

Cell & Gene Therapies: Rising to the challenge



July 2021

About Evohealth

The delivery of healthcare is complex.
Our focus is not.

Better health for all Australians.

Executive summary

Cell and gene therapies (CGTs) are changing the way that care is delivered to patients around the world.

CGTs are not traditional medicines. Distinct to treatments and interventions that treat symptoms or pathologies of disease, CGTs frequently target the underlying cause (1, 2). In doing so, these therapies aim to 'fix the problem at its source' and provide durable, preventive or curative effects. CGTs are distinct from traditional medicines which are typically synthetic chemicals (2).

Whilst often discussed together, these therapies have different mechanisms of action. Cell therapies transfer live cells into a patient's body, while gene therapies introduce, replace or alter DNA within cells. Some therapies, in fact, can be BOTH cell and gene therapies.

“Cell and gene therapies can be generically described as medical [interventions] in which cells or genes represent the medicinal product” (22)

CGTs are not limited to a single disease or therapeutic area. They can treat not only inherited genetic disorders but also some cancers and viral infections. Many CGTs target rare diseases that have a high unmet need. These diseases often have limited or no treatment options, such as cystic fibrosis, some ocular and a range of neuromuscular conditions.

CGTs give hope, where no hope has existed before.

This White Paper examines how prepared the Australian health landscape is for the many CGTs that are expected to seek funding in the coming years. Importantly, we explore what society expects of Government to enable CGTs to address the urgent, unmet need of many Australians. Valuable oversight and advice has been provided to the authors by an expert advisory committee that included the voice of the patient, clinician, industry and academia (further details on page 10).

CGTs – what are the challenges?

The innovation that these therapies represent is indisputable and there is a significant opportunity to improve health outcomes for some of Australia's most vulnerable citizens. Yet we know that funding these innovations will test our health system.

It is important that CGTs are evaluated to ensure that the outcomes delivered are clinically sound and that they provide benefits to society which are commensurate with costs. The duty to ensure that citizens receive access to safe and effective health care lies with the Australian Government, operating within constraints of a finite health budget.

We have identified five key characteristics that cumulatively make CGT both unique and challenging to evaluate:

- CGTs often target small patient populations with severe unmet need;
- CGTs can be transformative and significantly change the course of the disease, but there are limited data on long-term outcomes;

- Early diagnosis and detection are often vital to achieve the best outcomes;
- CGTs are not specifically a product, device or a service and can be a combination thereof, commonly with complex manufacturing, delivery, supply chains and high cost of goods; and
- The discovery of and subsequent investment into CGTs represents an area of exponential growth.

With over 2,000 CGTs currently in trials, the issue of how best to evaluate these therapies will only become increasingly more critical for the Australian Government (12, 13).

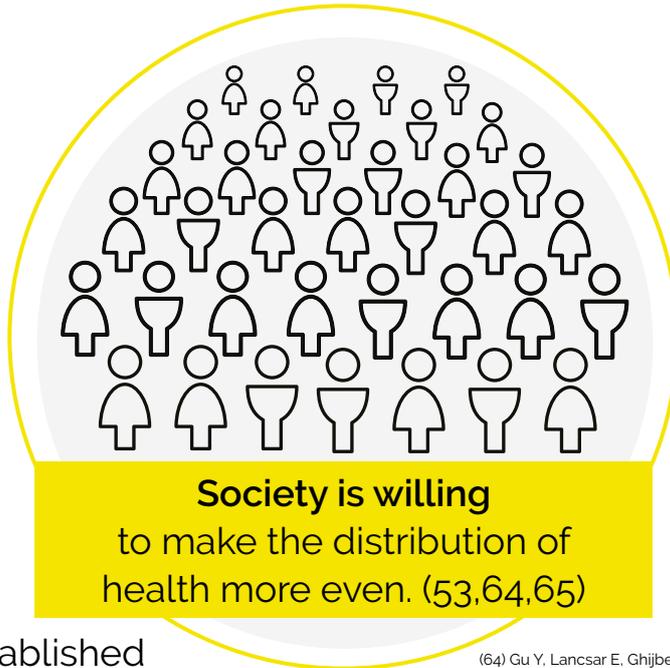
**The Australian Government
needs to act now.**

CGTs are testing the boundaries on a range of issues that have been around for a long time."
Australian Health Economist

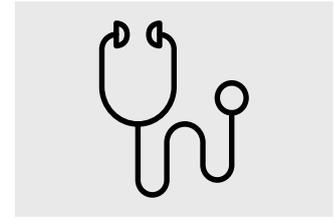
Some countries have already accepted the challenge. Of note, is the United Kingdom (UK) that has established the Cell and Gene Therapy Catapult to provide clinical, technical, regulatory and market access expertise for CGTs (4, 5).



CGTs are not traditional medicines



Society is willing to make the distribution of health more even. (53,64,65)



CGTs treat many diseases
cancer, viruses and rare inherited disorders



the UK has established a **"Cell and Gene Therapy Catapult"** (5)

(5) Catapult. Cell and Gene Therapy Catapult 2021. Available from: <https://ct.catapult.org.uk/>.

(53) Cookson R, Drummond M, Weatherly H. Explicit incorporation of equity considerations into economic evaluation of public health interventions. *Health Econ Pol'y & L.* 2009;4:236.

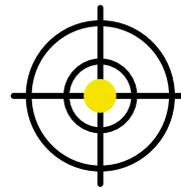
(64) Gu Y, Lancsar E, Ghijben P, Butler JR, Donaldson C. Attributes and weights in health care priority setting: a systematic review of what counts and to what extent. *Social Science & Medicine.* 2015;146:41-52.

(65) Chim L, Salkeld G, Kelly P, Lipworth W, Hughes DA, Stockler MR. Societal perspective on access to publicly subsidised medicines: a cross sectional survey of 3080 adults in Australia. *PLoS one.* 2017;12(3).

5,000

estimated inherited rare diseases (55)

(55) Department of Health. National Strategic Action Plan for Rare Disease. 2020.



CGTs target underlying causes and can treat, prevent or cure diseases (1)

(1) Salzman R, Cook F, Hunt T, Malech HL, Reilly P, Foss-Campbell B, et al. Addressing the Value of Gene Therapy and Enhancing Patient Access to Transformative Treatments. *Molecular Therapy.* 2018;26(12):2717-26.



2,000

2,000 current human clinical trials involving CGTs (12, 13).

(12) Department of Health. Inquiry into approval processes for new drugs and novel medical technologies in Australia Submission 15. In: Dea, editor.: Australian Government; 2020.

(13) Food U, Administration D. Statement from FDA Commissioner Scott Gottlieb, MD, and Peter Marks, MD: Ph. D., Director of the Center for Biologics Evaluation and Research on new ...; 2019.

80% **80 per cent of rare diseases are genetic in origin (20, 21)**

(20) Eichler HG, Pignatti F, SchwarzerDaum B, HidalgoSimon A, Eichler I, Arlett P, et al. Randomised controlled trials versus real world evidence: neither magic nor myth. *Clinical Pharmacology & Therapeutics.* 2020.

(21) Boat TF, Field MJ. Rare diseases and orphan products: Accelerating research and development. National Academies Press; 2011.

10-20 CGTs

the US FDA expect to be evaluating 10-20 CGTs per year by 2025 (12, 13).

(12) Department of Health. Inquiry into approval processes for new drugs and novel medical technologies in Australia Submission 15. In: Dea, editor.: Australian Government; 2020.

(13) Food U, Administration D. Statement from FDA Commissioner Scott Gottlieb, MD, and Peter Marks, MD: Ph. D., Director of the Center for Biologics Evaluation and Research on new ...; 2019.

\$500m allocated in the Medical Research Future fund to genomic research (102)



(102) O'Sullivan GM, Velickovic ZM, Keir MW, Macpherson JL, Rasko JEJ. Cell and gene therapy manufacturing capabilities in Australia and New Zealand. *Cytotherapy.* 2019;21(12):1258-73.



How does society expect Government to respond?

Rising to the challenge of CGTs is a deeper issue than providing access to new and exciting innovations. It lies at the very heart of our society.

We know through research, that society wants to make the distribution of health more even. That is, allowing patients with severe and debilitating conditions, as well as those experiencing significant unmet need, to access treatments to reduce inequality (16). In other words, society recognises that some people require more support than others. This is a core principle of social justice and something we see in everyday life; from progressive taxation to concession card discounts and out-of-pocket safety nets for people requiring greater levels of healthcare.

For the Government, making safe and effective CGTs available fulfills this expectation, that is, giving support where it is need the most. For example, CGTs often target rare diseases. Indeed, the majority of rare diseases (>80 per cent) are genetic in origin (20, 21). These patients carry a significantly higher disease burden, and an unmet clinical need (18, 19). By treating these conditions, CGTs will provide treatment options for the first time to many vulnerable Australians. This is what society expects.



Rising to the challenge

We argue that society wants to provide equitable access to care, including CGTs, to patients with a high unmet need. However, the current evaluation system in Australia is not currently able to consider health inequality. By comparison, the UK under the National Institute for Health and Care Excellence (NICE) has proposed changes to include incorporation of severity of disease and broader health inequalities into their evaluation methods (15). The Australian Government needs to do the same.

CGTs provide an important and urgent opportunity for our Government to address health inequity, consistent with what society expects. Rising to the challenge of evaluating and funding safe and effective CGTs, allows the Government to level the playing field for those Australians that need more support.

This White Paper argues that these innovative and life changing therapies urgently require a more adaptive approach so that equitable support can be realised. With thousands of candidate CGTs currently in trial, the time to act is now.

Summary of Recommendations

These recommendations will allow Australia to deliver on the promise of CGTs as a future of care for many Australians living with currently incurable cancers, viruses, and rare debilitating conditions.



Leverage recommendations from the National Strategic Action Plan for Rare Disease (which have been accepted by the Minister for Health in 2020).



Establish Office for Rare Diseases as a Portfolio Agency of Department of Health.



Develop incentives for CGTs to create opportunities for trials, manufacturing and commercial success in Australia.



Equality

Equity

We know that society is willing to pay more to make the distribution of health more even.



Establish a CGT expert advisory group to provide input and advice to the key evaluation bodies – the Therapeutic Goods Administration, Pharmaceutical Benefits Advisory Committee and Medical Services Advisory Committee.



Develop a national strategic approach to equitable and timely clinical care for CGTs via the National Health Reform Agreement framework.



The Minister for Health to establish a cross-functional working group including Departments of Health (both Federal and State/Territory), industry, patients and academics to consider current Health Technology Assessment processes for CGTs.



Enhance the role of horizon scanning via the Health Technology Reference Group, or equivalent.

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Disclaimer

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What are cell and gene therapies?

Cell and gene therapies can be generically described as medical procedures in which cells or genes represent the medicinal product" (22)

Genes are made up of DNA and, as well as containing our basic hereditary information, they contain 'instructions' that encodes everything from proteins that help us digest food to observable traits, such as eye colour (23). Our DNA is housed

within chromosomes that are found inside each of our cells (24). We have hundreds of different types of cells in our body including blood, skin and bone cells (Figure 1).

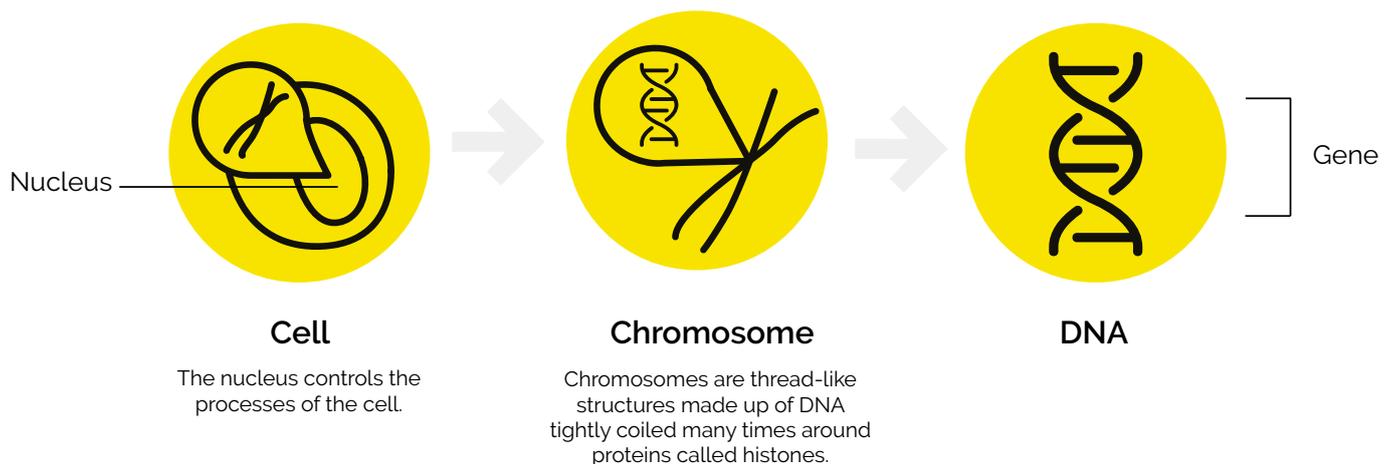


Figure 1 – What are cells and genes?

Although our cells and genes are the building blocks of human life, sometimes abnormalities within them can cause disease (24). By specifically targeting and correcting abnormal cells and genes, cell and gene therapies (CGTs) aim to prevent, cure or significantly change the course or progression of certain diseases.

CGTs are distinct to traditional medicines which are typically synthetic chemicals (2). Gene therapies can work in different ways. For example, gene replacement therapies can recognise a defective gene in a chromosome and 'cut it out' to effectively replace it with a functional gene.

Instead of replacing an entire gene, some of these therapies work by editing specific parts within genes (e.g. CRISPR/Cas9, see (25) for more details). Some gene therapies don't edit or replace DNA in the chromosome directly. For example, specific genes that express functional proteins might be delivered or 'introduced' into abnormal cells such that the cells can still generate functional protein but the chromosome itself remains unchanged (this can be thought of as 'extrachromosomal material'. For more details on gene therapies, see Mali (26) and Gonçalves and Paiva (23)).

Cell therapies involve the transfer of live cells into a patient's body. The cells may originate from the patient or even a donor (27). Some of the most commonly known examples of cell therapies are blood transfusions or bone marrow transplants.

In addition to being classified as distinct 'cell' or 'gene' therapies, some therapies can act as BOTH. For example, cells can be genetically modified before they are delivered to the patient, or cells

themselves can serve as vectors that carry genetic material into the body.

As a result, CGTs boast tremendous potential for treating inherited genetic disorders such as cystic fibrosis, sickle cell and a range of neuromuscular disorders; cancer and some viral infections (23, 28). CGTs are even being used as an alternative for surgical treatment (see Box-Cell therapies as an alternative to surgery).

CGTs and cancer

Cancer occurs when different types of cells grow and multiply in an uncontrolled way. Traditional cancer treatment might involve therapies, such as chemotherapy or radiation, which aim to kill these cancerous cells. Unfortunately, these treatments also affect healthy cells. By contrast, CGTs specifically target abnormalities in our cells or genes, and therefore ensure these healthy cells survive.

Chimeric antigen receptor therapy (CAR-T) treats patients with blood cancers (e.g., B-cell acute lymphoblastic leukaemia (ALL) or adult diffuse large B-cell lymphoma). In order to treat patients, T cells – a type of immune cell that normally targets and kills pathogen-infected cells and other abnormal cells – are removed from the patient and genetically modified to target the patient's specific cancer cells. These modified T-cells are then injected back into the patient where they

selectively identify and attack the cancer cells in the patient's body.

Some CAR-T have achieved remarkable remission rates in paediatric and adult patients with refractory or relapsed ALL and non-Hodgkin's lymphoma 2 (29). For relapsed ALL, which previously had an overall 5-year survival of 7 per cent with chemotherapy and stem cell transplantations, (30), CAR-T trials have seen a remission rates of 81 per cent at 3 months (i.e., no detectable leukaemia) (1, 29). Similarly, in relapsed or drug resistant cases of non-Hodgkin's lymphoma, 72 per cent of patients in trial achieve tumour size reduction or elimination and 51 per cent achieved complete remission 6 months after treatment (1). Prior to CAR-T treatment, the median overall survival with standard treatment was 6 months.

CGTs and inherited disorders

Many CGTs look to target inherited disorders and provide options for progressive conditions which previously had no, or limited, cost effective treatment options.

Gene therapies are designed to address the root cause of a range of genetic diseases known as monogenic diseases (31-33). Monogenic diseases are caused by a mutation in a single gene, or deletions (34, 35) and are therefore ideal candidates for targeted treatment. These inherited genetic conditions include cystic fibrosis, blood disorders, such as haemophilia, some ocular and a range of neuromuscular conditions. Two specific inherited diseases are discussed in detail below.

Metachromatic leukodystrophy (MLD) is a rare inherited and progressive disease (36). MLD is characterised by mutation in an enzyme (ARSA) and subsequent accumulation of fatty substances in the cells, particularly those in the nervous system. This build up eventually damages the white matter that protects nervous system cells and a loss of motor and cognitive function (36).

There are currently no effective treatments for this disease and, in most of the common form of MLD, late infantile form, the majority of children do not survive into adulthood. Aiming to restore function to the enzyme required to break down the fatty substances, a haemopoietic stem-cell

gene therapy has been developed which provides a functional copy of the DNA that encodes the functional ARSA enzyme (37).

With an estimated patient population of one in a million, lipoprotein lipase deficiency disease (LPLD) is another rare, inherited genetic disorder characterised by genetic mutations that cause deficiency in the enzyme lipoprotein lipase (38). The deficiency in this enzyme leads to issues with breaking down fat molecules that subsequently build up in the blood stream. This build-up of fat in the blood can lead to severe abdominal pain and potentially life-threatening pancreatitis (39). Up until recently, the main treatment for LPD was a low-fat diet (38). With the aim of correcting the genetic mutations causing lipoprotein lipase defects, gene therapy was developed which contains the 'correct' copy of the lipoprotein lipase enzyme (40).

Treating a range of critical and rare diseases,¹ CGTs are amongst the most important advances in science in recent years. By their very mechanism of action, CGTs are at the forefront of innovation. With innovation and change, comes challenges. However, before we delve into what those specific challenges are, we must at first examine, the current pathway to patient access in Australia.



Cell therapies as a potential alternative to surgery

Cartilage lesions in the knee increase risk of developing osteoporosis and require surgery, supported non-invasive care and at times, total knee replacements (41). In general, cartilage lesions do not heal. Cell-based therapies which contains autologous chondrocytes (healthy cells found in cartilage and derived from the individual) are currently being developed to potentially treat these lesions (42, 43).

1. In Europe, rare diseases are defined as diseases where less than one in 2,000 are affected. Australia does not have a legislated definition [55].

The current pathway to providing access to CGTs in Australia

Australia's universal healthcare system is a socialised system with responsibilities split between different tiers of Government (44).

Broadly speaking, the Federal Government is responsible directly for the funding of primary health, and also for inpatient public hospital care via payments made to States and Territory Governments. The delivery of services, in the hospital setting is the responsibility of States and Territories.

In addition to free inpatient public hospital care, all Australian citizens and permanent residents are entitled to free or subsidised out-of-hospital services, such as general practitioner care and prescription medicines.

Within this process, are two key steps in granting subsidised access to CGTs in Australia – regulation and reimbursement.

Regulation of CGTs

Regulation of CGTs falls under the remit of the Therapeutic Goods Administration (TGA). The role of the TGA is to assess therapeutic goods for safety, quality and efficacy. The TGA regulates medicines, medical devices, biologicals and blood.

In 2019, the TGA highlighted some of the challenges associated with CGTs, such as establishing a definition of gene therapies for

the purpose of regulation and understanding the long-term risks associated with genetic modification (45).

The TGA has commenced reviewing regulatory submissions of CGTs. Some therapies, such as CAR-T, have been evaluated by the TGA, listed and classified on the Australian Register of Therapeutic Goods (ARTG).

Reimbursement of CGTs

Once listed on the ARTG, CGTs can be assessed for clinical and cost-effectiveness, by either the Medical Services Advisory Committee (MSAC) or the Pharmaceutical Benefits Advisory Committee (PBAC) (46, 47). In general, the PBAC evaluates reimbursement of pharmaceuticals and MSAC covers healthcare services. This is referred to as Health Technology Assessment (HTA).

How a CGT is administered to a patient leads to different HTA pathways. For example, as with CAR-T, if genetic modification of patient cells happens outside of the body 'ex vivo' before being transferred back into the body, this is classified as a Class 4 biological (45). This distinction rendered CAR-T unsuitable for PBAC consideration. Conversely, if a gene product is directly

transferred into cells in a patient's body to make an 'in vivo' change, it is classified as a prescription medicine and able to be evaluated by PBAC (45).

The funding pathway from PBAC is relatively well-defined, PBAC recommendations accepted by the Minister for Health are listed on the Pharmaceutical Benefits Scheme (PBS) for Federal reimbursement. MSAC however has a broader remit and is less constrained by legislation. MSAC considers both items for listing on the Medicare Benefits Schedule (MBS) as well as conducting HTA for a range of broader treatments, interventions and diagnostics. The funding pathway following Ministerial acceptance of MSAC recommendation can include Federal schemes such as the MBS, National Blood Authority (NBA)

or nationally co-ordinated funding allocated to State and Territory hospitals, as is the case with CAR-T.

Irrespective of the pathway, the role of HTA is to determine value. This allows the Government

to make an informed funding decision. Some elements of how value is determined under HTA are discussed in the box – Determining value in Health Technology Assessments.

Determining value in Health Technology Assessments

The fundamental output from any given HTA process is to present the value of new interventions and technologies relative to a comparator. This value is generally presented as the incremental cost effectiveness ratio (ICER) and is used by payers to guide reimbursement decisions. Currently, this ratio considers clinical benefits, in terms of life-years and quality-adjusted life-years (QALYs) gained as well as 'relevant' healthcare costs (i.e., only costs related to the intervention are included (48)). Other costs, such as time spent by people undergoing the interventions, social services costs and productivity costs are not included (49,

50). In developing these measures, future clinical benefits and costs are discounted at a constant annual rate of 5 per cent (i.e., costs/outcomes accrued in the future are given less 'weight' than shorter term costs/outcomes) (14).

Under this framework, if an ICER is below an explicit or implicit willingness to pay threshold, it is deemed cost-effective (52). The processes used to develop this threshold operate by 'maximising health gain' such that health benefits (generally QALYs) are equally weighted irrespective of who receives the benefit or how the benefit is achieved (53).

The role of States and Territories

When a CGT includes an element of in-hospital care, there is a clear role for State and Territory Governments. In the case of CGTs, the framework is structured via the National Health Reform Agreement (NHRA – see box).

This agreement includes how funding for these therapies will be managed, along with involvement of one appointed State/Territory nominee, representing all jurisdictions, who liaises with MSAC and PBAC chairs to help facilitate and agree the HTA pathway (i.e., whether it will be evaluated through MSAC or PBAC).

National Health Reform Agreement 2020-2025

The 2020 – 2025 National Health Reform Agreement (NHRA) Addendum is an agreement between the States and Territories and the Commonwealth regarding the operation and funding of public hospitals (3). In terms of CGTs, these funding arrangements involve a 50/50 contribution from the Federal government and

the States and Territories for funding for high cost therapies, such as CGTs for patients treated as an inpatient in public hospitals (10, 11). It is anticipated that the high cost, inpatient therapies recommended by MSAC will also be funded via the arrangements within the NHRA.

CGTs are challenging our health system

CGTs are arguably amongst the most innovative therapies made available in recent times. But they are challenging how healthcare is delivered.

CGTs are unlike traditional medicines; in fact, they are not specifically a product, device or service and can be a combination thereof. They can be complex to manufacture with specialized therapeutic delivery and supply chain infrastructure. Patients are often at the centre of the CGT manufacturing process. In

some instances, CGTs are individualised to each patient. Coupled with small patient populations and small-scale manufacturing, CGTs are typically associated with a high cost of goods (54).

We have identified a range of attributes that cumulatively make CGTs unique. It is the combination of these attributes that are challenging health systems in Australia and around the world.

Small patient populations with high unmet need

There are an estimated two million Australians living with a rare disease (55). On average, individuals living with rare diseases represent smaller patient populations and experience high disease burden and unmet needs (18, 19). With the majority of rare diseases (>80 per cent) being genetic in origin, CGTs are expected to target these patient populations (20, 21). Against the backdrop of scarce treatment options, providing transformative treatments for patients with severe, progressive, debilitating or fatal conditions – particularly those that preclude individuals from social and economic participation – CGTs are poised to give much needed treatment options for patients, carers and families.

It is often difficult to generate evidence for CGTs from very small patient populations, or for populations with conditions that have limited, or no, effective treatment options available (56).² Randomised controlled trials are not always possible or feasible for CGTs. Indeed, with some treatments derived from patients themselves, CGTs may be individualised for each patient (20). To this end, evidence relies more heavily on adaptive clinical trials, 'within patient' disease trends, observational studies using case-control, single-arm trials, prospective cohort, or natural history designs (20).³

Transforming the disease trajectory

Distinct to treatments and interventions that aim to treat symptoms or pathologies of diseases, CGTs frequently target underlying causes of disease (1, 2). In doing this, these therapies aim to "fix the problem at its source" and provide durable, preventive or curative effects (2). However, although CGTs have the potential

to bring these benefits to patients, with these products in their infancy, there are limited data on long-term outcomes. In particular, when it comes to delivering permanent changes to the genome, there is significant uncertainty around intergenerational effects.

2. Many CGTs target rare conditions. As patients enrol in trials, it reduces the overall pool of patients available for other trials.

3. Registries and data collection is particularly important for developing the evidence base and, particularly for collecting real world evidence for pay-for-performance like contracts.

Limited data on long-term outcomes

The limited data available on long-term outcomes is particularly important for high cost CGTs. To address this uncertainty, a range of solutions reliant on data collection are utilised. These are often attached to proposed models of reimbursement such as, performance-based pricing and so-called value-based-contracts (57). Under these schemes value could be captured by performance against specified outcome measures within pre-specified time frames. However, in order to achieve these models of remuneration, data capture requiring substantial administration and infrastructure (e.g. registries) will be required.

There is currently no nationally consistent approach or framework to the management of patient registries in Australia, with some data held at hospital or State/Territory level, including variation in use of disparate electronic medical records. Some are also managed by patient support and advocacy groups themselves.

Likewise, payers across Europe and the United States (US) have indicated that they are willing to engage in value-based-contracts for high-cost innovation but remain concerned about the administrative burden and the paucity of evidence on long-term outcomes (57, 58).

Early diagnosis

Often, early diagnosis is vital to achieving the best outcomes for patients. With many CGTs targeting patients with progressive conditions, CGTs will need to be administered at the earliest possible stage to deliver the greatest benefits and

therefore the greatest value (59). As a result, there is a need for parallel patient and reproductive carrier screening programs with complementary genetic counselling services provided to affected patients and their immediate family.

CGT pipeline

Investment in CGT development represents an area of exponential growth. Horizon scanning performed by the European Medicines Agency (EMA) and the US Food and Drugs Administration (FDA) suggests that the number of CGTs coming to market will accelerate over the coming decade (20). There are more than 2,000 human clinical trials involving CGTs reported worldwide and the FDA has projected that by 2025, they will be

appraising 1020 CGT products per year (12, 13).

However, the road to funding CGTs is not easy. Although they can pose substantial clinical benefits, there remain important access implications for patients. As of 2018, of the 13 CGTs, that had received market authorisation in Europe, four have been withdrawn due to commercial and funding issues (60).

Summary

In summary, CGTs are unique.

They differ from traditional medicines in five key domains:



CGTs often target small patient populations with inherited disorders or severe unmet need.



CGTs can be transformative and significantly change the course of the disease, but there are limited data on the long-term outcomes.



Early diagnosis and detection are often vital to achieve the best outcomes.



CGTs are not specifically a product, device or a service and can be a combination thereof, commonly with complex manufacturing, delivery, supply chains and high cost of goods.



The discovery of and subsequent investment into CGTs represents an area of exponential growth.



CGTs are testing the boundaries on a range of issues that have been around for a long time."

Australian Health Economist

CGTs give hope to patients, where it did not exist before. But they are challenging the status quo of our system. Specifically, the five characteristics, as identified, are testing not only healthcare delivery, but how health technologies are evaluated. Governments will need to make informed decisions so that safe and effective CGTs can be made available to patients urgently in need.

How they respond is critical.



CGTs and ethical considerations

Whilst the focus of this report is on how Government can provide patient access to safe and effective CGTs, ethical considerations alone warrant careful examination.

CGTs raise important ethical considerations. For example, should CGTs modify the human genome, they can bring about permanent and heritable effects. Currently, the extent to which such editing may lead to off-target (e.g., preventing one disease may confer susceptibility to another) and uneven distribution of effects (i.e., some cells with edited DNA others without) are largely unknown (61, 62). Currently, no country has decided that heritable human genome editing is permissible, and the International Commission on the Clinical Use of Human Germline Genome Editing has stated that should initial clinical uses be considered, they should be limited to severe, single gene diseases, such as cystic fibrosis and sickle cell anaemia (63).

There are other considerations that need to be considered beyond the potential for genome editing. With some treatments individualised to each patient, there are difficulties in evaluating pre-clinical research and extrapolation of patient-specific results to predict broader cohort risks and benefits.

“ the personalised nature of these therapies places them outside the traditional paradigms of risk–benefit assessment” (22).

Extensive public deliberation, including consultation with bioethicists and researchers, will be vital to help inform what interventions should and should not be acceptable.

Responding to the challenge

Australia has an enviable healthcare system.

Providing Australians with universal access to innovative, safe and effective therapies is a critical component. Effective evaluation, including HTA, is the mechanism that ensures this is able to occur.

Today, the unique nature and innovation represented by CGTs is driving change to HTA systems around the world. The United Kingdom (UK) has established the Cell and Gene Therapy Catapult to support the Government over the coming years in understanding how best to respond to these challenges and integrate CGTs into their health system. See box – Cell and gene catapult – United Kingdom.

This White Paper considers how the Australian Government can evolve HTA to allow effective and efficient evaluation of CGTs. Our analysis is

framed against the five key attributes of CGTs identified earlier and begins with a discussion exploring equitable access from the perspective of society. We have also highlighted several areas of opportunity throughout the discussion.

We acknowledge that over time, HTA in Australia has adapted to ensure that new therapies are able to be critically considered and funded, where appropriate. One specific example is the enhanced and formal role of patient input into the submission process. This, along with an increase in the number of some specialty types on the PBAC, such as oncology and haematology, appointed by the Minister of Health over recent years, demonstrates consistent evolution in process.

Cell and gene catapult – United Kingdom

The UK Government has funded the Cell and Gene Therapy Catapult to provide clinical, technical, regulatory, and market access expertise for CGTs (4, 5). This body develops infrastructure that supports industry and patients in accessing CGTs. One key outcome recently developed by the Catapult is the development of a framework for reimbursing CGTs through outcomes based funding. They have also developed digital infrastructure which integrates with existing electronic medical record systems to record and compile the relevant outcomes to facilitate CGT reimbursement (4).



KEY OPPORTUNITY → Continue the evolution of Government processes, such as HTA, by including relevant experience that captures the diversity of new and innovative therapies, including CGTs.

What does society expect?

CGTs often treat patient groups that have inadequate treatment options, that is, there is a high unmet clinical need. It is reasonable to accept with so great a need that these patients, their carers and families would place a high value on accessing care. The larger question is however, how do we expect society, and ultimately Government, to value the impact of these innovations, relative to other patients, conditions and priorities?

Research has shown that society is willing to pay more for interventions that make the distribution of health more even. That is, those therapies and treatments that reduce inequality in health (16). We know that society is willing to give greater weight to therapies benefiting patients with severe and debilitating conditions, as well as those experiencing significant unmet need (53, 64, 65).

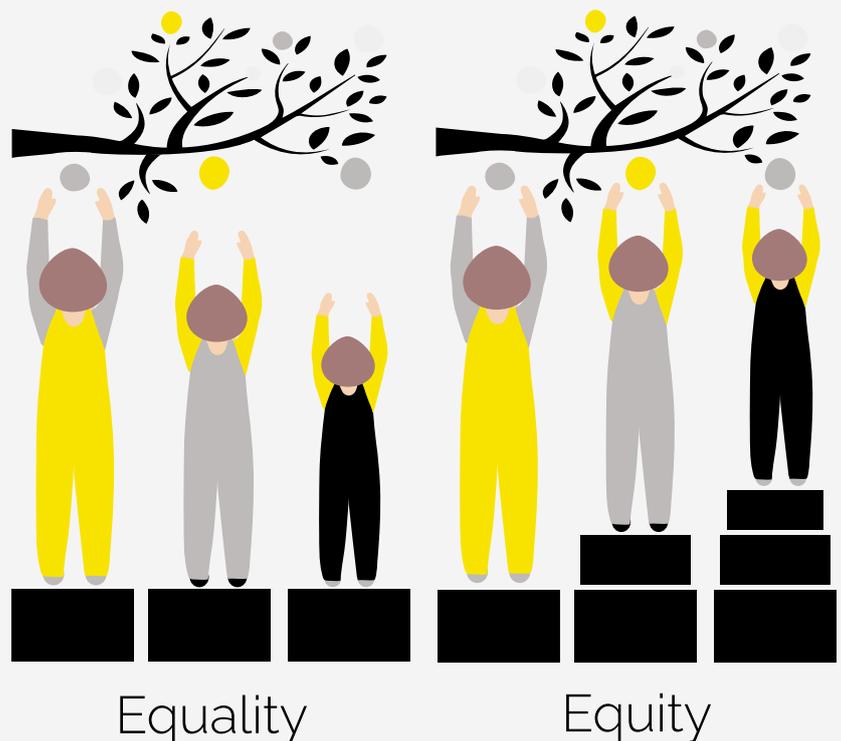
Equity vs equality

Firstly, we need to understand that equity and equality are two important but distinct concepts.

Providing equitable access to healthcare is crucial to achieve the greatest benefits in patient populations with the most need.

It is well understood that there are health inequalities in our society.

As a society, we are willing to trade off improvements in total health, to make the distribution of health more even. We recognise that some groups in our society might require more support than others. This is a core principle of social justice and something we see in everyday life; from progressive taxation, through to concession card discounts and out-of-pocket cost safety nets for people requiring significant healthcare interventions (e.g. with multiple morbidities).



We know that society is willing to pay more to make the distribution of health more even.

Equity in Australia's HTA

Australia's current HTA processes employ a utility maximisation approach⁴ which, by design, does not explicitly consider health inequalities – a QALY is a QALY irrespective of to whom it accrues (68). Refer to Box – Determining Value in Health Technology Assessments for definition of a QALY. Although generally, stated preferences of decision makers are that they do consider equity, revealed preferences do not always reflect this (69). This is perhaps unexpected given that the current HTA processes do not apply systematic weightings, for example specific inequality or severity. A recent analysis of 245 appraised interventions considered for public reimbursement in Australia, showed that more preventive interventions (e.g. vaccinations and diagnostics) generally fared worse⁵ than interventions for lifestyle related diseases and hospital inpatient treatments (70). A similar analysis of past PBAC funding decisions found that availability of other treatments was not a significant predictor for likelihood of reimbursement (69). Conversely, and more consistent with societal expectations, the same

study found that decision makers were more likely to make positive recommendations when considering more severe diseases (69).⁶

This research indicates that while there are not explicit thresholds or weighting mechanisms for specific populations in HTA, it does appear that, to an extent, context-specific approaches are being considered in decision-making processes.⁷ These studies suggest that there is an opportunity to employ more systematic approaches to considering equity in the traditional reimbursement processes:

By comparison, the United Kingdom, under NICE has proposed changes to include incorporation of severity of disease and broader health inequalities into their evaluation methods (15). NICE will consider the inclusion of "severity of disease" and "health equality" modifiers (i.e., QALYs could be weighted) (15). Definition and development of the modifiers is currently underway.

In Australia's current state of HTA, a QALY is a QALY irrespective of to whom it accrues" (76)

4. This approach assumes that societal wellbeing and welfare, as a whole, is the summation of individual utilities or preferences. This approach works to 'maximise' the average total population health regardless of to whom the health accrues. Numerous empirical research has demonstrated that individual preferences deviate from societal preferences [66,67].

5. Performance here was considered through the likelihood of receiving public funding and also the final willingness to pay threshold. That is, interventions with a lower willingness to pay threshold were deemed to have performed 'worse'.

6. Severity was generally based on baseline health-related quality of life and expected survival.

7. Here, 'context' refers to severity of the condition, availability of other treatments and ethical considerations [69].

Capturing the cost of care

In addition to equity, it is important to understand how the costs and benefits of diseases treated by CGTs are considered. Aside from the significant healthcare costs, those living with rare and debilitating conditions can experience substantial and lifelong social, emotional, psychological, and financial costs (71). These costs are shared by not only the individual with the condition but their families, carers and friends. Beyond Government costs for social care and support payments (e.g. disability support payments), there are immeasurable costs associated with

these conditions that matter to society. For example, reduced individual, and carer, social and economic participation (72). Moreover, families and carers of individuals with severe conditions consistently experience poorer health-related quality-of-life (73-75).

In Australia only "relevant" healthcare costs and benefits are included in HTA for all submissions, including CGTs. Including other costs, such as productivity was explicitly addressed in response to a previous PBAC submission:

"Including productivity in economic evaluations raises important equity issues as it implies interventions that improve the health of people in the workforce (or those who earn more) are of a higher value than other interventions (76)."

This position is valid if we consider that Australia has a single willingness to pay threshold across all groups. However, we know society is interested in reducing health inequalities and subsequently willing to provide more support for some populations over others. For example, populations which have previously been disadvantaged, such as those from lower socioeconomic backgrounds, people living with a disability and patients with high unmet clinical need. It is therefore reasonable to suggest that society is willing to place a higher value on interventions for some populations over others, specifically those requiring more support.

To this end, inclusion of all costs and benefits may be appropriate if we consider the patient who is receiving the benefit. Under such a framework, we could employ an explicit weighting methodology which specifies a lower willingness to pay threshold for productivity gains that accrue to those already in good enough health to work relative to those who are unable to work due to their condition.⁸

“the [HTA] process does not feature a means of systematically assessing how a technology may be of greater or lesser value in light of factors that are not captured by standard measures of cost effectiveness, but which are nonetheless important, particularly to the Australian community.” (78)

8. It is possible that domains that matter to society are, to an extent, captured through eliciting QALYs and thus including other societal costs may be "double counting". However, at least in terms of productivity, recent research has shown that "compensation for lost income failed to sufficiently improve utility scores... [and] the impact of double counting is negligible [77]."

Other costs

The extent to which costs beyond “relevant” healthcare costs are included varies across different HTA bodies globally. In the UK, NICE considers all costs that would otherwise have been paid for by the National Health Services (NHS) or Personal Social Services (PSS), including healthcare and social care services, as well as other public sector agencies (as deemed appropriate) (79). Through NICE’s Collaborating Centre for Social Care’s (NCCSC’s) economist and the Guidance Development Groups (GDG), NICE also considers interventions that free up resources that can be re-invested in other public sector social care (79). Further, while NICE does not consider productivity explicitly, they do consider the cost of informal caregiving (separately) if this care might otherwise have been provided by the NHS or PSS (80). All healthcare resources outside

of the NHS/PSS including productivity costs and carer’s costs can also be included in sensitivity analyses.

In France, the National Authority for Health has a broader perspective for costs in the base case analysis. These include direct healthcare costs as well as “transport, organisation of a health care program, time spent by people undergoing the interventions, and time spent by their care givers, as well as costs related to the treated disease during the added life-years” (81). The US Panel on Cost-effectiveness in Health and Medicine commends that all costs, both related and unrelated to the intervention, should be included in CEA (48). The Netherlands, Spain and Germany also require the inclusion of productivity losses in their base case analysis for HTA (81, 82).

Willing to pay more

The HTA bodies in Sweden and the UK apply higher willingness to pay thresholds for severe conditions and very rare diseases, respectively (83-85). For some conditions, there are even different thresholds and separately earmarked funding. For example, the UK Department of Health also implemented the Cancer Drugs Fund which allowed for higher thresholds for cancer drugs that would otherwise have been rejected by UK’s HTA body NICE⁹ (84).

From 2016, the Cancer Drugs Fund has become a part of NICE and if there is some uncertainty around the cost-effectiveness, NICE recommends the drug to inclusion within the Cancer Drugs Fund. After 2 years, and collection of more real-world data, NICE then re-assesses the drug. CAR-T therapies have been approved by NICE under the Cancer Drugs Fund. Similarly, in 2014, Scotland established a £40 million “New Medicines Fund” to provide access to non-NHS listed drugs for patients with rare conditions. This fund was increased to £90 million in 2017 (87).

“As health technologies advance, so too do methods of evaluation.” (15)

Ultimately, under a ‘one size fits all’ utility maximisation approach and limiting the payer perspective to direct and relevant healthcare costs, current HTA processes in Australia are unlikely to fully capture the impact of CGTs

on health equity nor the broader benefits and costs (49, 50). The net result is that this is out of alignment with how society expects a Government to respond to rare and debilitating diseases.



KEY OPPORTUNITY →

Adapt HTA processes so that they align with societal expectations.

9. In the US, the average willingness to pay threshold for cancer drugs is also generally larger than for other drugs [86].

Valuing future benefits

In targeting underlying causes, CGTs aim to deliver long-term benefits to patients (2). However, with many of these products in their infancy, there are limited data around the long-term outcomes. In particular, as is the case with CAR-T, some CGTs have 'one-off' administration and incur clinical benefits well into the future. In economics this is referred to as the accrual of benefits.

Discounting

The potential for long-term benefits and, in some instances, the large gap between intervention delivery and accrual of benefits has important implications for CGTs in current HTA processes. These characteristics are particularly important in another component of HTA – discounting. Discounting adjusts future values to the current

and is widely used in economic evaluation. While, to some extent we adjust for future outcomes because we are less certain about them, discounting is also applied under the philosophy that people would prefer to receive benefits or goods now but pay for them later (15, 88).



The higher the discount rate, the less important future costs and benefits are" (14)

With a constant annual discount rate of 5 per cent specified for both costs and outcomes, relative to similar countries, Australia's HTA agencies have comparatively one of the highest discount rates in

the world (14) – see Box – How do some countries adjust for future value?¹⁰ As a result, in Australia, CGTs that deliver their benefits over the long-term will be deemed less cost-effective (14).



KEY OPPORTUNITY → Evolve discount rates to reflect preferences of Australian society, with particular consideration to those interventions which deliver most of their benefits in the long-term.

10. This analysis presents information reported for base case HTA. Many countries allow for lower or differential discounting in sensitivity analyses.

How do other countries adjust for future value?

The Netherlands, Poland and Belgium specify differential discounting in their HTA processes such that health gains, or effects, have lower discount rates than costs (6, 7). All of these countries have lower discount rates for effects than Australia and have different justifications. Belgium, justifies this differential discounting (1.5 per cent for effects) to avoid penalising interventions that deliver most of their benefits in the future (8, 9). The Netherlands apply a 1.5 per cent for effects noting that the value of health has increased over time (9). New Zealand's 3.5 per cent discount rate for both costs and effects is based off actual social rates of time preferences (from the long-term, government bond rate) (9). The basis for Australia's 5 per cent discount rate remains unknown and has not changed since 1995 (14).

Although they traditionally use a 3.5 per cent discount rate for costs and effects, the UK's HTA agency NICE applies reduced discount rates in specific circumstances where long-term benefits (>30 years) are anticipated (14, 15). Recently, this was the case for a paediatric oncology drug whereby NICE decided to apply differential discounting under the proviso that "treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years)." Specifically, NICE stated that health benefits after 30 years should be valued at 1.5 per cent per annum provided the benefit was "curative and substantial" (17). In their current methods review, NICE has also acknowledged that "there is also a case to change how NICE values costs and health effects for health technologies in the future (through discounting)" (15). Finally, the World Health Organisation (WHO) maintains that differential discounting and the use of non-constant discount rates should be applied when evaluating effects over long-time scales (7).

Early diagnosis and detection

Given CGTs frequently target genetic, progressive conditions, early screening and diagnosis is vital in order to fully realise the potential long-term benefits (89). CGTs require additional supporting infrastructure and workforce, such as screening programs and genetic counselling for patients and affected family members.

Standard Australian newborn screening covers only a fraction of the estimated 5,000 inherited rare diseases. In fact, diagnosis or screening may not even be possible for many genetic conditions (55). Recently, MSAC recommended reproductive carrier screening for genetic conditions SMA, fragile X syndrome and cystic fibrosis to be funded under the MBS (90). This is a promising step to enable early diagnosis for

these conditions, including among asymptomatic parents with no family history (91). In addition to this reproductive screening, some targeted screening occurs in Australia as the result of individual projects and funding.

Two such examples include MacKenzie's Mission and screening of Prada-Willi and Angelman Syndromes. MacKenzie's Mission, the first project to be funded through the Australian Genomics Health Future's Mission, provides screening for couples to assess whether they are carriers for over 700 recessive and X-linked genetic conditions (92). The project began in Victoria, Western Australia and New South Wales and is now being expanded nationally, with couples being recruited since early 2020.



KEY OPPORTUNITY → Enhance opportunities for early diagnosis, detection and support to improve outcomes for patients and their families.

Co-ordination of patient care

Some CGTs have complex patient delivery protocols. As is the case with CAR-T, the patient and their blood products are at the centre of the manufacturing process. This, by its very nature, creates the need to develop complex and expensive logistics and supply chain networks.

It also will result in only a handful, or in some instances, only one, centre administering these treatments – a Centre of Excellence. In a federated health system, such as Australia, this creates complexities of funding as patients will need to travel between states for treatment. Whilst the NHRA has, in some way, gone to addressing how CGTs will be funded for hospital inpatients, some challenges remain, such as ongoing and sustainable budget allocation at both Federal and State/Territory level.

Coordination of care across Australia's federated system is as follows – the Minister of Health announces that they have accepted the MSAC recommendation of a CGT, the States and Territories will then be required to fund half of the expenditure. The State/Territory contribution will likely be unbudgeted at the time of the announcement. While the PBS and MBS have uncapped budget appropriations, State and Territory health budgets do not.

This could create delays in patient access while some jurisdictions process the request through the normal budget channels.

It is also unclear from the newly negotiated NHRA how cross-border patient funding will work. With small patient populations, it is likely that some CGTs delivered in one hospital will treat all of the patients in Australia. This then leaves that State/Territory with the administrative burden of seeking payment.

In addition to funding, there is also a need for other elements of patient delivery to be prepared such as reimbursement codes and nationally consistent referral, treatment and follow-up pathways. This includes other organisations, such as the Independent Hospital Pricing Authority (IHPA) to develop appropriate reimbursement codes. Again, it is unclear who is coordinating all of these elements. A lack of coordination can only result in further delay to access for patients, at a time of critical need.

Ultimately, the complexity of delivery of some CGTs requires coordination of many elements of Australia's health system, so that the time from the Minister's announcement to patient access is reduced. (Figure 2)

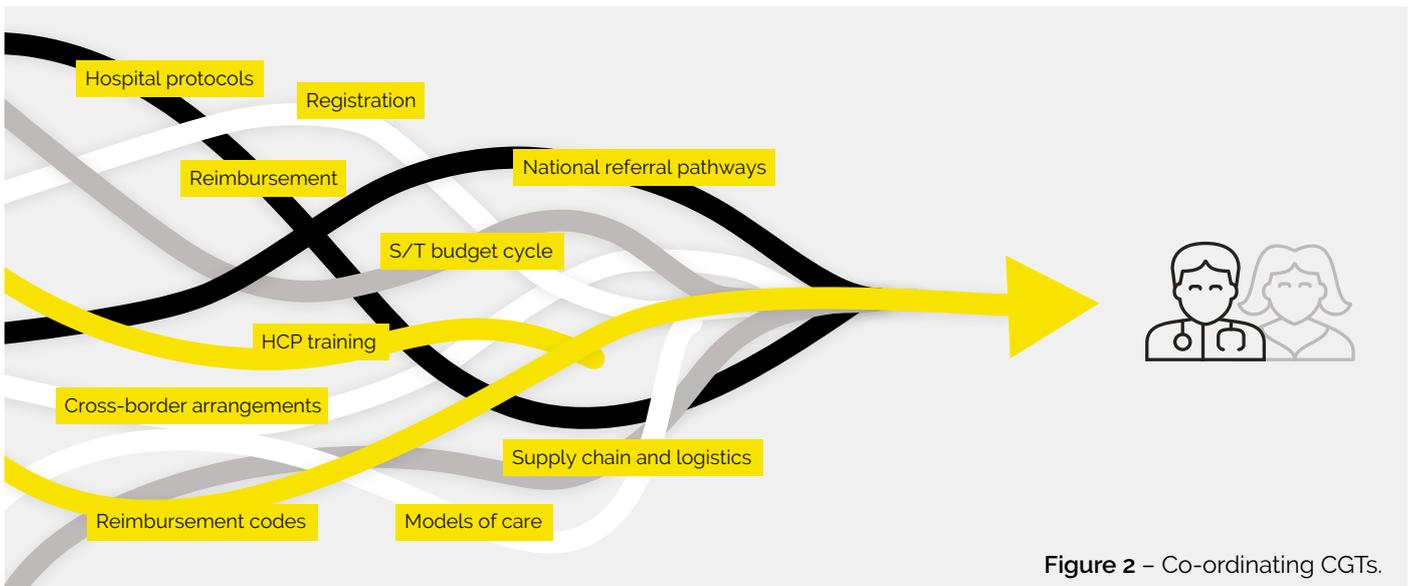


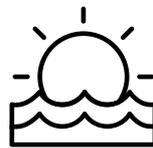
Figure 2 – Co-ordinating CGTs.



KEY OPPORTUNITY → Enhance national coordination of CGT implementation to reduce time from Ministerial decision to patient access.

CGT pipeline

As of 2020, there were 641 cell and 536 gene developers worldwide working on CGTs, with many being in the clinical stage of development (93).



How are other countries responding?

Many countries have established working groups to prepare and facilitate access and integration of CGTs into their healthcare system. In the UK, NICE is undergoing multiple methods reviews and have established the Accelerated Access Collaborative (AAC) and the CGT Catapult. The AAC performs the horizon scanning for the NHS and prepares for the integration of new interventions into their healthcare system, well ahead of product launch. The "Cell and Gene Therapy Catapult provides clinical, technical, regulatory, and market access expertise for CGTs" (4).

In America, the Institute for Clinical and Economic Review is developing methods to evaluate so called short-term and transformative therapies, with direct references to CGTs. Health Canada does not currently have specific guidelines or regulations pertaining to gene therapy products (94). However, they have recently established a Cell Therapy Stakeholder Group that engages in bilateral dialogue with Health Canada to address regulatory policy gaps surrounding cell therapies in Canada and propose solutions (94). Health Canada also participates in the Advanced Therapy Medicinal Product Cluster Meetings and the International Pharmaceutical Regulators' Forum for the Cell Therapy Working Group and the Gene Therapy Working Group (95).

Horizon scanning in Australia

Previously, the Australian Health Ministers' Advisory Council (AHMAC) provided advice and support to the Council of Australian Governments (COAG) Health Council regarding coordination of health services and future planning. The Health Technology Reference Group (previously known as HealthPACT), sat underneath AHMAC, performing the role of horizon scanning of new and emerging technologies. Their most recent report was published in 2017.

In 2020, the Federal Government established the National Cabinet, and ceased the COAG framework for intergovernmental cooperation. Subsequently, a review of the former councils and forums sitting under COAG was announced to be undertaken by Peter Conran. The review has recommended the rationalising of groups under COAG (96). At this stage, it is unclear how the National Cabinet will operate.

What is clear however, is that the role of horizon scanning will need to be re-established to prepare Australia's health infrastructure for the hundreds of CGTs currently in development and rapidly approaching commercialisation. This will allow Australia to prepare for consideration of appropriate care for those patients most at need and how best evaluation needs to be adapted to consider the innovation that these therapies present.



KEY OPPORTUNITY → Enhance horizon scanning of new and innovative therapies, and identification of priority patient populations, to allow adaptation of regulatory, reimbursement and clinical frameworks.

Recognising innovation

Some countries overseas, to varying degrees, have worked to include innovation in their approach to evaluation.

In addition to their role in Horizon Scanning, the UK's AAC expedites access of designated "innovative" interventions to patients (97). In this sense, interventions, whether they are drugs, diagnostics or CGTs, are marked for the AAC if they are deemed "ground-breaking" within a national priority therapeutic/research area.

Similarly, in Europe, the European Medicines Agency (EMA) has developed "PRIME" to support

innovations that specifically target serious diseases with high unmet medical need, with the goal to provide "enhanced interaction and early dialogue with developers of promising medicines, to optimise development plans and speed up evaluation so these medicines can reach patients earlier" (98, 99). Under this scheme, prioritised interventions undergo an expedited assessment process which takes 150 days rather than 210 (84, 98).

"In the ideal scenario, industry would work directly with horizon scanning bodies to ensure that agencies were across the pipeline and could be better prepared to integrate upcoming technologies into the healthcare system." – **State Government Health stakeholder**

Funding CGTs

Funding the significant pipeline of CGTs promises to have a major impact on Australia's health budget, should many of them be deemed safe, efficacious and cost-effective. In light of the current fiscal environment, it is unlikely that healthcare systems will be able to afford all these innovations, irrespective of their effectiveness (100). Novel reimbursement models and structural retransformation will be required to make CGTs affordable for the healthcare system and, most importantly, available for patients (101). With blockbusters being replaced by the "niche busters", regulatory bodies around the world need to adapt processes and policy to prepare for the brave new world of precision medicine.

Whilst there has recently been significant government investment into research and development (R & D), as well as infrastructure pertaining to the development of CGTs in Australia, there is currently no funding allocated at the other end of development life cycle, patient access. As noted earlier, a mechanism for providing access across Federal and State/Territory systems is included in the NHRA, without adequate budget line allocation.

In 2018, the Australian government announced \$1.3 billion in the National Health and Medical Industry Growth Plan with the overarching aim

to develop capability in genomics and precision medicine (102). Within the Medical Technology and Pharmaceutical Sector, a key area of planned growth is within genomics and precision medicine, with \$500 million being promised over 10 years (103). The recently developed Medical Research Future Fund (MRFF) has also earmarked approximately \$500 million to be invested in genomic research over the next 10 years under the Genomics Health Futures Mission (104) with a key focus on translating research into clinical trials. Similar funding has also been provided through the Stem Cell Therapies Mission and Therapeutic Innovation Australia (102).

While the Genomics Health Futures Mission states that some funding will be allocated to embedding gene therapy into policy, as of yet no projects surrounding this specific issue have been funded. Their website indicates that "[integrating] genomics into health policy" will be considered in financial year 2025, with the majority of priority funding over the next five years being dedicated to early phase development and implementation research (105).

In essence, the funding in Australia is currently directed at R & D and early-stage commercialisation, not patient access.



KEY OPPORTUNITY → Enable broader investment in CGT in Australia, including providing earlier access to patients.

The opportunity to improve equity of access to CGTs



Consistent with the principles of social justice, Australian society understands that some of our citizens need more support than others. This report argues that many patients who will need to access innovative CGTs now and in the coming years are those citizens.

By their very nature, CGTs present challenges to our current health system. This report has highlighted that these challenges lie in the unique characteristics of CGTs, specifically that:

- CGTs often target small patient populations with severe unmet need;
- CGTs can be transformative and significantly change the course of the disease, but there is limited data on long-term outcomes;
- Early diagnosis and detection is often vital to achieve the best outcomes;
- CGTs are not specifically a product, device or a service and can be a combination thereof, commonly with complex manufacturing, delivery, supply chains and high cost of goods; and
- The discovery of and subsequent investment into CGTs represents an area of exponential growth.

It is clear that these innovative and life changing therapies urgently require a more adaptive approach so that the equitable support that Australian society expect the Government to deliver can be realised. With thousands of candidate CGTs currently in trial, the time to act is now.

The opportunity that lies before the Australian Government is to embrace the key opportunities and potential that CGTs represent, so that these Australians are able to enjoy a quality of life that the rest of us enjoy.

Summary of Recommendations

To embrace this potential and fulfil the expectation of society we have developed seven key recommendations.

These recommendations will allow Australia to deliver on the promise of CGTs as a future of care for many Australians living with currently incurable cancers, viruses, and rare debilitating conditions.



Leverage recommendations from the National Strategic Action Plan for Rare Disease (which have been accepted by the Minister for Health in 2020).



Establish Office for Rare Diseases as Portfolio Agency of Department of Health.



Establish a CGT expert advisory group to provide input and advice to TGA, PBAC and MSAC.



Enhance the role of horizon scanning via the Health Technology Reference Group, or equivalent.



The Minister for Health to establish a cross-functional working group including Departments of Health (both Federal and State/Territory), industry, patients and academics to consider current Health Technology Assessment (HTA) processes for CGTs.



Develop a national strategic approach to equitable and timely clinical care for CGTs via the NHRA framework.



Develop incentives for CGTs to create opportunities for trials, manufacturing and commercial success in Australia.

Detailed Recommendations

1 Leverage recommendations from the National Strategic Action Plan for Rare Disease (which have been accepted by the Minister for Health in 2020).

Many of the recommendations from the National Strategic Action Plan for Rare Disease support the recommendations in this report. Amongst these recommendations already accepted by the Minister for Health are:

- Provision of education materials for use by individuals and families following access to genetic testing;
- Enhanced education resources for primary care physicians and health workers;
- Ensure rare disease expertise exists, or can be accessed, on all reimbursement pathways and HTA advisory bodies;
- Enable all Australians to have equitable access to the best available health technology;
- Enhance infrastructure to support delivery of treatment for rare disease, including workforce;
- Build rare disease expertise within the Office of Health Technology Assessment (OHTA) that is responsible for analysing potential rare disease impacts; and
- Develop policy that supports people living with a rare disease to have timely and equitable access to new and emerging health technologies

2 Establish Office for Rare Diseases as Portfolio Agency of Department of Health.

Establish a separate office responsible for the consideration of rare diseases, with a broad remit. The functions of this office could include:

- Developing registry standards to inform collection of data for monitoring long-term patient outcomes. This office could seek to provide the function of accreditation of data collection from various sources (electronic medical records, MBS, PBS, etc.), in a nationally co-ordinated and consistent manner;
- Education of patients and the healthcare community to raise awareness of rare diseases;
- Inform regulation and reimbursement processes, including HTA, on how best to evolve to allow effective consideration of CGTs. This could include frameworks for effective pay for performance mechanisms; and
- To play a key role in research of rare diseases including treatments and policy.

It will be crucial to the success of such an entity that key stakeholders are involved in discussion and activities including patients, clinicians, industry and State and Territory Governments.

It is recommended that this office be established as a portfolio agency of the Department of Health. This would create efficiencies in Government in this growing area of health.

3 | Establish a CGT expert advisory group to provide input and advice to TGA, PBAC and MSAC.

In the past, the mix of speciality types of the various HTA committees has adapted over time to ensure that the appropriate expertise is available to consider contemporary practice and treatments. Until members with skills in CGT are able to be recruited or appointed, it is recommended that a CGT Expert advisory committee (CGT-EAG) be established to provide this critical input, similar to the function provided by the TGA Advisory committee on Biologicals or the Australian Technical Advisory Group on Immunisation (ATAGI).¹¹

The CGT-EAG would sit within the Office for Rare Diseases and provide input on an ad hoc or as required basis. It is important to note that this group will have no ability to make recommendations to the Minister for health or any decision-making function.

This group would include experts in CGTs including clinicians, as well as State and Territory representatives working in CGT delivery, such as those attached to clinical centres of excellence. Given the ethical considerations around some CGTs, including a bioethicist in this group would provide significant value and insight.

4 | Enhance the role of horizon scanning via the Health Technology Reference Group, or equivalent.

It is recommended that the Government urgently re-establish horizon scanning for new and emerging therapies. The remit of this group is to ensure that CGT are considered as part of any horizon scan. It would be critical for this group to meet regularly and publish outcomes, reports and briefings. The group will need to be established in accordance with the Government accepted recommendations of the recent Review of COAG Councils and Ministerial Forums by Peter Conran (96).

Connecting this function to the regulatory, reimbursement and clinical infrastructure, such as patient pathways, registries, will be critical to improve the efficiency of CGT consideration and reduce time to providing access to patients, by enabling system readiness.

Another role for this body could be to identify priority areas and populations with significant unmet need and liaise with HTA bodies to perform expedited assessment to provide more timely access to patients. This is consistent with the approach in Europe and the UK (via PRIME and AAC respectively).

11. The Minister for Health and the TGA can seek independent advice from the Advisory Committee on the safety and efficacy of cell and tissue therapy products, commonly referred to as 'biologicals' [106] and the Australian Technical Advisory Group on Immunisation (ATAGI) provides advice to the Minister and PBAC for advice on the National Immunisation Program.

5 | **The Minister for Health to establish a cross-functional working group including Department (both Federal and State/Territory), industry, patients and academics to consider current Health Technology Assessment (HTA) processes for CGTs.**

With a range of opportunities to align HTA with society's expectations around equity of access for our most vulnerable citizens, it is recommended that a review of current HTA processes is conducted.

Commissioned by the Minister this cross-functional working group could include the current chairs of the PBAC and MSAC, as well as Department of Health, State and Territory representatives, patients and academic leaders in health economics and other appropriate disciplines. This group, reporting directly to the Minister, would be able to include applicable recommendations following on from the current Inquiry into approval processes for new drugs and novel medical technologies in Australia.

The Terms of Reference in the committee would include both treatment, diagnosis and screening. Consideration can also be given to some of the global advancements in consideration of CGTs such as health inequalities, costs and benefits beyond "relevant" health care costs and discounting.

6 | **Develop national strategic approach to equitable and timely clinical care for CGTs via the NHRA framework.**

With the 2020 announcement of the NHRA, an important step was made towards providing patients with access to CGTs. However, opportunities remain to improve the coordination of equitable and timely clinical care across the country. This requires a national strategic approach to co-designing patient care pathways, with consistent protocols, referral pathways, treatment algorithms and data collection. A true co-design process would include patients, clinicians and Governments (both Federal and State/Territory).

Coordination of this would be much improved through the Federal Government providing early advice of Ministerial decision to allow commencement of the above co-design process, but to also allow time for State and Territory Governments to initiate their budget approval processes.

It is also recommended that the NHRA considers facilitating an evidence based, epidemiological approach, somewhat similar to the Nationally Funded Centres process.¹² This will improve coordination cross-border patient care and improve State and Territory budget predictability.

A further function of this approach is to facilitate consistent data collection via registries (accredited with the Office of Rare diseases, see recommendation two) to allow evaluation and administration of CGTs, including any pricing agreements.

12. Established in 1990, the NFC program allows for each State and Territory to provide funding based on epidemiological estimates per intervention. Reconciliation of actual spend per jurisdiction is then done periodically and funding adjusted.

7 | **Develop incentives for CGTs to create opportunities for trials, manufacturing and commercial success in Australia.**

It is recommended that the Government consider providing broad incentives to the CGT sector in Australia. It is acknowledged that in recent years the Federal Government has allocated important funding to research and development in the sector. The current funding allocation is not across the life cycle of a CGT. Funding that is targeted at patient access is urgently required. This is because it is currently unclear how the Australian Government will allocate resources to the many CGTs expected to seek reimbursement in the near future.

Whilst funding is important, other incentives for consideration could include supporting patient access to trials and alternative access programs as well as support for diagnostics and collection of real-world evidence to support future HTA.

Summary of recommendations and opportunities

This White Paper identified a range of opportunities that exist for Government to evolve the HTA process in Australia to enable effective introduction of CGTs for Australian patients. This summary table aligns these opportunities against the recommendations commended to Government (Table 1)

		Recommendations			
		Leverage recommendations from the National Strategic Action Plan for Rare Disease.	Establish Office for Rare Diseases as a Portfolio Agency of Department of Health.	Establish a CGT expert advisory group to provide input and advice to TGA, PBAC and MSAC.	Enhance the role of horizon scanning via the Health Technology Reference Group, or equivalent.
Opportunities identified	Continue the evolution of Government processes, such as HTA, by including relevant experience that captures the diversity of new and innovative therapies, including CGTs.			✓	✓
	Adapt HTA processes so that they align with societal expectations.	✓	✓	✓	✓
	Enhance opportunities for early diagnosis, detection and support to improve outcomes for patients and their families.	✓	✓	✓	
	Evolve discount rates to reflect preferences of Australian society, with particular consideration to those interventions which deliver most of their benefits in the long-term.				
	Enhance national coordination of CGT implementation to reduce time from Ministerial decision to patient access.	✓			
	Enhance horizon scanning of new and innovative therapies, and identification of priority patient populations, to allow adaptation of regulatory, reimbursement and clinical frameworks.		✓	✓	
	Enable broader investment in CGT in Australia, including providing earlier access to patients.	✓	✓		

Table 1 – Summary of White Paper opportunities and recommendations.

Recommendations

	The Minister for Health to establish a cross-functional working group to consider current HTA processes for CGTs.	Develop national strategic approach to equitable and timely clinical care for CGTs via NHRA framework.	Develop incentives for CGTs to create opportunities for trials, manufacturing and commercial success in Australia.	
Opportunities identified	Continue the evolution of Government processes, such as HTA, by including relevant experience that captures the diversity of new and innovative therapies, including CGTs.	✓		
	Adapt HTA processes so that they align with societal expectations.	✓	✓	
	Enhance opportunities for early diagnosis, detection and support to improve outcomes for patients and their families.	✓	✓	✓
	Evolve discount rates to reflect preferences of Australian society, with particular consideration to those interventions which deliver most of their benefits in the long-term.	✓		
	Enhance national coordination of CGT implementation to reduce time from Ministerial decision to patient access.		✓	
	Enhance horizon scanning of new and innovative therapies, and identification of priority patient populations, to allow adaptation of regulatory, reimbursement and clinical frameworks.	✓	✓	
	Enable broader investment in CGT in Australia, including providing earlier access to patients.			✓

Table 1 – Summary of White Paper opportunities and recommendations.

Abbreviations

Abbreviations	Meaning
AAC	Accelerated Access Collaborative
AHMAC	Australian Health Ministers' Advisory Council
AR-DRG	Australian Refined Diagnosis Related Group
ATAGI	Australian Technical Advisory Group on Immunisation
ATMPs	Advanced Therapy Medical Products
CADTH	Canadian Agency for Drugs and Technologies in Health
CATAG	Council of Australian Therapeutic Advisory Groups
CGT	Cell and gene therapy
COAG	Council of Australian Governments
EMA	European Medicines Agency
FDA	US Food and Drug Administration
GDG	Guidance Development Group
HSTP	Highly Specialised Technologies Programme
HTA	Health Technology Assessment
HTRG	Health Technology Reference Group
ICER	Incremental cost effectiveness ratio
IHPA	Independent Hospital Pricing Authority
LSDP	Life Savings Drug Program
MAP	Managed Access Program
MBS	Medical Benefits Schedule
MES	Managed Entry Scheme
MLS	Metachromatic leukodystrophy
MSAC	Medical Services Advisory Committee
NICE	National Institute for Health and Care Excellence
NHRA	National Health Reform Agreement
NHS	National Health Services (UK)

Abbreviations	Meaning
OHTA	Office of Health Technology Assessment
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Schedule
PHARMAC	Pharmaceutical Management Agency
PSS	Personal Social Services (UK)
QALY	Quality-adjusted life-year
RPBS	Repatriation Schedule of Pharmaceutical Benefits
SMA	Spinal muscular atrophy
TGA	Therapeutic Goods Agency
WHO	World Health Organisation

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