cobimetinib	BRAF V600+ melanoma
			Encorafenib	BRAF V600E+ or V600K+ melanoma
			Binimetinib	BRAF V600E+ or V600K+ melanoma
			Sorafenib[a]	HCC, RCC
			Sunitinib[a]	RCC, GIST, pancreatic NET
			Pazopanib[a]	RCC, STS
			Axitinib[a]	RCC
			Cabozantinib[a]	RCC
			Lenvatinib	HCC, liver, thyroid
	Mammalian target of rapamycin (mTOR) inhibitors	Block mTOR, an enzyme which enables cancer cell growth and spread	Everolimus	Pancreatic NET, RCC, TSC
	Poly ADP ribose polymerase (PARP) inhibitors	Prevent PARP protein from repairing damaged DNA in cancer cells	Olaparib	BRCA+ (germline or somatic) epithelial ovarian, fallopian tube, or primary peritoneal

Source: Cancer Council, PBS.gov.au, International Journal of Cancer Research and Treatment

Abbreviations: ALL, acute lymphoblastic leukaemia; ALK, anaplastic lymphoma kinase; BRAF, proto-oncogene B-Raf; BRCA, breast cancer gene; CEL, chronic eosinophilic leukaemia; CLL, chronic lymphocytic leukaemia; CML, chronic myelogenous leukaemia; DFSP, dermatofibrosarcoma protuberans; EGFR, epidermal growth factor receptor; GIST, gastrointestinal stromal tumour; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; HNSCC, head and neck squamous cell carcinoma, HR, hormone receptor; NET, neuroendocrine tumour; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; ROS1, c-ros oncogene 1; SCLC, small cell lung cancer; STS, soft tissue sarcoma; TSC, tuberous sclerosis complex

a. Also has antiangiogenic activities (like VEGF inhibitor bevacizumab)

Appendix II: Clinical Evidence

Table 16. Evidence for use of matched therapies informed by genomic test results

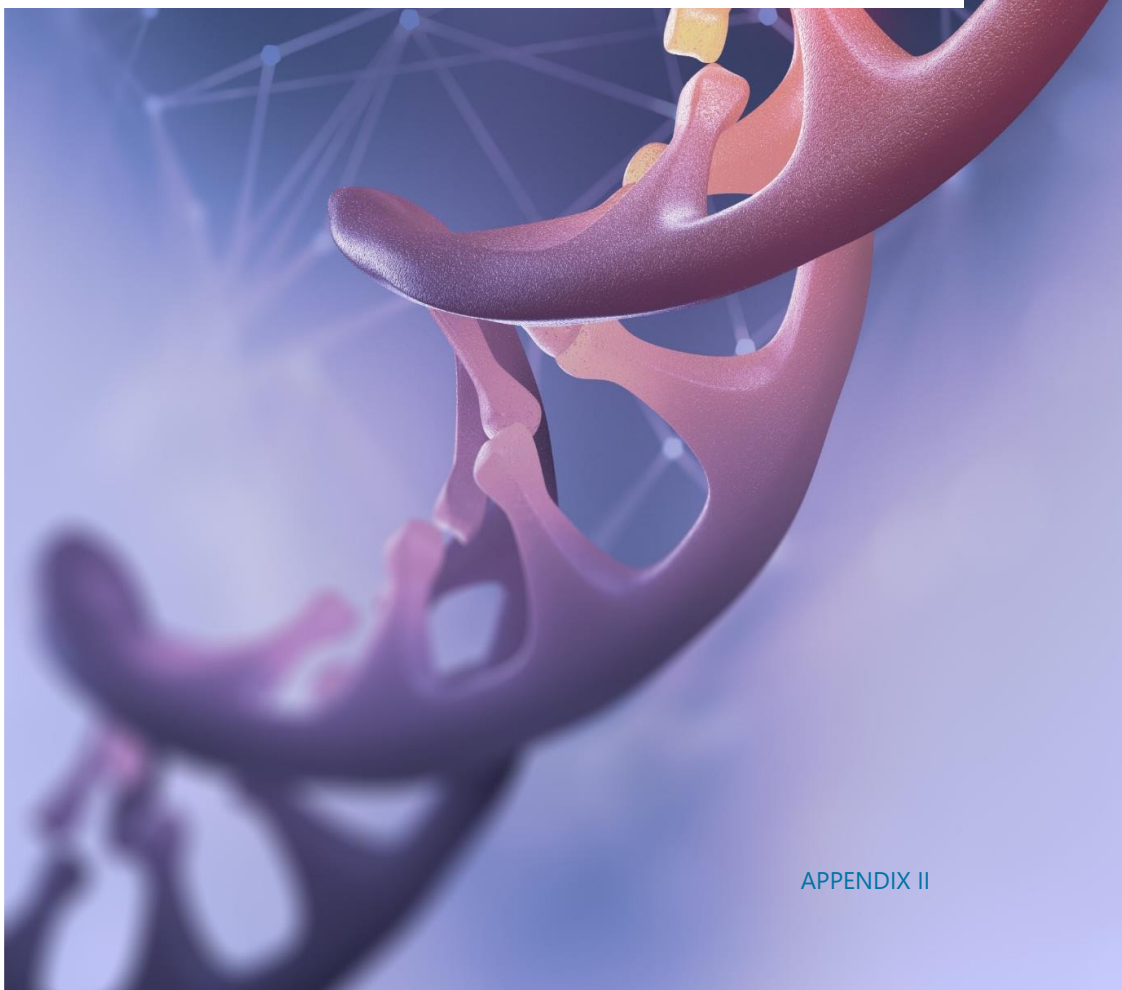
Study	Sample size	Tumour types	Reported outcomes
Jardim 2015	58 drugs FDA-approved between 1998 and 2013 (57 randomised [32% personalised] and 55 non-randomised [47% personalised]). Outcomes in personalised trials compared with outcomes in non-personalised trials.	All cancers	• RRR: 3.82 vs 2.08 • Longer PFS
Schwaederle 2015	32,149 patients (meta-analysis)	All cancers (phase II trials)	• RR: 31% vs 10.5% • PFS: 5.9 vs 2.7 months • OS: 13.7 vs 8.9 months
Schwaederle 2016b (meta-analysis)	Personalised approach	All cancers (phase I trials)	• RR: 30.6% vs 4.9% • PFS: 5.7 vs 2.95 months • RR: 5.1% vs 4.7% (non-personalised vs cytoxic) • PFS: 3.3 vs 2.5 months (non-personalised vs cytoxic)
	Targeted therapy using biomarker selection approach vs targeted therapy without biomarker selection approach		• RR: 31.1% vs 5.1%
	Genetic biomarker-based therapy vs protein biomarker-based therapy		• RR: 42% vs 22.4%
Van der Velden 2019 (Drug Rediscovery Protocol)	215 (136 targeted therapy, 79 immunotherapy)	Patients who have exhausted or declined standard therapies, and who have malignancies with potentially actionable variants for which no approved anti-cancer drugs are available	• ORR: 34% (across targeted and IO therapies) • Median duration of clinical benefit: 9 months • MSI tumours: 63% had clinical benefit from nivolumab • Low TMB CRC: limited benefit from IO
Haslem 2018	44 (22 matched, 22 historical controls)	Metastatic	• OS: 51.7 vs 25.8 weeks
Nadauld 2015	72 (36 matched, 36 control)	Advanced	• PFS: 22.9 vs 12 weeks
Tsimberidou 2017 (IMPACT)	637 (390 matched, 247 unmatched)	Advanced	Responder vs non-responder: • FFS: Matched – 7.6 vs 4.3 months; unmatched – 6.6 vs 4.1 months • OS: Matched – 23.4 vs 8.5 months; unmatched – 15.2 vs 7.5 months
Tsimberidou 2019 (IMPACT)	1307 (711 matched, 596 unmatched)	Lethal/ refractory advanced cancer; mostly	• ORR: 16.4% vs 5.4%

Study	Sample size	Tumour types	Reported outcomes
		gastrointestinal, gynaecological, breast, melanoma, and lung	• ORR & stable disease ≥ 6 months: 35.3% vs 20.3% • PFS: 4.0 vs 2.8 months • OS: 9.3 vs 7.3 months • 3-year survival: 15% vs 7% • 10-year survival: 6% vs 1%
Sicklick 2019 (I-PREDICT)	83 (73 matched, 10 unmatched)	Refractory after median 2 lines prior therapy; mostly gastrointestinal, gynaecological, breast, and CNS	• Higher matching score was a predictor of higher disease control, longer PFS, and OS • PFS: 6.5 vs 3.1 months • OS: not reached vs 10.2 months
Wheler 2016	188 (122 matched, 66 unmatched)	Refractory after median 4 lines prior therapy; mostly ovarian (18%), breast (16%), sarcoma (13%), and renal (7%)	• Higher matching scores were independently associated with greater frequency of SD ≥ 6 months/PR/CR: 22% (high scores) vs 9% (low scores)
Rodon 2019 (WINTHER)	303 consented; 107 were evaluable for therapy. 69 in Arm A: DNA sequenced with 236-gene panel; 38 in Arm B: RNA expression. All received therapy guided by sequencing results.	Mostly colon, head and neck, and lung. Median three lines prior therapy.	Patients' previous PFS were used as controls: • Stable disease ≥ 6 months, partial remission, or complete remission: 26.2% (arm A: 23.2%, arm B: 31.6%) • PFS ratio (PFS2/PFS1) of >1.5: 22.4% (arm A: 20.3%; arm B: 26.3%) • PFS ratio (PFS2/PFS1) of >1.3: 25% • Fewer previous therapies, better performance status, and higher matching score correlated with longer PFS
Tsimberidou 2012	291 (175 matched therapy, 116 control)	Colorectal, melanoma, lung, ovarian	• ORR: 27% vs 5% • TTF: 5.2 vs 2.2 months • OS: 13.4 vs 9 months
Aisner 2016	187 (112 matched, 74 control)	Lung adenocarcinoma	• OS: 2.8 vs 1.5 years
Kris 2014	578 (260 matched, 74 control)	Lung	• OS: 3.5 vs 2.4 years
Kostenko 2016	EGFR+ (25 3rd-gen EGFR-TKI, 83 control)	NSCLC	• OS: 55 vs 22 months
	ALK+ (19 next-gen ALK inhibitor after crizotinib failure, 45 crizotinib)		• OS: 35 vs 23 months
	BRAF+ (32 matched)		• OS: 23 months
	HER2+ (11 matched)		• OS: 25 months

Study	Sample size	Tumour types	Reported outcomes
	ROS1+ (13 matched)		• OS: not reached
Singal 2019	1135 with driver alteration (575 targeted, 560 non-targeted)	NSCLC	• OS: 18.6 vs 11.4 months
	1290 treated with anti-PD-1/PD-L1 (161 high TMB, 1116 low TMB)		• OS: 16.8 vs 8.5 months
Stockley 2016	245 (84 matched, 161 control)	Gynaecological, lung, breast	• ORR: 19% vs 9%
Radovich 2016	101 (44 matched therapy, 57 control)	Soft tissue sarcoma, breast, colorectal	• PFS: 86 vs 49 days
LeTourneau 2015 (SHIVA)	195 (99 matched, 96 control)	Gastrointestinal, breast, brain	• No difference in PFS
Schwaederle 2016a	180 (87 matched, 93 control)	Gastrointestinal, breast, brain	• PFS: 4.0 vs 3.0 months • TRR: 34.5% vs 16.1% achieving SD/PR/CR
Pishvaian 2020 (Know Your Tumour)	189 (46 matched, 143 unmatched); 488 no actionable alterations	Pancreatic	• OS: 2.58 (matched) vs 1.51 (unmatched) vs 1.32 (no actionable alteration) years

Abbreviations: ALK, anaplastic lymphoma kinase; BRAF, proto-oncogene B-Raf; CR, complete response; DNA, deoxyribonucleic acid; EGFR, epidermal growth factor receptor; FFS, failure-free survival; HER2, human epidermal growth factor receptor 2; IO, immunotherapy; MSI, microsatellite instability; NRSI, non-randomised study of the effects of interventions; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PFS, progression-free survival; PR, partial response; RNA, ribonucleic acid; ROS1, c-ros oncogene 1; RR, response rate; SD, stable disease; TMB, tumour mutational burden; TTF, time to treatment failure

Note: matching score reflects the proportion of identified molecular alterations targeted by treatment

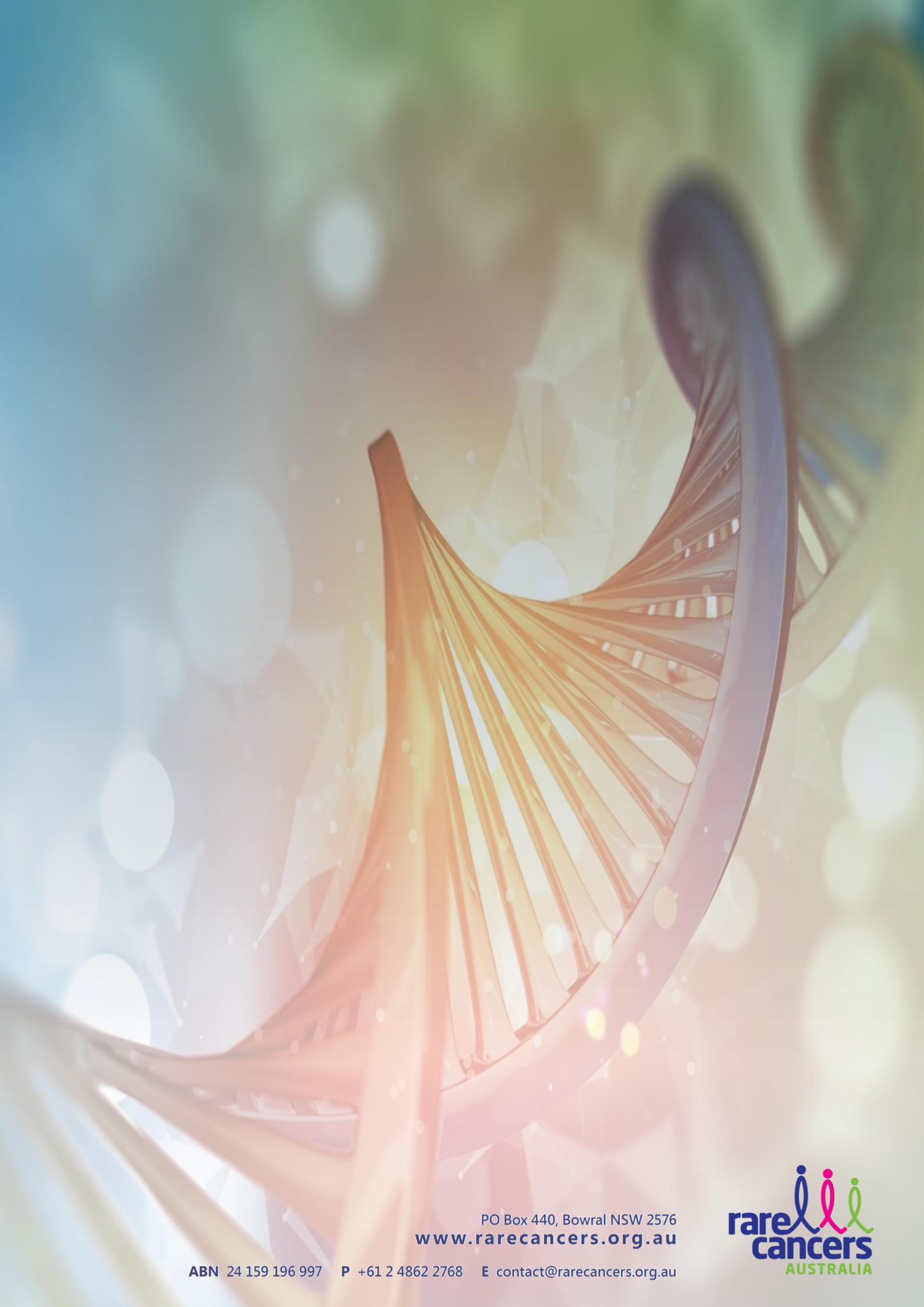


Appendix III: Acknowledgements

We are grateful to all the individuals who participated in this research:

Table 17. Stakeholders interviewed

Name	Organisation
Alan Paul	Ipsen
Professor Andrew Spencer	The Alfred Hospital, Monash University
Professor Andrew Wilson	Menzies School of Health Research
Annree Wogan	Annree Wogan Consulting
Doctor Bicheng Yang, Doctor Oliver Bonaccorso	BGI
Cathy Taylor	Foundation Medicine
Professor David Goldstein	UNSW, Prince of Wales Hospital
Professor David Thomas	Garvan Institute, Kinghorn Cancer Centre, Omico
Dean Whiting	Pathology Technology Australia
Doctor Debra Graves, Professor Sandra O'Toole, Doctor Kym Mina, Linda Mundy	Royal College of Pathologists of Australasia
Delaine Smith	Australasian Leukaemia & Lymphoma Group
Elizabeth de Somer	Medicines Australia
Eric Low	Low Consulting
Greg Cook	Bristol Myers Squibb
Greg O'Toole	AstraZeneca
Professor Hamish Scott	Centre for Cancer Biology, SA Pathology
Professor Ian Frazer AC	University of Queensland, Australian Infectious Diseases Research Centre
Professor John Zalcberg OAM	Monash University, Australian Clinical Trials Alliance
Professor Keith McNeil	Queensland Genomics
Kirsten Pilatti	Breast Cancer Network Australia
Mark Brooke	Lung Foundation Australia
Professor Mark Cowley	Children's Cancer Institute
Michelle Burke	AusBiotech
Nicholette Conway, Andrea Kunca, Rebecca Stratford, David Thomson	Oncology Industry Taskforce Sub-Committee
Peter Orchard	CanTeen
Professor Rory Clifton-Bligh	University of Sydney, Royal North Shore Hospital
Professor Sanchia Aranda	Cancer Council Australia
Tiffany Boughtwood	Australian Genomics



PO Box 440, Bowral NSW 2576
www.rarecancers.org.au

ABN 24 159 196 997 **P** +61 2 4862 2768 **E** contact@rarecancers.org.au

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