RAREFICATION

Personalised medicine in the genomic revolution

rare cancers AUSTRALIA

About Rare Cancers Australia

Rare Cancers Australia (RCA) is a charity whose mission is to improve the lives and health outcomes of Australians living with rare, less common and complex cancers. We believe that no Australian should have to go through their cancer journey alone, which is why we provide 360-degree personalised support to patients and their loved ones, and drive change in access, affordability, and quality of care for the patients of today and tomorrow.

For more information visit
www.rarecancers.org.au

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Foreword

Conservatively, cancer kills at least 10 million people each year. This is despite a global investment of well over US$100 billion every year for cancer research.

So why is cancer such a difficult disease to treat and cure?

The best description of the challenge it presents was one I heard at a conference I attended recently:

> **The number of different types of cancer is exactly equal to the number of cancer patients.**

Essentially, a person's cancer is as unique as their fingerprint. Every cancer, even those considered 'common' such as breast and lung cancer, is as unique as the person diagnosed with the cancer.

Another way of thinking about cancer is to consider our DNA as the 'app' that controls our body. If it is hacked by whatever means (for example smoking, alcohol, asbestos, a virus or other carcinogen), it can malfunction and start the uncontrolled production of abnormal body cells. These cells then mutate and are devilishly clever at evading and bypassing many of our current treatments.

The answer, then, lies in understanding where cancer-causing glitches have occurred in DNA, and using that genomic information to identify and deliver more targeted treatments. We are already seeing success in personalised medicine, but it's not widely accessible or available.

The challenge is enormous and if we are to design research, treatment and care programs that will improve outcomes we need our politicians, public servants, and the Australian community to understand that cancer is different from other diseases and needs specific solutions.

This report is essential reading for every health decision-maker in Australia. My hope is we will seize the opportunity to dramatically improve the lives and health outcomes of all Australians living with cancer.

Richard Vines
CEO and Co-Founder
Rare Cancers Australia

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Executive summary

Since Rare Cancers Australia (RCA) was formed in 2012 more than 1.6 million Australians have been diagnosed with cancer. There are more than one million people in Australia who are either currently living with, or who have previously had, cancer[1] and many more who have sadly lost their lives.

When RCA began, our goal was clear – to improve awareness, support and treatment for all Australians with rare and less common (RLC) cancers. In our efforts to achieve this goal, we have published many reports detailing the key challenges facing people living with RLC and complex cancers and advocating for action to improve equity in outcomes and experience.

This report, *Rarefication: Personalised medicine in the genomic revolution*, aims to explain the scientific advances, particularly in precision oncology. It focuses on the significance of these advances for people diagnosed with cancer and how we can deliver their potential benefits for everyone facing a cancer diagnosis.

Because without really understanding how our cancer knowledge is evolving and what the future looks like, we won't be able to take the steps necessary to deliver a healthcare system fit to achieve the best outcomes and experience for everyone, equitably.

Based on current definitions, 27% of cancers diagnosed in Australia are defined as RLC (i.e. those with incidence rates below 12 cases per 100,000 people) but they account for 37% of all cancer deaths.[2] However, over the past two decades, our ability to rapidly obtain genomic information on an individual and their cancer has led to a dramatic shift in how health professionals can assess, treat, monitor, and prevent cancer. So, the question arises – are we classifying cancers in the right way given what we now know about cancer genomics and how such technologies have increased our understanding of the biology of cancer?

Our evolving understanding of genomics has been assisted by the development of sequencing technology, which, coupled with the capability to analyse vast amounts of data, now enables comprehensive genomic profiling to be performed in the real-world clinical setting. As a result, we have discovered that many cancers that were otherwise considered common are now being increasingly characterised by the discovery of RLC genetic subtypes. People with lung cancer, for example, previously understood to be a common cancer, used to be diagnosed as one of two possibilities – small cell or non-small cell lung cancer. Now, we understand there are more than 30 distinct subtypes of lung cancer – many of which are rare.

Knowledge of the molecular mechanisms that drive cancer development and progression has also facilitated the creation of range of new therapies that either target specific cancer cells or manipulate our own immune system to attack the cancer cells.

Unlike traditional chemotherapy drugs, these therapies can specifically target cancer cells while avoiding damaging normal cells. Due to their targeted nature, these therapies often produce better responses and are less toxic. Collectively, this has enabled a shift from the traditional one-size-fits-all approach based on the location of cancer to a new era of precision medicine, where treatment is based on the genomic make-up of each person's cancer.

Our ability to obtain greater insights into an individual's genomic, environmental, and lifestyle data brings us closer to our vision of precision medicine and improved cancer care. It is, however, crucial that the healthcare system can deliver the best technologies and treatments to people at the earliest opportunity.

It is time for Australia to realise the full potential of precision oncology and deliver equitable outcomes across all cancer types. To do so we need to acknowledge that our current health system relies upon outdated models of cancer care delivery and make the necessary changes to revolutionise our healthcare system, so that it is fit for purpose and ready to deliver into the future.

To achieve our goal of timely and equitable access to precision oncology for all Australians diagnosed with cancer, RCA recommends government and key stakeholders act to:

1. **Progress a coordinated national genomics strategy**, leveraging existing Government commitments to Cancer Australia and Genomics Australia to:
   - ✔ ensure all people diagnosed with cancer have access to comprehensive and cost-effective genomic profiling as standard of care,
   - ✔ ensure people have access to matched targeted therapies, immunotherapies, cell and gene therapies, personalised cancer vaccines, and combination therapies, where there is identified clinical benefit, and
   - ✔ ensure that RLC cancers are defined as a priority population to deliver equitable care, experience and outcomes.
2. Ensure that the substantial Government research investment through the National Health and Medical Research Council and the Medical Research Future Fund adequately **prioritise research into genomic studies and precision oncology**, to ensure people with cancer – particularly RLC - can access precision oncology trials and translational genomic knowledge is furthered in Australia.
3. **Develop a new pathway in our Health Technology Assessments** that:
   - ✔ assesses precision oncology companion diagnostics and therapies together,
   - ✔ recognises limited clinical data that arise from small patient populations and encompasses broader value measures,
   - ✔ accommodates multiple indication, genomic focussed applications to be assessed to expedite access for RLC patients.
4. **Direct AIHW to include data on molecular subtypes** and support the establishment of appropriate registries to adequately facilitate data collection.

For the past decade, RCA has been advocating for changes to our healthcare system that would provide the best possible person-centred care for all people diagnosed with cancer; care that truly meets their idiosyncratic needs. Thanks to the potential of personalised medicine, we now have the tools to make this a reality; it just remains up to us all to work collaboratively and deliver it.

1 Introduction

Rare Cancers Australia (RCA) was formed in 2012 with a view to improve awareness, support and treatment of Australians with rare and less common (RLC) cancers. In almost every year since, we have published reports detailing critical challenges facing people living with RLC and complex cancers, calling for action to improve their outcomes and experiences.[3] Invariably the introduction to each of these reports has included a reference to the recent significant scientific advances in our understanding of cancer, without too much time being spent on exploring what those advances are, and why they are significant. This report aims to address that, because without really understanding how cancer knowledge is evolving, where we are now, and what the future looks like, we can't hope to understand the extent of change required in the health system.

The Australian Institute of Health and Welfare (AIHW) estimates there will be 165,000 people diagnosed with cancer, and 51,000 people who died from cancer, in 2023.[2] Overall five-year cancer survival has improved significantly in the past 30 years, from 53% to 71%, thanks in part to increasing access to screening and early diagnosis.[2] As a result, there are more than one million people alive in Australia who are either currently living with, or who have previously had, cancer.[1]

Based on current definitions, 27% of cancers diagnosed in Australia are defined as RLC (i.e. those with incidence rates below 12 cases per 100,000 people) but they account for 37% of all cancer deaths.[2] However, are we classifying cancers in the right way given what we now know about cancer genomics and how such technologies have increased our understanding of the biology of cancer?

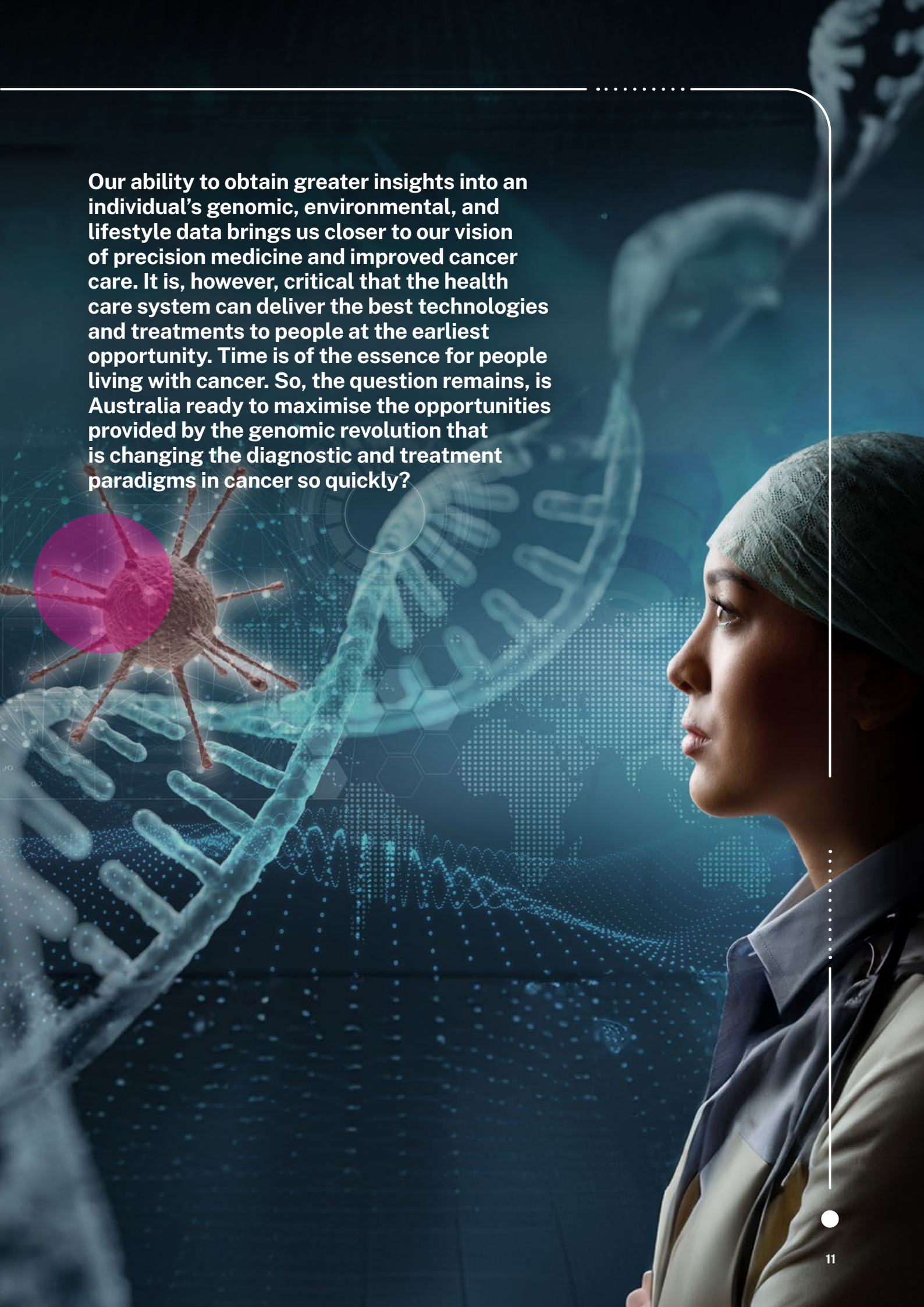
In recent decades, our ability to rapidly obtain genomic information on an individual and their cancer has led to a dramatic shift in how health professionals can assess, treat, monitor, and prevent cancer. As a result, RLC subtypes of what are otherwise considered common cancers are being increasingly recognised through the discovery of genetic variations that characterise each of these subtypes differently. People with lung cancer, for example, previously understood to be a common cancer, used to be diagnosed as one of two possibilities – small cell or non-small cell lung cancer. Now, we understand there are more than 30 distinct subtypes of lung cancer – many of which are rare.

For a long time, chemotherapy, which is a method of killing or inhibiting the growth of tumour cells by chemical drugs, was the preferred approach to cancer drug therapy. It remains a mainstay of treatment for many cancer types. Although improvements in survival have been achieved with chemotherapy, its inability to distinguish cancer cells from normal cells means many patients suffer significant toxicity and debilitating side effects.

However, over the past two decades, cancer medicine has been evolving from the traditional one-size-fits-all approach, where the choice of treatment was primarily based on the location of a person's cancer, to a new era of precision medicine. As a result, there has been a tremendous shift in cancer treatment from broad-spectrum cytotoxic drugs to targeted therapy and immunotherapy. Compared with traditional chemotherapy drugs, targeted therapies can specifically target cancer cells but spare normal cells, hence providing high potency and lower toxicity. Immunotherapy is often better tolerated than chemotherapy and associated with long-lasting responses.

Our evolving understanding of genomics has enabled the development of targeted treatments that have proven effective for people with cancers with specific genomic alterations. Furthermore, cancer cells' ability to continually evolve – known as plasticity – necessitates monitoring to detect the changes in real time and initiate appropriate therapies in a timely fashion.

Knowledge obtained through research in recent years has rapidly been translated into the clinical setting, helping to improve patient outcomes – with a 20% increase in five-year survival observed for all cancers combined over the past 30 years in Australia.[3] Technological advances and the collaborative efforts of researchers and health professionals have enabled these rapid increases in our knowledge of cancer. However, to see further improvements in survival and attain five-year survival above 90% for all cancer types, our healthcare system needs to adapt to translate evidence-based knowledge quickly and seamlessly to people in the real-world clinical setting. This is particularly important for histologically rare cancers, which have always tended to have worse outcomes.



Our ability to obtain greater insights into an individual's genomic, environmental, and lifestyle data brings us closer to our vision of precision medicine and improved cancer care. It is, however, critical that the health care system can deliver the best technologies and treatments to people at the earliest opportunity. Time is of the essence for people living with cancer. So, the question remains, is Australia ready to maximise the opportunities provided by the genomic revolution that is changing the diagnostic and treatment paradigms in cancer so quickly?

2 A cancer biology and genomic perspective on the evolution of cancer and new therapies

It is true to say that our knowledge of cancer has increased significantly over the last 50 years – new discoveries have improved our understanding of the driving forces behind each cancer and have led to improved outcomes for many people living with cancer. For example, technological advances have enabled the analysis of the entire genome, with the aim of identifying certain genetic variations associated with particular tumour types.[4] Our evolving understanding of genomics has led to the development of molecularly targeted therapies that attack or inhibit the specific genetic variations of specific tumour subtypes, heralding a new era of personalised medicines.[5, 6]

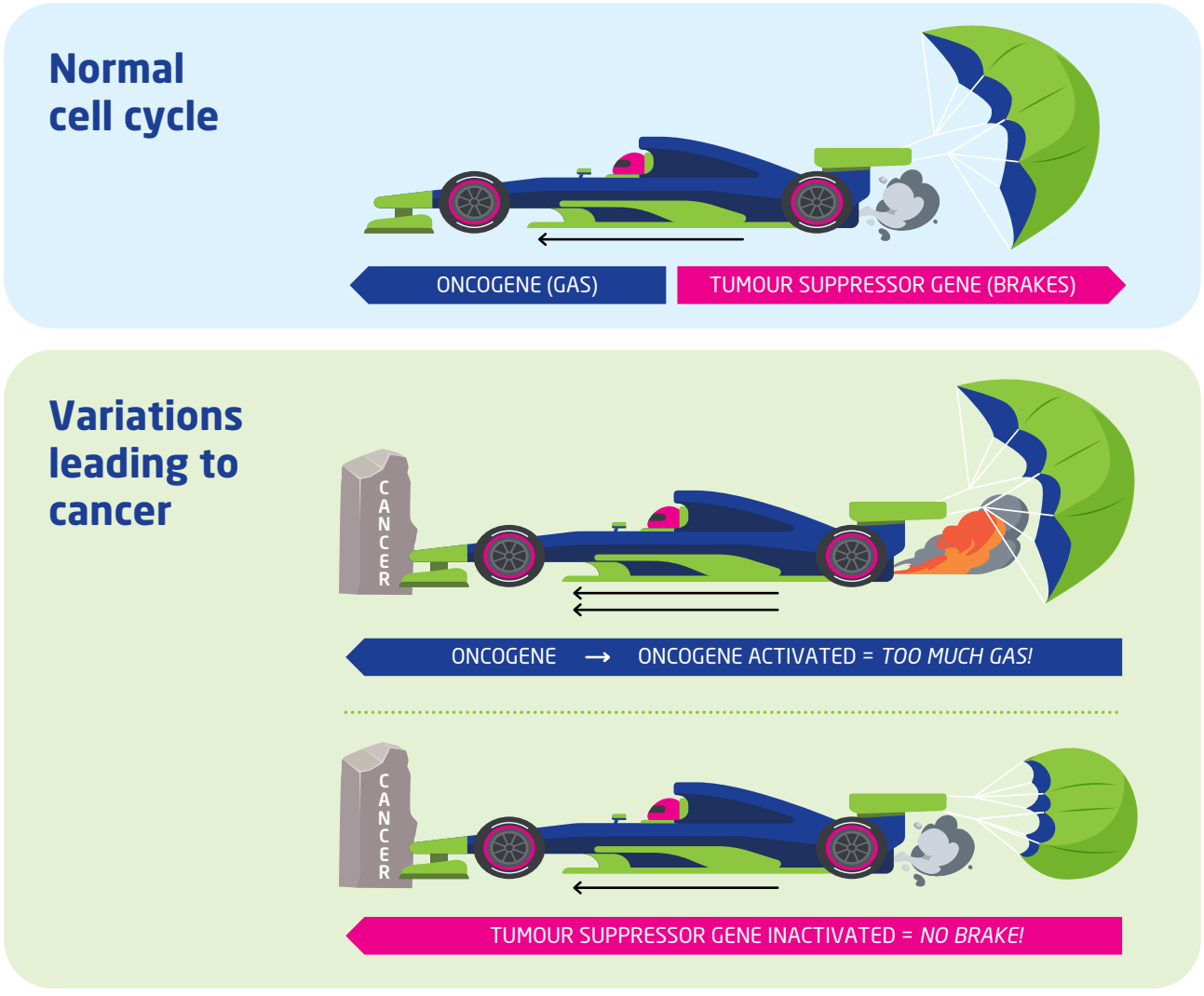
So, how did we get here? What were the discoveries that led to the advances that have been achieved? Why are they significant for people with cancer? And what will come next? Here we provide an overview of the major milestones in our genomic understanding of cancer over the past 50 years and how this knowledge continues to drive advances in precision medicine.

2.1 1970 – 1990

Paving the way for targeted therapies – oncogenes and tumour suppressor genes

The identification of oncogenes (genes that promote cancer growth) and tumour suppressor genes (genes that regulate/inhibit uncontrolled cell growth and prevent cancer), provided insights into the genetic basis of cancer and paved the way for targeted therapies (see figure 1).

Figure 1: The role of oncogenes and tumour suppressor genes in cancer development.



Adapted from: Jack Westin, MCAT Content. Cancer as a failure of normal cellular controls, oncogenes, tumour suppressor genes.[7]

2.2 1990 – 2000

Development of targeted therapies

Oncogenes are genes that, when switched on (activated), can potentially drive cancer development by promoting uncontrolled cell growth. In normal cells, these genes are temporarily switched on to send signals when required (e.g. after traumatic injury) and are then switched off (to an inactive state) when healing has occurred. However, in cancer, abnormalities within, or near, specific genes can result in persistent aberrant gene activation, leading to tumour development.

The first reported human oncogene, RAS, was associated with cancer in 1982. A single variation within the gene was shown to activate the RAS protein in a human bladder cancer cell line.[8-10] Many studies have subsequently confirmed the tumour-initiating properties of mutant RAS,[11] as well as the discovery of many other cancer-associated oncogenes, including (but not limited to) BRAF, BCR-ABL1, EGFR, ERBB2, MYC and RET. In each case, abnormalities within or near the gene result in the sustained activation of the associated protein and tumour development.

Tumour suppressor genes are crucial in regulating cell growth and preventing cancer development. When abnormalities occur within tumour suppressor genes, their normal function of preventing cancer is lost. This inactivation can lead to uncontrolled cell growth and the development of cancer.

In 1986 the first human tumour suppressor gene, the retinoblastoma gene (RB1), was identified. Inactivating variants within RB1 were associated with retinoblastoma, a malignant tumour in children's eyes.[12] Genetic mapping studies led to the discovery of many other cancer-associated tumour suppressor genes, including (but not limited to) APC, BRCA1, BRCA2, TP53, PTEN, WT1, NF1, and VHL.

Understanding how genetic abnormalities activate (switch on) or inactivate (switch off) our genes provides clues for the development of therapies that can restore normal gene function and help slow the growth of cancer.

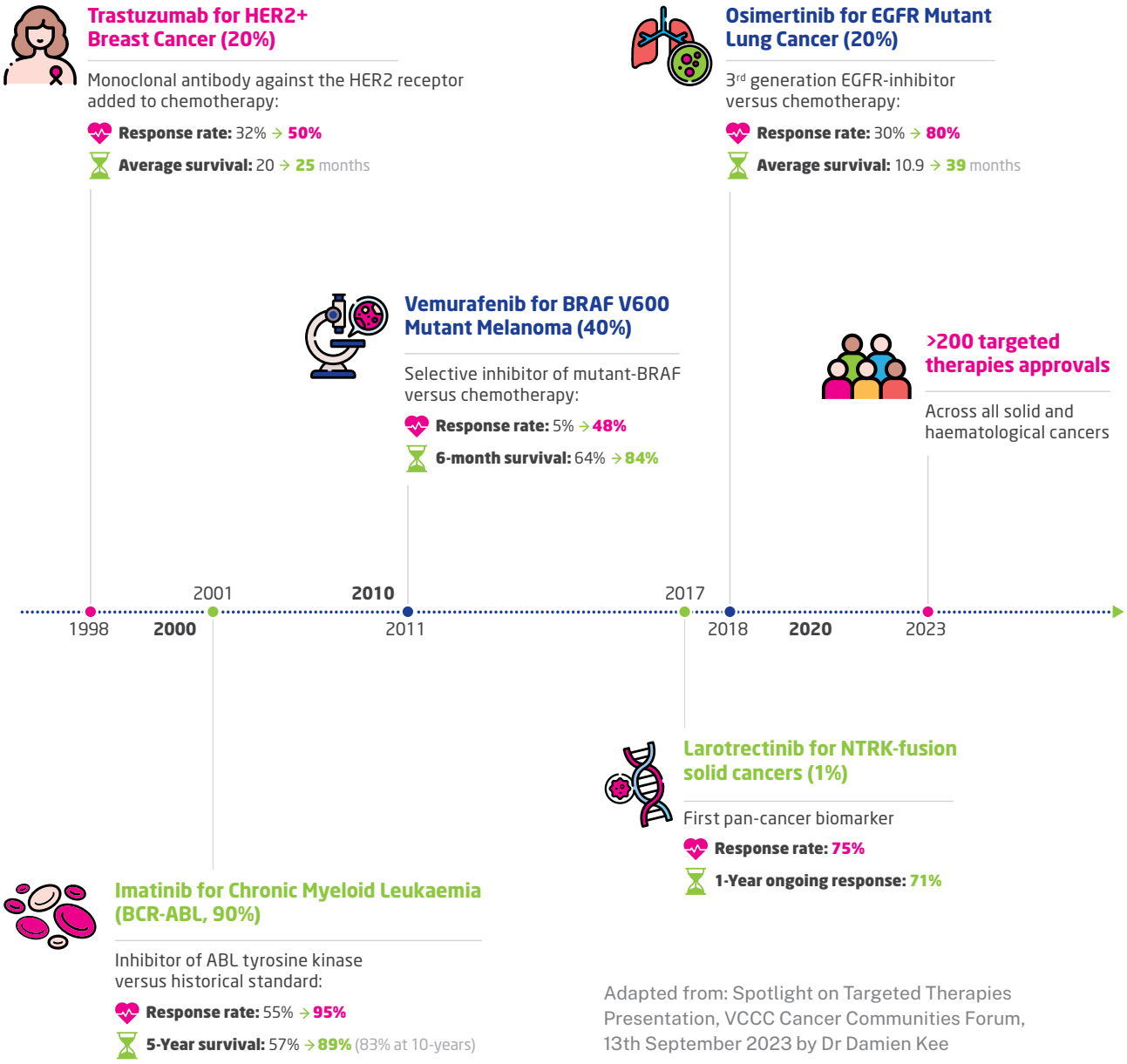
The ability to detect activated and deactivated genes in cancer due to genetic abnormalities enabled the development of therapies targeted explicitly towards defective genes, aiming to block the activity of oncogenes or restore the function of tumour suppressor genes, thereby inhibiting tumour growth and progression. Due to their targeted nature, these therapies often produce better responses and are less toxic.

The early development of targeted therapies was primarily focused on inhibiting activated oncogenes. Imatinib was the first selective targeted therapy to be approved for use in humans (see figure 2). Imatinib targets a specific genetic abnormality created by a chromosomal rearrangement that results in the joining of the BCR and ABL genes – known as the BCR-ABL fusion protein. This fusion, present in nearly all cases of chronic myeloid leukaemia (CML), leads to the activation of ABL's tyrosine kinase activity, thereby triggering unregulated cell growth. Researchers hypothesised that a specific ABL tyrosine kinase inhibitor may block the activity and be a valuable therapy for CML and other leukaemia with a BCR-ABL fusion. In CML disease models, various tyrosine kinase-inhibiting drugs were assessed for their ability to slow or halt cell growth. These studies identified imatinib as a drug that may be useful in treating leukaemia with a BCR-ABL fusion.[13] Further development and assessment in clinical trials led to the approval of imatinib, the first selective BCR-ABL tyrosine kinase inhibitor (TKI) in 2001 – this single well-tolerated drug dramatically improved outcomes for people with BCR-ABL leukaemia.

The development and approval of imatinib marked a milestone in cancer treatment, demonstrating the potential for such therapies to target cancer cells while sparing healthy cells. It paved the way for developing numerous other targeted therapies that have revolutionised cancer treatment. For example, gefitinib and erlotinib target specific variations within the epidermal growth factor receptor (EGFR) that are associated with lung cancer

(see case study 1); trastuzumab, a monoclonal antibody, targets activated human epidermal growth factor receptor 2 (HER2) in breast cancer and gastric cancer; and rituximab, a monoclonal antibody targeting an activated protein expressed on the surface of B cells (CD20) in non-Hodgkin lymphoma and chronic lymphocytic lymphoma. These are just a few examples of many targeted therapies currently approved for use with various types of cancer.

Figure 2: Advances in targeted therapies, important landmarks in targeted therapy drug approvals.



Adapted from: Spotlight on Targeted Therapies Presentation, VCCC Cancer Communities Forum, 13th September 2023 by Dr Damien Kee

The evolution of targeted therapies that specifically block the activity of oncogenes or restore the function of tumour suppressor genes has led to significant clinical benefits – improving patient outcomes and leading to more personalised and effective approaches to cancer treatment. These selective targeted therapies allow the appropriate choice of treatment, in many instances, based on the specific genetic alterations present in a patient's tumour.

2.3 2000 – 2010

Insights into whole cancer genomes

Our ability to accurately map all the genomic information within a person has significantly contributed to our knowledge of the genomic drivers of cancer. This map is like a big manual, containing genes and other information, that is necessary to instruct our bodies how to work. The mapping of the human genome is possible through the use of a powerful tool, known as DNA sequencing, that enables us to read and understand the information stored in our DNA.

A draft of the entire human genome was first published in 2001[14] – the culmination of 10 years of a dedicated, global collaborative effort at an estimated cost of USD 3 billion. Several years later, significant advances in sequencing technology, coined next-generation sequencing (NGS) or massively parallel sequencing, enabled the rapid sequencing of whole human genomes. These advances marked the beginning of huge international efforts to characterise the genomes of all cancer types comprehensively.

The first complete map of a human cancer, glioblastoma – the most common primary brain tumour in adults – was published in 2008. This study provided new insights into the genomic basis of glioblastoma – identifying abnormalities previously unknown and providing an overview of altered biochemical pathways – while demonstrating how comprehensive genomic profiling could rapidly expand our knowledge of the molecular basis of cancer.[15] This was the first of many studies led by The Cancer Genome Atlas (TCGA). This cancer genomics program brought together researchers from diverse disciplines and multiple institutions to molecularly characterise the genomes of more than 33 cancer types.[16] These studies highlighted the power of whole genome sequencing as a tool with which to identify previously unknown genetic abnormalities that were responsible for the development of cancer. This information has greatly improved our ability to diagnose, treat and prevent cancer.

Our ability to map the whole genome has greatly assisted the continued evolution of targeted therapies. An early success of tumour wholegenome sequencing was the discovery of a specific abnormality within the BRAF gene, referred to as V600E, that was present in many cancer types. One study showed that this specific variation occurred frequently in melanoma, the most aggressive type of skin cancer. This variation activates a specific pathway for sending signals in our body and is therefore a target for therapy.[17] Drug discovery efforts culminated in the approval of the first BRAF-selective inhibitor, vemurafenib, in 2011 for treating patients with unresectable or metastatic melanoma with BRAF V600E variations. Additional compounds targeting and inhibiting the BRAF V600E mutant in melanoma, non-small cell lung cancer, thyroid cancer, solid tumours, and low-grade glioma have subsequently been developed and approved.

Many other targeted therapies were approved for use in various cancer types between 2000 and 2010, all of which target the altered cellular functions captured by the cancer hallmarks. These include gefitinib, an EGFR tyrosine kinase inhibitor (2001, for lung cancer); bevacizumab, the first drug to target VEGF and block the growth of blood vessels that contribute to tumour growth (2004, for metastatic colorectal cancer); and lapatinib, a HER2/EGFR inhibitor (2007, for breast cancer). Continued development of additional agents targeting these altered pathways has led to further approvals of more refined therapies and their use in other tumour types.

CASE STUDY 1

Learning the lessons from lung cancer

Lung cancer is the fifth most commonly diagnosed cancer in Australia.[2] Unfortunately, for most people diagnosed with lung cancer, symptoms usually occur at a late stage and by the time a diagnosis is made it is often incurable; as a result, lung cancer continues to be our leading cause of all cancer deaths.[3] Collectively, lung cancer is considered a common cancer, however, advances in genomic profiling have led to the discovery of many gene variations and targeted therapies that have heralded a new era in the management of lung cancer.[18]

For example, since the discovery in 2007 of the rearranged anaplastic lymphoma kinase (ALK) gene, there has been a significant advance in treatment options and hence improved survival of people with ALK-positive lung cancers.[19-21] The ALK gene rearrangements are a rare and unique molecular subset of non-small cell lung cancer (NSCLC), present in approximately 5% of cases overall.[19] The ALK incidence rises to greater than 30% of cases in patients under the age of 40, particularly affecting a younger and light-/never-smoking population.[19]

Over the last 15 years, we have seen the treatment and survival of ALK-positive lung cancers revolutionised by the differential treatment of this important sub-population with high-impact targeted therapies. Many ALK inhibitors have delivered unprecedented survival in advanced disease, with the median life expectancy now more than 7 years.[19, 21]

Unfortunately, despite great gains with patient survival now measured in years and improved quality of life with targeted therapies, drug resistance is inevitably encountered in this rare and unique molecular subset of lung cancer, and patients will eventually succumb to the disease.[19, 20] Drug resistance profiling and further strategies are being explored through clinical trials, including the evaluation of sequential drug application and combinations to overcome such resistance and improve survival.[20]

With increasing real-world data, we are now seeing improvements in quality and length of life for people with this disease that exceed all previous expectations in advanced lung cancer.[20]

As we look ahead to how we might improve outcomes for people with ALK-positive lung cancers in the future, we will need to deliver a personalised and dynamic approach to care.[19] Such a proactive approach would be informed by precision imaging, and by regular plasma sampling intended to deliver personalised therapeutic switches prior to relapse. This will require a complete paradigm shift in the way we approach the treatment of advanced cancer, including formal investigation and clinical trial design; however, evidence to-date in ALK-positive lung cancers supports this new frontier of investigation.[19]

It is important we recognise the significance of the shift that has occurred in ALK-positive lung cancers as the lessons may lead the way for further oncogene subgroups and molecular therapies and provide a framework for improving outcomes universally.

> “All people should have the opportunity to receive gold standard evidence-based diagnostics and a dynamic personalised therapeutic approach for improved quality and quantity of life.
>
> **Dr Malinda Itchins**
>
> Medical Oncologist, Royal North Shore Hospital and North Shore Private

2.4 2010 – 2023

Immunotherapy and molecular-based treatment decisions

2.4.1 Immunotherapy

Over the past decade, advances in immunotherapy have significantly impacted the cancer treatment landscape, improving outcomes and survival for many people with cancer. These therapies are often better tolerated than chemotherapy and are associated with durable responses.

Our immune system is a complex network of cells, tissues, and organs that work together to defend the body against infections, foreign substances, and abnormal cells. Cancer cells, as they arise from our own tissue, can sometimes avoid being detected by our immune system, enabling cancer to grow unchecked. Immunotherapy enhances the body's immune system, allowing it to recognise and eliminate cancer cells more effectively in some tumour types. In addition to the more manageable side effects compared to traditional treatments, a key feature of immunotherapy is its ability to elicit long-term responses to treatment.

There are different types of immunotherapies, including:

- Checkpoint inhibitors, which block specific proteins that are expressed on the surface of immune cells (i.e., PD-1, CTLA-4, LAG-3, TIM-3, PD-L1) or cancer cells (i.e., PD-L1). These cell surface 'checkpoints' (i.e., CTLA-4, PD-1, LAG-3, TIM-3) can prevent immune cells from recognising and attacking cancer cells. The immune system modulators now available can help the immune system recognise and target cancer cells by blocking these checkpoints more effectively.
- Chimeric Antigen Receptor (CAR) T-cell therapy – known as CAR-T cell therapy – involves modifying a patient's T-cells (an essential part of the immune system) to express special receptors that recognise and bind to specific cancer cells. These modified T-cells are then infused back into the patient, where they can target and destroy cancer cells.
- Cancer vaccines – stimulate the immune system to recognise and attack cancer cells by presenting specific cancer-related antigens.

Ipilimumab, a checkpoint inhibitor, was the first targeted immunotherapy approved in patients with advanced melanoma (see case study 2). The monoclonal antibody targets the cytotoxic T-lymphocyte antigen-4 (CTLA-4) and improves survival for patients with advanced melanoma by stimulating the immune system to attack cancer cells.[22] The increased anti-tumour immune response seen following the use of ipilimumab is achieved by removing the 'brake' that usually controls the intensity of immune responses. There are currently eight checkpoint inhibitors approved for the treatment of 18 different types of cancer,[23] although not all are available in Australia yet. Additionally, from a cell and gene therapy perspective, as of 2020, there were 641 cell and 536 gene developers worldwide working on cell and gene therapies, with many in the clinical stage of development.[24]

As with most therapies, immunotherapy has limitations (i.e., only a proportion of patients benefit, autoimmune-like toxicities are common, and fewer immune cells within some cancers limits the ability to enhance the immune response). Continued research is focused on addressing these shortcomings.

2.4.2 Molecular-based treatment decisions

During the past decade, further development of sequencing technology, coupled with the rapidly evolving capability to analyse vast amounts of data, has assisted in enabling the mapping of human genomes for people in the clinical setting: genomics is no longer restricted to research environments. Our knowledge of the molecular landscape of cancer continued to evolve with the genomes of more than 30 cancer types mapped between 2011 and 2018.[16] This provided great insights into the mechanisms that underlie the development of specific cancers and uncovered commonalities that span cancer types.

This insight into shared genomic alterations across different cancer types led to an international collaborative effort – the Pan-Cancer Analysis of Whole Genomes Consortium (PCAWGC) – in which more than 2,600 whole cancer genomes from 38 different tumour types were collectively analysed. This study identified common variant patterns spanning the different tumour types and showed that, on average, cancer genomes contain four to five driver[a] variants.[25] Through this study, it became clear that many different types of genomic abnormalities can occur across individuals within the same tumour type. The study highlights the **unique nature of each tumour and, therefore, the importance of treating each tumour based on its unique genomic drivers, not simply based on the anatomic origin of the tumour** (i.e. breast cancer, colon cancer etc.). These insights spurned the next phase of precision medicine, with therapies for individuals selected based on the molecular profile of their tumour.

This new knowledge of genomic alterations spanning different cancer types demonstrated the need to change how oncology clinical trials were designed and conducted. NCI-MATCH (Molecular Analysis for Therapy Choice; NCT02465060), launched in 2015, was one of the first clinical trials to determine whether treating cancer based on the specific genetic changes in a person's tumour was effective, irrespective of the cancer type.

In the trial, people with cancer had genomic sequencing as well as other tests to determine the genetic makeup of their cancer cells. People then received treatment that matched the genetic changes observed within their cancer. Nearly 6,000 patients underwent molecular testing, with more than 1,500 assigned to a therapy matched to a genomic alteration in their tumour. The study showed many people with advanced cancer benefited from the use of genomic sequencing to help identify a suitable treatment.[26]

Australian researchers continue to play a pivotal role in shaping precision medicine. In 2016, the Molecular Screening and Therapeutics (MoST) study used the power of genomic technology to identify changes in a patient's cancer that could help guide the choice of suitable targeted therapy. The success of MoST lead to the establishment, in 2023, of the Precision Oncology Screening Platform Enabling Clinical Trials (PrOSPeCT) program, which links major cancer centres throughout Australia and plans to sequence the genomes of more than 23,000 people living with cancer.[27] The program identifies genetic variations in each person's tumour and matches them with appropriate targeted therapies. A unique feature of the program is the identification of therapies available through clinical trials and therapies in common use. The program aims to help thousands of Australians with cancer who otherwise might not have access to genomic screening.

a Driver variations are specific genetic alterations that play a central role in the development and the progression of cancer.

CASE STUDY 2

Molecular advances in melanoma

Melanoma is often referred to as Australia's national cancer due to Australia having the highest incidence rates in the world and, with more than 16,800 people expected to be diagnosed this year,[28] it's not historically been considered a 'rare cancer'. Fortunately, many of these tumours are detected before they spread to other organs. Prior to the genomic and immunologic era, the prognosis of people with advanced melanoma was measured in months. However, in the last decade, we have seen huge advances in survival for people diagnosed with advanced melanoma, from less than 10% five-year overall survival in 2011 to more than 50% in 2021.[28] So how has this been made possible?

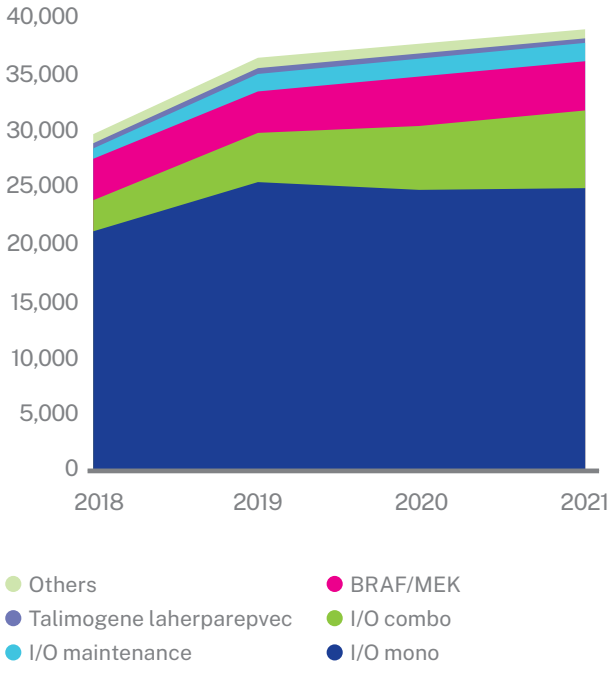
Cutaneous melanoma is an aggressive tumour responsible for 90% of mortality related to skin cancer.[29] In recent years, the use of high-throughput genomic technologies has facilitated the genomic profiling of melanoma and the discovery of the driving variations has led to improved treatment approaches.[29] As a result, new therapeutic strategies like kinase inhibitors for BRAF-mutant melanoma and immune checkpoint blockers have proven successful in improving survival.[30]

The importance of combination therapies in treating melanoma

Approximately 40% of metastatic cutaneous melanomas have a BRAF V600 variation which can be targeted by BRAF inhibitors,[30] however emergence of resistant cells is common, frequently associated with activation of a signalling molecule MEK. MEK can be successfully targeted with MEK inhibitors leading to combinations of the BRAF and MEK inhibitors that have been successful in improving progression-free and overall survival, their use together (in combination) has led to greater improvements in survival.[30]

Other treatments for melanoma have been increasing over the last five years, and according to the IQVIA Global Oncology Trends 2022 report, there has been a 30% growth in the number of combination treatment regimens between 2018 – 2021 (see figure 3).[31] The report notes that immuno-oncology checkpoint inhibitors play an important role in the treatment of melanoma, with monotherapy immuno-oncology checkpoint inhibitors being the most common treatment regimen used for melanoma, accounting for 64% of treatments in 2021.[31] The report further notes that immuno-oncology checkpoint inhibitors are increasingly used in combination with other drugs, with checkpoint inhibitor combination treatment regimens more than doubling since 2018 and now representing 18% of treatments (up from 10%).[31]

Figure 3: Number of patient treatment regimens in the U.S., 2018–2021.[31]

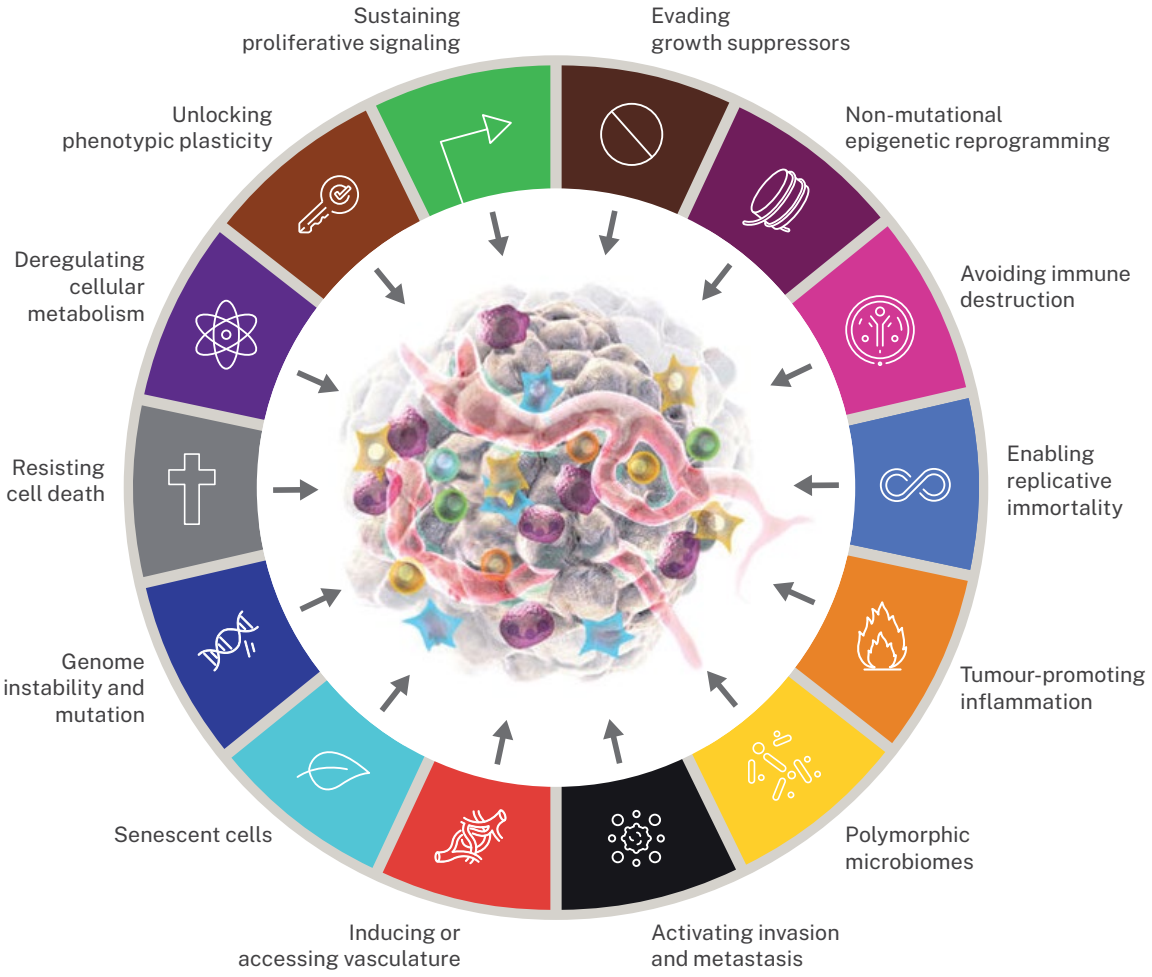


> The use of combination immune checkpoint inhibitors or combination targeted therapies has led to striking reductions in the mortality from melanoma.
>
> **Professor Grant McArthur**
> Executive Director of the Victorian Comprehensive Cancer Centre

2.5 The current state: a framework for the development of precision medicine

Our current knowledge of the complex and adaptive nature of cancer has been distilled into a framework that captures the shared mechanisms used by all cancers to grow and develop (see figure 4). The *Hallmarks of Cancer* were originally proposed by Douglas Hanahan and Robert Weinberg in 2000 and continue to evolve as research uncovers new insights.[32-34] For many cancers, one of these mechanisms will drive the formation of the initial tumour. However, to grow and survive, the cancer will then employ additional mechanisms.

Figure 4: Hallmarks of cancer – new dimensions



Adapted from: The hallmarks of cancer: new dimensions, by Hanahan, 2022.33

One of the more recently proposed hallmarks – plasticity – encompasses cancer's ability to adapt and change characteristics, behaviour, and function in order to survive. This capability allows cancer to evade the body's normal defence mechanisms, spread to other parts of the body, and become resistant to treatments. Understanding the ways in which cancer cells use plasticity to survive provides clues for the development of more effective and targeted therapies.

A well-known example of plasticity arises when cancer cells lose their ability to remain stationary and connected to neighbouring cells, and develop characteristics that enable the cancer cells to move away from the original tumour and spread (metastasise) to other parts of the body. This process, known as epithelial-to-mesenchymal transition (EMT), is involved in the spread of various tumour types, including ovarian cancer.[35] As more than 90% of cancer-related deaths are a result of metastatic disease,[36] understanding the mechanisms – like plasticity – that promote and sustain the spread of cancer is a necessary step in combating cancer metastasis and post-therapeutic recurrence.

Epigenetic reprogramming is another of the recently proposed mechanisms that enables the development of cancer. Normally, epigenetics plays a role in regulating gene expression and does this by switching genes on (activating) or off (silencing) to ensure the different cell types in our body function properly. If this process is disrupted, it can lead to uncontrolled cell growth and the development of cancer. Environmental factors (such as diet and nutrition, or exposure to chemicals and toxins) and genetic variations can affect normal epigenetic programming and have been linked to many cancer types. For example, research has shown that alcohol consumption may cause epigenetic changes that contribute to the development of some types of cancer, such as oesophageal carcinoma, head and neck squamous cell carcinoma, liver hepatocellular carcinoma, and pancreatic adenocarcinoma.[37]

Knowledge of epigenetic reprogramming in cancer is currently being used to help guide treatment decisions. One such example is glioblastoma, a common and highly aggressive form of brain cancer, where improved response and survival to temozolomide is associated with epigenetic silencing of the MGMT gene.[38] Understanding epigenetic reprogramming in cancer will enable the appropriate use of existing therapies, as well as guide the development of new therapies.

Knowledge and insights into each of the hallmarks (figure 4) have revolutionised the field of cancer biology. This window into the processes that drive the development of cancer guide ongoing research into more effective therapies.

2.6 What's the future of precision medicine?

Our ability to gather molecular insights into an individual's cancer moves us closer to our goal of precision medicine, where the optimal treatment for a specific cancer subtype is provided at the right time.

However, as with all rapid advances, challenges must be overcome before this vision is fully realised.

Research continues to build on existing knowledge and address the challenges that people with cancer face in the reality of the clinical setting. For example, not all people will see benefits from the therapies they receive. This is known as treatment resistance and is a significant barrier to people having a long-term response to treatment. Some patients may not be responsive to therapy from the outset (primary resistance), while others may respond to treatment initially and then, over time, become resistant to treatment (acquired resistance). The ability of cancer cells to adapt and evade therapy is a significant barrier to achieving sustainable remission.

The continually evolving nature of cancer and the way in which it employs different mechanisms to grow and survive highlights the need for effective combination therapies. By combining multiple therapies that target the different mechanisms cancer uses to thrive, treatment outcomes can be improved and the development of resistance to therapy reduced. The use of combination therapies is not new, with many examples of combination chemotherapy. However, the availability of various targeted therapies has shifted the focus towards chemotherapy-free combinations.

An example of this is the combination of lenalidomide plus rituximab, which was the first combination chemotherapy-free treatment approved for patients with follicular lymphoma.[39] In this combination, lenalidomide enhances the activity of immune cells to target and destroy cancer cells, while rituximab binds to the CD20 protein on the surface of B cells, marking them for destruction by the immune system. The approval was based on the results of a clinical trial in which the combination of lenalidomide and rituximab in patients with recurrent follicular lymphoma was shown to halve the risk of disease progression when compared to the single-agent standard of care (rituximab alone).[39]

Another example of continued research focus is the ability to monitor response to treatment and disease progression. Liquid biopsy is an innovative approach of looking for circulating DNA in the bloodstream in order to help understand cancer in real-time, avoiding the need for repeated biopsies. Not only can it be used to monitor the progression of disease, but it can also be used to diagnose cancer. The ability to track disease in real-time – based on a simple blood test – is gaining traction, particularly in cancer.[40]

Australian researchers are at the forefront of this innovative approach, and through the support of Australian Cancer Research Foundation (ACRF), the Children's Cancer Institute (Sydney) has established the Child Cancer Liquid Biopsy Program.[41] This program uses a simple blood test and, applying cutting-edge science and technology, can provide a window into the tumour. The method can be used throughout a child's cancer journey, providing crucial real-time information on treatment response and tumour progression. The liquid biopsy also provides genetic information on the tumour, which can help predict relapse and guide subsequent treatment. The program is a good example of how leading-edge technology can improve how cancer diagnoses and treatments are managed.

The increasing relevance of genomics for the management of people with cancer highlights several considerable challenges. Generating vast amounts of data requires technology and systems that can rapidly, effectively, and accurately collate and interpret data. The outcomes of this analysis also need to be easily accessed and understood by the doctors who communicate results with patients. Further, empowering patients to work with their doctors to tailor treatment plans that align with their wishes and values is also part of the overall goal of precision medicine. Ideally, precision medicine will evolve to encompass prevention. Our knowledge of an individual's genomic, environmental, and lifestyle data will prevent more cancers before they can develop and require treatment.

However, the essential next step in precision medicine is to ensure universal access to genomic screening and targeted therapies for all Australians.

Our ever-evolving understanding of cancer highlights the complexity and continually changing nature of this disease. Therefore, the solutions must also reflect the dynamic and multi-faceted nature of cancer, with an approach to combining treatments that target the different mechanisms used by all cancers to grow and develop.

3 Current barriers to precision oncology in Australia

In 2020 when RCA launched our *Vision 20-30: Building an Australian Cancer Futures Framework* report we explored how the advances in genomic science could only be equitably translated to the clinical setting if our health system evolved to take advantage of emerging technologies.[42] Here we discuss how our current research and healthcare systems create barriers to the implementation of precision oncology.

3.1 Clinical trial design for rare cancers

Clinical trials are research studies that investigate the health outcomes of new treatments or tests. Clinical trials are an essential part of the development of all cancer treatments and tests and without the research findings, we cannot determine whether there is a clinical benefit, or the significance of that benefit.

Large scale randomised controlled trials (RCTs) have typically been the gold standard in terms of determining a test or treatment's clinical benefit. As a result, RCTs have formed the basis of the evidentiary requirements in health technology assessments (HTA), which is the process by which the Government's regulatory bodies decide whether to fund treatments and tests (see section 3.2).

The design and analysis of clinical trials for rare and ultra-rare diseases pose unique challenges to researchers.[43] By virtue of being rare, it is very often impossible to design RCTs for rare cancers, due to small patient populations. As studies often span years, it can take a long time to achieve conclusive results and many people do not get the opportunity to access treatments, particularly when it comes to precision oncology. Alternatively, for rare cancer trials, populations are often so small that trial sites won't even open or may never find a patient if they do. This problem of small patient populations is exacerbated by advances in genomics where it becomes unrealistic to investigate the broad spectrum of genetic sub-populations by traditional clinical trial designs.[44] We therefore need to take a closer look at how we generate suitable evidence through novel trial designs that offer a practical alternative.

Novel trial designs include basket trials, umbrella trials and platform trials. Basket trials refer to designs in which a targeted therapy is evaluated on multiple diseases that have common molecular alternations.[44] Umbrella trials, on the other hand, evaluate multiple targeted therapies for a single disease that is stratified into subgroups by molecular alternations.[44] Basket trials and umbrella trials both employ a molecular screening protocol that allows either recruitment of different diseases with the common molecular variation(s) or that differentiates the single disease into different molecular subtypes.[44]

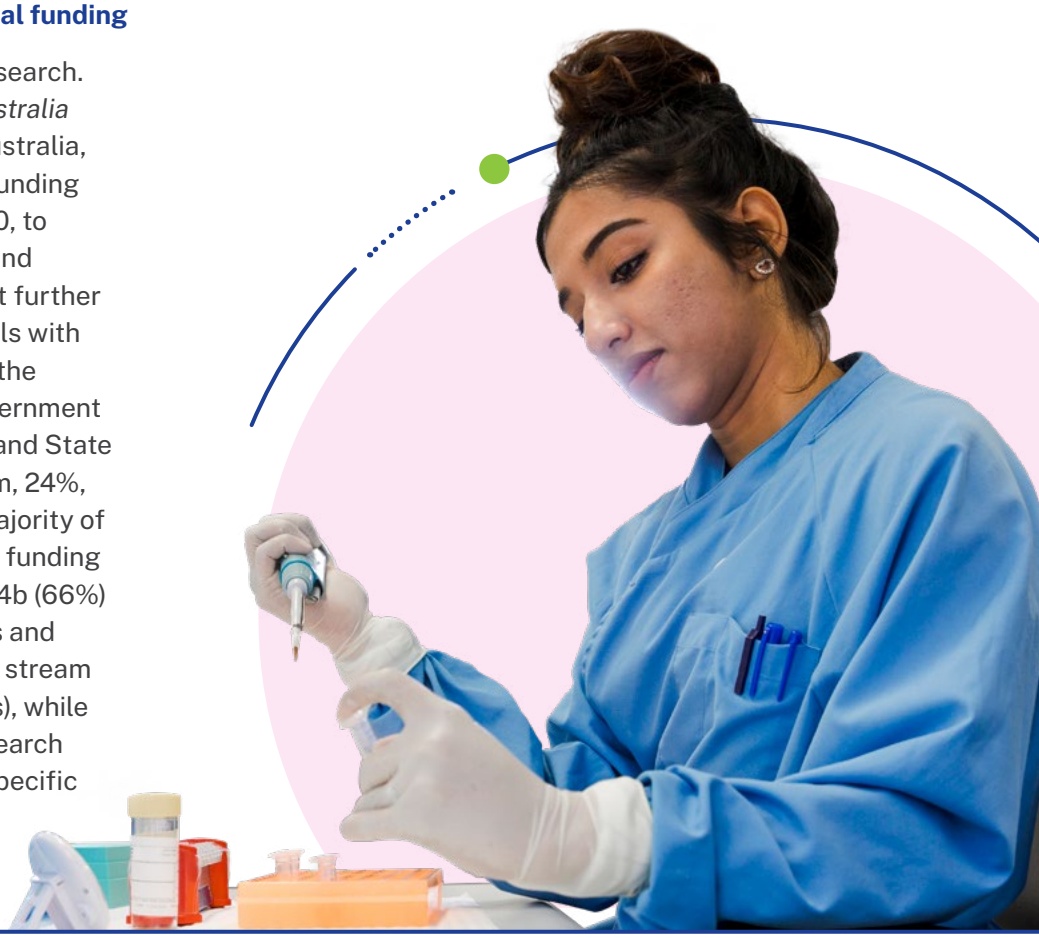
According to the latest Global Oncology Trends report, in 2021, there was a record number of new oncology trials started, up 56% from 2016. Furthermore, two-thirds of new trials over the last decade focused on bringing new treatments to cancers with smaller patient populations.[31] The report also demonstrated that oncology trials more frequently use novel trial designs than trials for other diseases, and have nearly quadrupled in the last decade.[31]

3.1.1 Research and clinical trial funding

Australia is a leader in cancer research. The 2023 *Cancer Research in Australia* report,[45] published by Cancer Australia, identified $2.12 billion in direct funding provided between 2012 and 2020, to 4,813 cancer research projects and programs in Australia. The report further identified 419 cancer clinical trials with a total of $315m funding during the same period. The Australian Government ($147m, 47%, 193 clinical trials) and State and Territory governments ($77m, 24%, 45 clinical trials) provided the majority of funding.[45] Of the $2.12b in direct funding for cancer research projects, $1.4b (66%) was for cancer research projects and programs with a specific tumour stream focus (single or multiple tumours), while $712m (34%) was for cancer research projects and programs with no specific tumour focus.

Despite the 2023 National Audit of Cancer Research Funding demonstrating that total funding for cancer research has increased in recent years, the total funding required to close the gap between funding and the burden of disease and mortality caused by RLC cancers compared to common cancers remains significant. Clinical trials into the effectiveness of novel, targeted therapies in small patient populations require collaborative trial development and research that crosses traditional boundaries of trials currently being undertaken in Australia.

In the past few years, we have seen promising increases in government funding for innovative trials. For example, the PrOSPeCT program at Omico (see case study 3) received $61.2 million from the Australian Government in July 2023. And while we have also seen significant investment, through the Australian Government's Genomics Health Futures Mission (GHFM), which is investing $500 million over 10 years (2018-19 to 2027-28) in genomics research,[46] we need to increase our commitment if we are to realise the potential of genomics in oncology, and other diseases.



CASE STUDY 3

Genomic profiling trials at Omico

Omico is a not-for-profit nationwide network of research and treatment centres that facilitates, supports, and promotes clinical trials in genomic cancer medicine. Central to this is the use of precision medicine for the prevention and treatment of cancer. By bringing together Australia's major cancer centres, leading research institutes, Federal and State governments, industry partners and patients, Omico is facilitating the delivery of genomic cancer medicine clinical trials to thousands of Australians suffering from advanced and incurable cancer.

Omico aims to improve outcomes for Australians with cancer by accelerating the use of precision oncology, growing clinical trials and modernising the Australian healthcare system. Together, Omico's members treat more than 100,000 new cancer patients each year, of which more than 20,000 have rare or less common cancers.

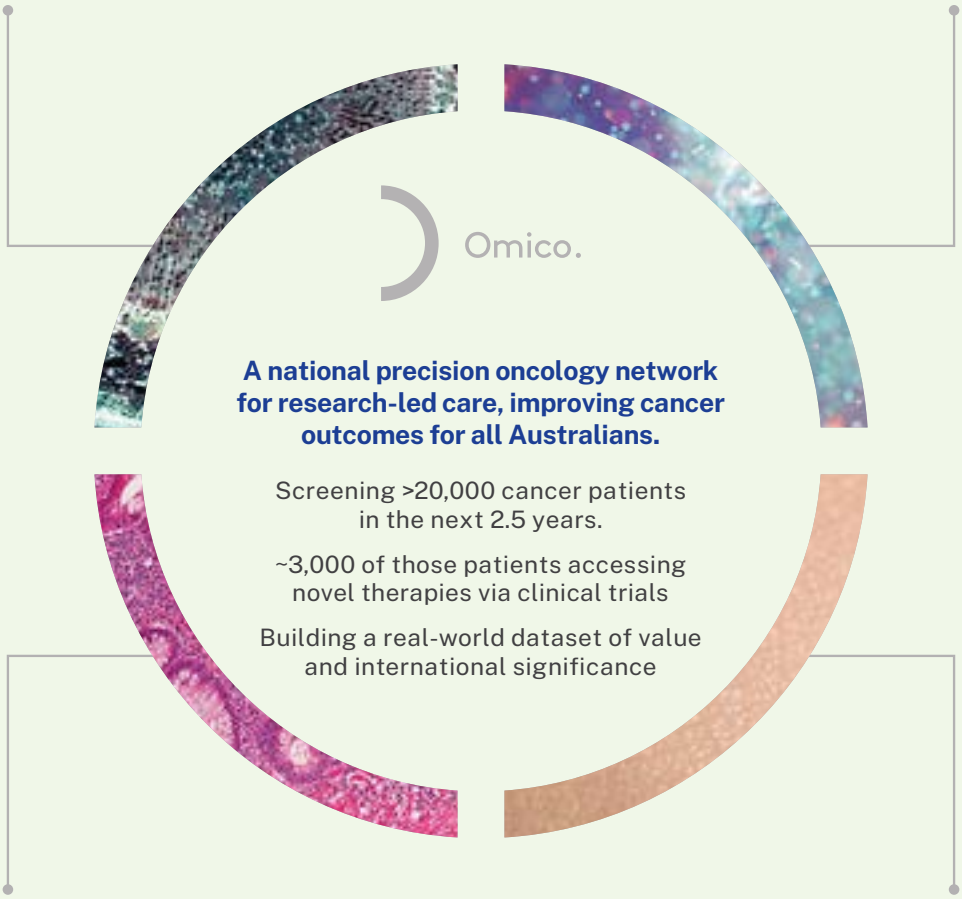
Omico's mission focuses on four pillars:

Molecular screening & therapeutics

Tumour profiling to evaluate biomarker-driven treatments for patients

Health system reform

Leading health system reform through evidence



Personalised risk management

Using heritable genetic information to assess cancer predisposition and investigate clinical risk management

Patient support & advocacy

Supporting patients and families today and planning the health system for tomorrow

By the end of June 2023, the Molecular Screening and Therapeutics (MoST) program had reached more than 7,600 participants, well ahead of the original five-year forecast of 2,400 participants. Of these, more than 700 went onto biomarker-dependent clinical trials. Omico has opened 22 clinical trials over the past five years and preliminary analyses of patient outcomes show that patients who receive a therapy closely matched to the biomarker identified in their tumour more than double their expected survival. This shows the power of rational drug development, which in turn is critically dependent on the tumour profiling that Omico provides to patients and clinicians through the MoST study.[47]

In 2022, the MoST program continued to expand the pan, blood, lung and pancreatic cancer groups. For example, the partnership with the Thoracic Oncology Group of Australia and Roche Australia established the ASPiRATION subprogram of MoST, which focused on 1,000 Australians with newly diagnosed metastatic, non-small cell lung cancer (recruitment closed June 2023). These people represent an additional 1,000 individuals accessing comprehensive genomic profiling (CGP) or molecular profiling for their cancer. Meanwhile, the partnership with the Australasian Leukaemia and Lymphoma Group has led to the development of the subprogram in haematologic cancers (MoST-LLy).

Funding support from the Leukaemia Foundation, Tour de Cure, MRFF and philanthropic supporters has provided an additional 480 patients access to molecular profiling for their blood cancer.[47]

In addition to MoST, Omico's landmark program Precision Oncology Screening Platform Enabling Clinical Trials (PrOSPeCT) is working with its partners to establish a long-term business model which aims to increase access for all Australian cancer patients to genomic profiling and clinical trials, both commercial and academic. Omico is also working with its partners to enhance workforce training and education, rural and regional clinical trials access, and access of indigenous cancer patients to genomic profiling and clinical trials.

PrOSPeCT was approved by the Federal Department of Industry, Science and Resources as part of the Modern Manufacturing Initiative. PrOSPeCT is a private-public partnership pulling together more than $190m in funding to enable the screening of another 23,000 Australians with advanced or incurable cancers, linked to the expansion of the clinical trials in Australia through foreign direct investment by the global pharmaceutical sector. PrOSPeCT will change options for thousands of Australian cancer patients, stimulate Australian research and development, and grow the high-tech economy in Australia,[47] and offers a new approach to clinical trials for the future.

3.2 Challenges for precision medicines in our health technology assessment system

Health technology assessment (HTA) was introduced in Australia for the reimbursement of pharmaceuticals in 1992, and in the following years for procedures, diagnostic tests and devices.[48] Our current HTA system was designed to inform decisions about the reimbursement of treatments for population-based conditions such as hypertension. While our HTA may still be fit-for-purpose for these and other health interventions such as prostheses, and anatomical pathology services, their appropriateness for advanced health interventions such as genomics and advanced therapeutics, or indeed more sophisticated imaging techniques such as MRI, are being increasingly called into question for a number of reasons, discussed below.

3.2.1 Evidentiary requirements and small populations

Our HTA system was designed to assess evidence from large scale RCTs (see section 3.1) that recruited thousands of people and to compare outcomes to an existing standard of care, providing new treatments for diseases in which interventions were not time critical (e.g. hypercholesterolemia). However, the increasingly complex nature of cancers due to advances in precision oncology creates challenges for our HTA system, as large-scale RCTs simply aren't feasible in small patient populations and the nature of the range of treatments under development is such that randomisation may not be feasible or ethical. Where innovative trial designs are used, or where data is limited because of rarity, the HTA system is incapable of the flexibility required to make assessments and ensure rapid access for patients with limited options.

Indeed, in recent years, we have seen treatments for rare cancers rejected by the Pharmaceutical Benefits Advisory Committee (PBAC) because only single-arm (non-randomised) study data were available; in the meantime, overseas, the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) have increasingly accepted single-arm trials. In the US, for example, between 1 January 2002 and 31 December 2021, the FDA granted 176 new malignant haematology and oncology indications based on single-arm trials, including 116 accelerated approvals and 60 traditional approvals.[49] In the appropriate context, single-arm trial evidence can allow patients expedited access to novel therapies and will increasingly serve a role in advancing drug access in oncology.[49]

3.2.2 Tumour-agnostic assessments

Over the last 10 years, HTA bodies have faced new challenges in establishing the benefits of targeted therapies, both for individuals and for the health system. For example, there are now 10 molecularly distinct subtypes of non-small cell lung cancer (NSCLC) for which there are effective therapies, accounting for more than 50% of all people with NSCLC. However, only three of these therapies are currently reimbursed in Australia,[50] leading to a situation where people are forced to either self-fund treatments that are known to be effective, or miss out.

Another issue that increasingly needs addressing is that of tumour-agnostic regulatory approval of targeted therapies (see case study 4).[51] Tumour-agnostic regulatory approval refers to an approach for approving a specific therapy based on its effectiveness in treating a particular genetic or molecular alteration in tumours, regardless of where the tumour originates in the body. For example, PD-1 inhibitor therapies for micro-satellite unstable cancers, where there is clear clinical benefit across cancer types regardless of histology. As long as we continue to approve new tests and therapies on the basis of tumour location alone, people living with the rarest indications will continue to face delays to access.

3.2.3 What are we valuing in our assessments?

Compounding this issue, the Medical Services Advisory Committee (MSAC) and PBAC are constrained by rigid assessment paradigms that fail to consider secondary order effects of genomics (to family, carers), real world evidence (lived experience) and limit 'value' to the patient to quality adjusted life years (QALY). Yet, for many people living with cancer, the concept of a QALY may raise concerns and utilising QALYs to conduct value assessments can be seen as reductive. Specifically, concerns include the inadequate sensitivity and the omission of numerous personal elements that have an impact on both the individual and the wider community. For instance, the importance of significant life events and the ability to maintain employment are disregarded within the framework.[52]

With rapid health innovation in genomics, our conventional health infrastructures and policies, including HTA, need to evolve to take full advantage of the promise of genomics to people with rare cancers. The current Health Technology Assessment Policy and Methods Review[53] (HTA Review) has a distinct PBAC focus; however, a more holistic interrogation of both MSAC and PBAC is needed to support system-wide adaptation to the genomic revolution. Through the HTA Review, underway at the time of this publication, there is an opportunity to adapt our HTA system to consider different levels of evidence, as well as novel trial designs, such as basket trials or umbrella trials, that consider multiple targeted therapies across multiple cancers.

CASE STUDY 4

History of immune checkpoint inhibitors

Since 2010, we have seen the emergence of many immunotherapies and their widespread use in cancer treatment. The first of these was ipilimumab, a CTLA-4 checkpoint inhibitor. Ipilimumab was followed by a range of immune checkpoint inhibitors (see section 2.4), such as PD-1/PD-L1 immunotherapies, which work to reactivate the immune system to attack tumour cells by blocking a protein known as programmed death receptor 1 (PD-1). PD-1 is found on immune cells called T-lymphocytes, which, when left unchecked, allows cancer cells to pass undetected by the body's natural immune defences.[54]

Since 2014, there have been seven PD-1/PD-L1 inhibitors approved by the United States the Food and Drug Administration (FDA) for a range of haematological cancers and solid tumours.[31, 55] The first of these was pembrolizumab, again for use in melanoma. This has been followed by seven other PD-1/PD-L1 inhibitors, namely nivolumab, atezolizumab, avelumab, durvalumab, cemiplimab, dostarlimab, and most recently, retifanlimab.

These treatments have been registered for use with an increasing number of cancer types, however, their availability in Australia has lagged significantly by comparison to the United States. To illustrate the challenge Australian patients face we have tabled the availability of pembrolizumab, as an example.

Pembrolizumab was first available to Australian patients in September 2015 when it was listed on the Pharmaceutical Benefits Scheme (PBS) for people with metastatic melanoma. It is now publicly funded for 12 types of cancer and there are currently around 3,500 Australians receiving pembrolizumab through the PBS (see figure 5). As an example of access, each bar in the graph opposite represents the time between FDA approval and PBAC approval, with many that are ongoing and yet to be recommended. It should be noted that the payer systems in USA and Australia are vastly different, and this example is purely an illustration of time-to-patient across various diagnoses for the same therapy.

Figure 5: Timelines of pembrolizumab approvals by FDA to PBAC[a] approval, by indication.

Abbreviations:

BCG	Bacillus Calmette-Guerin
cSCC	cutaneous Squamous Cell Carcinoma
dMMR	deficient DNA Mismatch Repair
GEJ	Gastroesophageal Junction
HNSCC	Head and Neck Squamous Cell Carcinoma
MSI-H	Microsatellite Instability-high
NSCLC	Non-small Cell Lung Cancer
PMBCL	Primary Mediastinal B-cell Lymphoma
RCC	Renal Cell Carcinoma
TMB-H	Tumour Mutational Burden-high
TNBC	Triple Negative Breast Cancer

a While FDA approval may be more analogous to Therapeutic Goods Administration (TGA) approval than PBAC recommendation, the time between FDA and PBAC recommendation has been used here to demonstrate the point at which a therapy is accessible to a person requiring treatment.

* Keytruda was initially approved by the FDA for second line (2L) therapy, which was never applied for in Australia. As a result, the PBAC in Australia approved Keytruda as a first line (1L) treatment for advanced melanoma before the FDA.

** Tumour-agnostic approval based on a biological marker (e.g., dMMR, MSI-H, TMB-H).

We estimate that at least 3,500 more people would be eligible for treatment with a PD-1/PD-L1 inhibitor if PBS funding was available for all indications that are currently approved in the US. It is estimated that around 7,000 more Australians will be eligible once the remaining indications are eventually approved.

The increase in use of PD-1/PD-L1 inhibitors is accelerating. According to the IQVIA Global Oncology Trends 2022 report there are currently 5,761 trials globally testing PD-1/PD-L1 inhibitors, a 283% increase over the last five years. And nearly 90% of clinical trials with PD-1/PD-L1 inhibitors that started in 2021 are investigating their use in combination with other drugs, while monotherapy trials have been declining.[31] These combination trials include drugs across 300 different targets and pathways, with PD-1/PD-L1 in combination with chemotherapy accounting for 14% of all PD-1/PD-L1 trials.[31]

Perhaps most importantly for improving access to immune therapies, such as those named above, we are finally seeing pan-cancer, tissue-agnostic therapies being approved overseas. For example, pembrolizumab was approved by the FDA, in 2017, for people with tumours characterised as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).56 Larotrectinib and entrectinib were also FDA approved in 2018 and 2019 for advanced solid tumours (independent of anatomic location of the tumour i.e. tumour-agnostic) with NTRK fusions.[56] Pan-cancer, tissue-agnostic therapy approvals are crucial to accelerating access for patients with the rarest cancers.

3.3 Considerations for expanding access to genomic testing

Genomic testing can be undertaken on a tumour (called somatic testing) or normal tissue e.g. blood (called germline testing, inherited gene changes that can be passed down in families). Comprehensive genomic profiling of tumours using genomic testing (somatic) and identification of molecular subtypes of cancers are the foundation for delivering personalised treatment approaches. Genomic testing may also be used to screen for familial risk of cancer (germline), establishing a molecular diagnosis, understanding disease progression and to direct the best course of treatment.[42]

Despite the enormous potential benefits of genomic testing, there remain a number of barriers to equitable access. Barriers to adoption into standard health care include: lack of genomic education and support for non-genetic oncologists, surgeons and other healthcare providers; blurred lines of responsibility for which health professionals should offer genomic testing (i.e., oncologist, surgeon); lack of trained healthcare professionals to cope with the influx and demand; few strategies to ensure equity of access for high unmet need populations (i.e., Aboriginal and Torres Strait Islander people, culturally and linguistically diverse groups, and rural and remote communities) and rural and remote patients; and limited funding and infrastructure for genomic testing.[57]

3.3.1 Co-dependent technologies in HTA

One of the main barriers to access for genomic testing is caused by our HTA processes (see section 3.2). Because genetic tests are often matched to a targeted therapy, they go through a 'co-dependent' applications process with MSAC and PBAC which may be very slow due to the involvement of many committees.[58] In order to reduce these barriers, the process of co-dependent evaluations needs to be streamlined, to ensure that assessments occur concurrently.

3.3.2 Cost of funding genomic testing

Added to the challenges of how co-dependent tests are assessed, there are also very few Medicare Benefits Schedule (MBS) funded tests for screening and diagnosis for RLC cancers, and there is no reimbursement for comprehensive cancer genomic profiling.[58] Without subsided access to comprehensive genomic profiling, people are put in a position where they have to either pay the full cost themselves to have access to potential targeted therapies, or miss out and accept standard therapies. The inequity experienced by those who cannot afford tests or treatment is a situation that should not exist in Australia, and urgently needs addressing.[58]

3.3.3 Ethical challenges in genomics and life insurance

In 2020 we published the *Australian Cancer Genomics Landscape Assessment* report,[56] which explored the current landscape of Australia's genomics capabilities in cancer diagnostics, treatments and management. The report showed that there was considerable opportunity to create a world-leading cancer genomics infrastructure in Australia. But, while the opportunities for genomics to improve outcomes for people living with cancer are significant (see case study 5), there are also ethical challenges and barriers to accessing testing that must be addressed to maximise the reach and potential of genomic medicine.

Currently in Australia, the life insurance industry is legally permitted to use genetic test results in underwriting, which can lead to discrimination and is known to deter people from having genetic testing or participating in genomic research.[59] RCA is concerned about the lack of consumer protections against genetic discrimination in risk-rated insurance, and the lost opportunity for the potential role of genomic medicine for cancer prevention and care.

In 2018, a Joint Parliamentary Committee Inquiry into the Life Insurance Industry recommended that Australia urgently implement a moratorium on the use of genetic test results in life insurance underwriting.[59] In 2019, the life insurance industry peak body, the Financial Services Council (FSC), introduced a partial moratorium requiring applicants to disclose genetic test results only for policies above certain financial limits. However the FSC Moratorium is industry self-regulated, with no government oversight, and only applies up to certain policy limits.[59]

To investigate the effectiveness of the FSC Moratorium, the Commonwealth Government funded the *Australian Genetics and Life Insurance Moratorium: Monitoring the Effectiveness and Response* (A-GLIMMER) Project from 2020 – 2023. This independent project, led by Monash University in collaboration with researchers and consumer groups across Australia, gathered evidence to assess the effectiveness of the FSC Moratorium, and report findings to Government and other stakeholders.[59] The project conducted research with stakeholder groups including consumers, patients, health professionals, researchers and financial services personnel, and delivered its final report in June 2023. It found that the FSC Moratorium is inadequate to address and prevent genetic discrimination in life insurance. It recommended a legislative model of prohibition, with its specific recommendations being that:

1. The Australian Government amend the *Disability Discrimination Act 1992* (Cth) ('the Act') to prohibit insurers from using genetic or genomic test results to discriminate between applicants for risk-rated insurance, and consider amendments to the regulation of financial services to ensure insurers are subject to a positive duty to not discriminate.
2. The Australian Government allocate responsibility and appropriate resources to the Australian Human Rights Commission ('AHRC') to enforce, promote, educate and support individuals and all relevant stakeholders to understand and meet the new legal obligations under the Act. The AHRC should consult with a range of genetics and genomics experts and stakeholders to achieve this goal.[59]

If the potential of genomics in cancer care is to be maximised, we need to remove the barriers to participation in genomic testing and research, including as an urgent priority, protection for people against discrimination on the basis of genetic results. RCA supports the A-GLIMMER Project's recommendations and urges the Australian Government to implement the recommendations as a matter of urgency.

CASE STUDY 5

Role of genes in sarcoma predisposition

Sarcomas are rare cancers arising in bone, muscle, fat, or cartilage. Often occurring in children and young adults, sarcomas make up about 20% of the cancers diagnosed in people under the age of 20.[60] Until recently, there has been little research into the genetic basis of sarcomas.

However, a new global research study has generated a comprehensive map of how the inheritance of gene changes may impact families affected by sarcoma and showed that one in 14 individuals diagnosed with sarcoma carry a clinically important gene change that explains why the cancer arose.[61]

The findings uncovered by this research are so important, because by understanding how individuals develop sarcomas, we move closer to earlier detection and better outcomes.

Dr Mandy Ballinger

Group Leader at the Garvan Institute of Medical Research

In addition, the research team identified a previously unrecognised genetic pathway specific to sarcomas, opening up new cancer biology required to improve health outcomes.[60]

The research used data collected from the International Sarcoma Kindred Study (ISKS) and the Genetic Cancer Risk in the Young (RisC) studies. The ISKS, established in Australia in 2008, is the largest sarcoma genetic study in the world, including more than 3,700 families recruited from 23 cancer centres in seven countries.[60]

The research paves the way for future testing of people impacted by sarcoma to assess their genetic risk of developing the disease (see section 3.4). With an increased understanding of heritable predisposition, people (and their families) can be empowered to better understand and manage underlying risks. Earlier detection of sarcoma generally results in improved outcomes. Knowledge of sarcoma predisposition means that risk management strategies such as increased surveillance can be implemented. Lifestyle, reproductive and treatment decisions are more personalised and informed and may lead to far better outcomes.

PERSONAL PERSPECTIVE

Access to genomics, emerging new treatments and clinical trials – a choice or a privilege?

By Caitlin Delaney

I am so grateful to still be alive today, defying the odds! I live with incurable, stage 4 clear cell ovarian cancer, a rare and nasty variant of the deadliest women's cancer. Since my diagnosis over six years ago, I have observed many barriers to potentially lifesaving genetic tests, treatments, and clinical trials. Not all cancers are created (or treated) equal, especially if you have a rare cancer! Further, access to genetic tests, treatments and trials is dictated not only by the patient's type and stage of cancer, but also where they live, their background, age, bank balance, who their treating oncologist is (the doctor is the gatekeeper for all test and treatment information), and how empowered and informed the patient is.

Despite being disadvantaged by having an advanced and rare cancer, I am still here – in part due to luck, tenacity, genetics, and the compassionate care I have (for the most part) received. Yet, it has been my ability to self-advocate for genetic tests and emerging new treatments, or off-label drugs, that has really changed the trajectory of my story – making those 'sliding door' moments lean in my favour.

I was diagnosed in February 2017, aged 39, after just starting my family (my daughters were only 2 and 4 years old). I have no known risk factors and no obvious cancer in the family, so it was a huge shock. After a gruelling six months of weekly chemo and a seven-hour debulking surgery, I obtained cancer-free status. Due to being stage 4, I was able to remain no evidence of disease (NED) with the help of PBS-funded Avastin (Bevacizumab), which saved me $45,000. But the funded maintenance drug Avastin only lasted a year. I sourced funding for a second year but just months after stopping Avastin, the cancer came back in my liver and lymph nodes.

Unfortunately, chemo didn't work when I recurred, nor did an immunotherapy clinical trial. Due to my rare pathology, I am not a candidate for the many clinical trials, nor the PBS-listed drugs that could prolong my life. Like all rare cancers, there are simply not enough people to warrant a trial, or to gather meaningful data – by definition, there never will be! This is infuriating, especially since genetic testing of my tumours shows I have variations that can be targeted by certain drugs. Frustratingly, both funded and compassionate access to drugs is often determined by tumour origin and pathology, rather than variations.

I was however able to access another immunotherapy drug combination off-label, which had worked in a different gynaecological cancer setting. These two drugs, Keytruda and Lenvima, were recommended due to my tumour genetic profile, by my third opinion oncologist in Singapore – an expert and leading researcher in clear cell ovarian cancer. This drug combination had no clinical trials open at the time that I was eligible for, which is not uncommon. Often the trials or drugs are there, but it isn't easy to get connected to the right trial at the right time. Without a trial, I had to access my life insurance to afford the off-label drugs, which cost up to $12,000 a month – a sound investment, given that they kept my disease relatively stable for 2.5 years and enabled me to witness many family milestones, including my eldest daughter turning double digits! I appreciate that extrapolation of previous clinical trial data enabled me to access these drugs off-label, and for that I am extremely grateful. Yet, to be financially penalised and denied trial access due to my disease pathology seems unethical.

Whilst on this drug combination, I advocated for radiation of two of my liver metastases that were progressing (all other disease was stable).

SBRT radiation is not standard treatment for ovarian cancer in Australia, yet in other countries it has shown good results for my cancer. I am so grateful to have pursued this, as all my liver lesions are still inactive two years on!

Sadly, this drug combination has run its course. My Singapore expert recommended I next test my tumour tissue for the HER2 variation, which is commonly associated with breast cancer (this test is not routinely offered to ovarian cancer patients). Results show that I am HER2 positive – so I am currently on a waiting list for two HER2 clinical trials. Genomics is yet again offering me and my family and I that ever-elusive hope.

My cancer experience has taken me places I would never have dreamed of – from meeting the current and previous Prime Ministers, to starting my own business CareFully, which empowers and trains healthcare professionals to deliver compassionate care. As patients we often feel powerless and vulnerable. Healthcare can be dehumanising at times; it's easy to forget to see the whole person. A growing body of scientific research shows that compassion and communication are superpowers in healthcare – I have discovered that it's often the little things that can make a BIG difference to patients.

Here are some other key things I have learnt these past six years:

- **You are not your diagnosis, or a statistic** – other people's stories are not my story. Challenging the status quo and thinking outside of the box is crucial, especially when diagnosed with advanced and/or rare cancer.
- **You must self-advocate.** I can't stress this enough. No-one knows your body better than you do (we live in it 24 hours a day after all!). As patients we are entitled to second or third (or more) opinions, without feeling we are offending our initial treating doctor. These additional opinions can be critical if you have a rare cancer that your treating team may not have encountered many times before (if at all!). It can be hard to speak up, but I just remind myself that the stakes are pretty high! There is no doubt that my healthcare professional background has equipped me with the skills to self-advocate. But what about those patients who live in regional areas, or who aren't health literate? I see so many of these patients slip through the cracks.
- **Genomics, personalised medicine, emerging new treatments, and clinical trials** are changing the cancer landscape and have the power to radically transform outcomes – particularly for those living with metastatic disease. But we need to fast-track the process of bench to bedside and adopt a more 'living evidence' approach (N = 1) and a paradigm shift, as current healthcare models do not reflect current science.
- **Patients can live with advanced cancer for many years**, and live rich, full, rewarding lives. But they need support to deal with the collateral damage. Survivorship involves a multidisciplinary approach, and integrative oncology is essential for patients to not just survive, but really thrive too.

As we move to a more tumour agnostic treatment approach with germline and somatic genetic testing, and thus more personalised treatments, we need to ensure that ALL cancer patients are offered such tests, and that insurers don't discriminate. And these tests need to be provided in a timely manner with the support of a reliable, transparent, truly collaborative, and sophisticated clinical trial platform to ensure that no patient is left behind.

4 What do we need to do to overcome the barriers to equitable access to precision oncology?

4.1 Making 'genomics as standard of care' a reality in Australia

4.1.1 Increasing access to testing

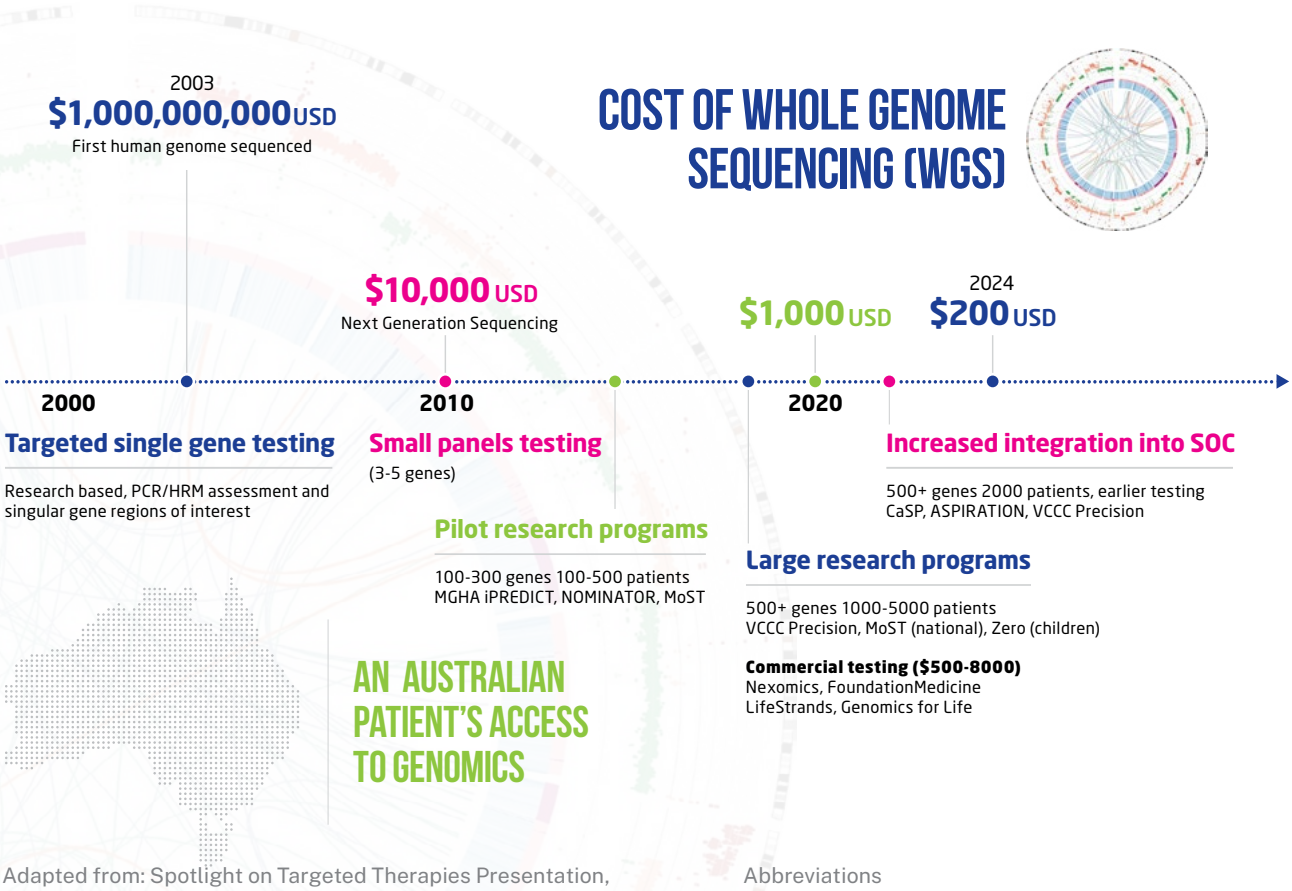
Genomic sequencing technology has enabled new discoveries in cancer research, drug development and clinical care by offering the potential for precise and personalised approaches to cancer treatment. This is especially relevant for people with rare cancers who suffer from limited access to new targeted cancer treatments that offer hope for improved survival and quality of life.[56]

It is time for us to recognise that the advances in genomics, and their applications in oncology, require us to adapt our approach and health systems to ensure all Australians have access to the best available diagnostics and therapies. By acknowledging the opportunities presented by genomics and adapting to deliver them, we can improve the outcomes and experience for every person diagnosed with cancer, while at the same time delivering efficiencies and cost savings for the health system.

To achieve this, we should commit to creating a health system that is ready to provide all Australians with the earliest and best possible access to precision oncology, including genomic testing and matched targeted therapies, where they exist. As we look abroad to how other countries are approaching integrating genomics in their health systems, we can learn some valuable lessons. There are international examples, such as in the National Health Service (NHS) funded by the United Kingdom (UK) government (see case study 6), where they are already scaling up their precision oncology and cancer screening and increasing the eligibility for genetic profiling of their cancer.[58]

While in the past, the cost of delivering such an ambitious genomics program may have been too high, the price of genomic sequencing has decreased rapidly and is becoming increasingly cost-effective to deliver at scale (see figure 6). As the technology continues to evolve and the benefits of delivery increase, Australia needs to be ready to deliver.

Figure 6: Improved access to genomic testing, advances in speed and cost of testing and improving equity of access.



Adapted from: Spotlight on Targeted Therapies Presentation, VCCC Cancer Communities Forum, 13th September 2023 by Dr Damien Kee

Abbreviations
PCR Polymerase Chain Reaction
HRM High Resolution Melt

CASE STUDY 6

NHS Genomic Strategy

The UK government has been investing in delivering genomics through the NHS over the last decade, including through the ground-breaking 100,000 Genomes Project, which has laid the foundations for the use of genomics in routine clinical care.[62]

Over the next five years, the NHS will improve care and treatment options, developing shared clinical and access standards, data platforms and governance, and an interoperable informatics infrastructure.

As the NHS delivers the benefits of genomics to patients and our population, it has identified the need to take a comprehensive and ambitious national approach covering prevention, diagnosis and targeted treatments that enables people, families and carers to participate in shared decision-making.[62]

The strategy sets out four priority areas to this approach:

- Embedding genomics across the NHS, through a world-leading innovative service model from primary and community care through to specialist and tertiary care.
- Delivering equitable genomic testing for improved outcomes in cancer; rare, inherited and common diseases; and in enabling precision medicine and reducing adverse drug reactions.
- Enabling genomics to be at the forefront of the data and digital revolution, ensuring genomic data can be interpreted and informed by other diagnostic and clinical data.
- Evolving the service through cutting-edge science, research and innovation to ensure patients can benefit from rapid implementation of advances.

This NHS genomics strategy signals the next big step in healthcare in the NHS and the journey to realise the potential of genomics for patients, communities and the population it serves.[62]

4.1.2 Upskilling the workforce to deliver precision oncology across Australia

The availability of treating practitioners who are familiar and comfortable with offering genetic research and clinical trial opportunities to their patients is essential.[58] Currently, some research projects give patients access to molecular testing and comprehensive genomic profiling, with subsequent access to novel treatments.

All organisations involved in the delivery of health services need to create a culture of research – making awareness of, and access to, precision oncology and clinical trial delivery a priority for their sites. To do this, they must afford healthcare professionals the time and opportunity to upskill in genomics, the delivery of research and clinical trials and to lead these activities at their sites, and remove unnecessary barriers.[58] Added to this, the curriculum for future healthcare professionals must include sufficient genomic and molecular biology components to enable the delivery of precision medicine.

4.1.3 Delivering consistency in pathology

As with many new and rapidly evolving technologies, systems develop to simply meet the needs at that time. As precision oncology becomes the standard of care, our disparate systems need to evolve. For example, we need consistency between laboratories, tests, presentation of results and prices. Ideally, this is where the peak medical bodies such as the Royal Australasian College of Pathologists should be asked to expedite the establishment of relevant guidelines to ensure people accessing tests receive a consistent standard of care.

4.2 Making the most of clinical trials for precision oncology

As discussed earlier in this report, innovative trial designs are necessary for conducting rare cancer research and genomic-based clinical trials. Public and private funding is key to delivering these innovative trials, as we have seen from the success of Omico, and so we need to foster an environment that encourages and promotes future investment through these funding partnerships.

We also need to focus on facilitating alternative approaches to rare cancer research, including genomic-based clinical trials. For example, applying Bayesian methods to genomic cancer trials can help identify biomarkers associated with treatment responses, refine patient stratification strategies, and guide the development of more targeted and personalised cancer therapies. It allows for a data-driven approach that leverages prior knowledge and adapts to emerging evidence in the rapidly evolving field of cancer genomics. GBM-AGILE is one example of such an approach. Through its adaptive design, it can rapidly accelerate the pace at which new treatments are tested in patients with glioblastoma (GBM), an aggressive form of brain cancer. In doing so, it would be useful to collaborate with regulatory agencies to ensure the Bayesian design of rare and genomic cancer trials, including those with combination therapies, aligns with regulatory requirements and ethical standards and will be accepted as meeting evidentiary requirements (see section 4.3).

4.3 Pathways in HTA for precision oncology

As identified in the last chapter, there are a number of issues for precision oncology tests and therapies progressing through our HTA system and the reality is our current HTA processes are not fit for purpose for precision oncology. If we are to ensure swift and equitable access to the best available tests and therapies, we must address the issues arising from evidentiary requirements for small indications, co-dependent technology barriers, combination therapies, and the need for tumour-agnostic applications.

One way to achieve this is to revisit previous recommendations for a new process for tumour-agnostic registrations. In August 2017, RCA launched a report *Rare solutions: a time to act*[62] at CanForum in Parliament House. The report was launched by the then Health Minister, Greg Hunt, who announced at the time that he had charged the PBAC with the task of developing a new process for 'pan-tumour' (tumour-agnostic) assessments.[64] While tumour-agnostic applications create complexity for health systems, they provide an opportunity for people with rare cancer subtypes to be treated effectively with the same targeted therapy.

There is currently a lack of publicly available tumour genetic testing in Australia, however, where genetic tests are available, they should be considered a first line test. Where possible, genetic tests should also be offered as comprehensive panel tests involving multiple genes which are tested concurrently rather than as separate tests on single genes, which again saves valuable time.[58] A new pathway for precision oncology tests and therapies would help overcome the rigidity of the existing assessment frameworks and should be explored under the current HTA Review process.

4.3.1 Is precision oncology a cost or an investment?

The other crucial area for the HTA Review to consider is how our HTA system values precision oncology. As we discussed in our 2022 report *Counting the cost: the true value of investing in cancer treatment*,[65] we need to look beyond standard measures of cost-effectiveness based on clinical outcomes alone, and move to a model that adequately assesses and values the social benefits derived from cancer treatments. The analysis conducted for the report evaluated the social impact of improving the prognosis of a non-curative cancer diagnosis and found that for every $1 invested in cancer treatments, there is $3.06 of social and economic value created.[65]

As an example, the benefits of precision oncology go far beyond the simple clinical outcomes; targeted therapies are, in general, better tolerated, with fewer side effects than cytotoxic chemotherapies, and ensure people have a better quality of life while undergoing treatment. It is right, therefore, to measure the social benefits that come with improving quality of life and assessing the value for people beyond their treatment outcomes.

4.4 Changing how we capture data on the molecular subtypes of cancer

As already noted in this report, a rare cancer is defined as an incidence of less than six per 100,000, and a less common cancer is an incidence between six and 12 per 100,000 of the population.[3] However, we know that many cancers that were previously considered common are becoming increasingly rare through the discovery of multiple subtypes with distinct clinical behaviour and outcomes, that can be linked to the discovery of genetic variations. As a result of our improved understanding of genomics in cancer, we now need to expand what we think about when we say 'rare and less common cancers'. As an organisation, under this umbrella term, we now include both the RLC cancers based on the cancer location and the rare molecular subtypes of common cancers.

It is important to note that these rare molecular subtypes of common cancers are not yet included in the statistics collated by the AIHW and, as a result, estimates for the proportion of all cancer cases in Australia that are RLC are significantly underestimated. We should therefore add to the ways that our cancer data is collected and categorised, to ensure we truly understand the proportion of all cancers diagnosed in Australia that are rare, and how we can provide equitable support for people with rare cancers. A good example of how molecular type is incorporated into how we think about cancers is seen with the classification of gliomas.[66]

PERSONAL PERSPECTIVE

Working in the cancer centre and then becoming a patient

by Dr Srividya Iyer

In January 2020, I was accepted at the Melbourne Dental School to start my dental specialist training in Oral Medicine and so my husband, 2-year-old daughter and I moved to Melbourne. I was fit, vegetarian all my life, hardly drank, never smoked and had no genetic predisposition. Little did I know there was a major roadblock ahead of us that was going to change everything forever.

I started developing some right groin pain which would come and go but wasn't enough to stop what I was doing. Then, in the last week of August, I started experiencing an extreme bloating sensation. I put it down to changing my diet to dairy-free products, as I was keen to go vegan. But I felt my tops were tight and I was struggling to walk and climb stairs without puffing. My weight jumped from 61 kg to 68 kg within a week, which I thought was just my scales being dodgy. Of course, I asked my husband, and he said it was just a lack of exercise due to the pandemic and my love for ice-creams!

By the end of August, my husband insisted I go to the emergency department to get things checked – by then I looked like I was six months pregnant. I had some initial tests done and after a three-hour wait a junior doctor came to tell me my bloods were normal, and my urine sample had some blood. He examined my belly, and the right abdominal area had some tenderness. He asked if it was okay to get a senior doctor to examine me. The senior doctor said I may have IBS due to my recent change in diet and asked me to come back the next day for an ultrasound. Because of my clinical commitments I said no and instead pushed for a CT scan straight away.

Once my CT scan was completed, I was escorted to a separate room where the penny dropped – I was told there was a big mass on the liver and ovary, it is malignant and has spread into my abdomen. I was in denial saying I have had a pap smear and my gynaecological history has been totally clear as I had my daughter just two years ago.

I don't know what was worse – the diagnosis or hearing it alone with my husband at home. I was numb and gathered some courage to call my husband who thought I was calling him to say come and collect me. He just kept saying "no, that's not possible" and we both cried, the word 'malignant' kept echoing in my head.

That night, I was transferred to the Women's and greeted by the nurse who said something I still practice. She said to me, "well, you know it is going to be a tough time ahead, so you have two options: stay awake and think about it all night or take this sleeping tablet and get some sleep and prepare for what's ahead". I chose option 2.

When they woke me in the morning, I learned my diagnosis. It was ovarian cancer, it was not good, and I had a few months up my sleeve. I was lined up for paracentesis to drain all the fluid in my abdomen followed by a horrendous MRI. The waiting game to receive my staging depending upon my scanning was the most impatient I have ever felt.

I was still awaiting my husband to come and see me while all this was unfolding, due to COVID-19 restrictions. With whatever remaining courage I had, I called my sister who lives in the USA. She and I could not stop crying and I said to her, "what are we going to do and how are we going to tell our parents?"

The toughest part of my whole journey was telling my parents. They were in India and desperate to be by my side. They finally managed to get a flight to Sydney and, due to quarantine, arrived after my first cycle of chemotherapy.

My oncologist said to me, the first time I saw her, "we are going to get through this. It is bad but it could have been worse. So, let's get this done and I want to see you in the corridors as a professional working here at Peter MacCallum". Her calm demeanour really made me and my husband at ease.

I was prepared to have three rounds of chemotherapy, then a CT to see if the tumour had shrunk enough to operate. My primary tumour was 13cm on my right ovary and the rest were numerous small masses along with one on top of my liver. I got scalp cooling to reduce and limit my hair loss, however I went ahead and shaved my hair as I didn't care how I looked, it was just hair. I managed to continue exercising, working and my specialist training during my treatment and my work colleagues at dental oncology and dental school kept my hopes and spirits up.

After my third round of chemotherapy, my CT showed I'd had some shrinkage, but not enough, and would also need some liver resection. My heart sank and this was the only time I felt defeated. I was asked to prepare for a major surgery. The week before surgery I learned I'd had a great response – the lesion was limited to just my liver and omentum. I met the surgeon who has been amazing, along with lower GI surgeon who decided against laparoscopic approach and to open me up from sternum to my pubic bone. My surgery was on 13 November, a day before Diwali, a significant Indian festival and I still remember kissing my daughter and mum before leaving home and saying to myself, "my work here is not yet finished". I held onto my daughter's picture and my Ganesha idol while getting wheeled into the theatre.

My surgery lasted eight hours, and I regained consciousness to see all my family in the recovery area saying the surgery was successful. All the cancer was removed. I felt weak but determined to complete my chemotherapy, to be told that I was cancer-free with my CA 125 markers falling from 6200 to 21 at the end of five cycles.

I met a new oncologist who was filling in for my routine one and she recommended I get tested to see if my tumour had a HRD, to give me the best shot at beating this nasty disease. Testing would cost $5,000, and as the drug was not on the PBS in a frontline setting, it would also cost me $7,500 a month. I told her I was prepared to sell my house back in Perth to fund the medication.

Three weeks later I found out I was positive for the test and advised to contact Rare Cancers Australia to help generate the funds and raise awareness about this dreadful disease. My pride and being a private person made me first say no, but when my husband and oncologist asked me to look at the bigger picture of raising awareness, I decided to go public. Within four weeks we had managed to raise $200,000. I never imagined we would be able to raise this amount. I started my PARP inhibitor journey, which came with 16 months of nausea and fatigue. But I would advocate and hope that PARP inhibitors become available on the PBS as frontline treatment for all people diagnosed with ovarian cancer, regardless of their variant status, so more lives can be saved.

My journey so far has been tough and life changing. When I am treating cancer patients, I understand their fears and concerns. I don't just say that I know what they are going through, but I have been there and done that myself. This diagnosis has changed me but does not define me and I am not letting it decide how I lead my life. I am the best version of me; physically, mentally and emotionally. Cancer doesn't discriminate and can affect anyone, even fittest of the fit.

What I have learnt is to control the controllable and leave the rest to the power above. I continue to be in remission, and I hope for a cure to be able to see my beautiful daughter grow up, grow old with my husband and look after my parents. I want to tell everyone to advocate for yourself and listen to your body. Raising a child needs a village and I would say the same about cancer, my village is my rock and I have needed them all. I was able to work throughout my treatment, I managed to submit my Masters thesis, get on a plane and go to the outback as part of the Royal Flying Doctor Service and have almost finished my specialist training. I couldn't have done this without my family.

This is me. Vidya Iyer, an Oral Medicine Specialist in training, a mum, a wife, a daughter, a sister and an ovarian cancer survivor!

5 It’s time to realise the full potential of precision oncology

We recognise that in Australia we are fortunate to have world-leading cancer outcomes, particularly as a result of advances in common cancers. However, if we are to fully realise the potential of precision oncology and deliver equitable outcomes across all cancer types, we need to acknowledge that our current health system relies upon outdated models of cancer care delivery. This in turn creates barriers to equitable access to newer, more precise approaches. In recognising those barriers, we can make the necessary changes to revolutionise our healthcare system, so that it is fit for purpose and ready to deliver into the future.

To achieve our goal of timely and equitable access to precision oncology for all Australians diagnosed with cancer, RCA recommends government and key stakeholders act to:

1. **Progress a coordinated national genomics strategy**, leveraging existing Government commitments to Cancer Australia and Genomics Australia to:
   - ensure all people diagnosed with cancer have access to comprehensive and cost-effective genomic profiling as standard of care,
   - ensure people have access to matched targeted therapies, immunotherapies, cell and gene therapies, personalised cancer vaccines, and combination therapies, where there is identified clinical benefit, and
   - ensure that RLC cancers are defined as a priority population to deliver equitable care, experience and outcomes.

2. Ensure that the substantial Government research investment through the National Health and Medical Research Council and the Medical Research Future Fund adequately **prioritise research into genomic studies and precision oncology**, to ensure people with cancer – particularly RLC - can access precision oncology trials and translational genomic knowledge is furthered in Australia.

3 **Develop a new pathway in our Health Technology Assessments** that:

- assesses precision oncology companion diagnostics and therapies together,
- recognises limited clinical data that arise from small patient populations and encompasses broader value measures,
- accommodates multiple indication, genomic focussed applications to be assessed to expedite access for RLC patients.

4 **Direct AIHW to include data on molecular subtypes** and support the establishment of appropriate registries to adequately facilitate data collection.

For the past decade, RCA has been advocating for changes to our healthcare system that would provide the best possible person-centred care for all people diagnosed with cancer; care that truly meets their idiosyncratic needs. Thanks to the potential of personalised medicine, we now have the tools to make this a reality; it just remains up to us to work collaboratively and deliver it.

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