Final Report

Priorities for Australian Gene-Related Therapies Research

Gene Related Therapies Incubator Project

February 2024

Australian Genomics

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1. Purpose

This report, generated from the gene-related therapies incubator project, highlights research and implementation challenges facing gene therapy in Australia, as identified through a national consultation process. The recommended research priorities outlined in section 4 of this report serve as valuable guidance for future Australian Genomics research investments including through the Medical Research Future Fund's (MRFF) Genomic Health Future Mission (GHFM).

The incubator project model is designed to address critical areas of health genomic research in Australia that at the time of the GHFM Roadmap and Implementation Plan release[1, 2, 5, 6], may not have been sufficiently mature for substantial funding or were at risk of fragmented submission through competitive calls. These initiatives are being carried out by Australian Genomics as part of their grant program for 2021-2023.

A national working group of experts guided the project with the aim of identifying mechanisms to advance gene therapy research within Australia and facilitating its translation into clinical practice. These recommendations emerged from a comprehensive two-phase consultation process, including interviews with key Australian stakeholders and a nationwide stakeholder survey. This report represents a comprehensive effort to provide a strategic framework for optimising gene-related therapy research in Australia, aligning with the overarching goals of the GHFM.

2. Background

In recent years, gene therapies have achieved significant advancements, representing some of the most advanced and intricate medical treatments in development. Gene therapy aims to restore, alter, or even introduce novel functions to proteins by precisely targeting a patient's genetic makeup. The applications for gene therapies are wide and include cancer, infectious disease, rare and inherited diseases, and neurodegenerative conditions. This new approach to treatment can cure or significantly improve the management of diseases with few or no treatment alternatives. By directly targeting the genetic and molecular drivers of disease, these therapeutic approaches are the epitome of precision medicine.

At the time of publication, 10 cell and gene therapies have been registered by the Australian Therapeutic Goods Administration (TGA) Australia for the treatment of a broad spectrum of diseases including advanced-stage cancer, haematological conditions, and rare and inherited disorders (Table 1). There are many more therapies in development that target genetic diseases at their core, and these novel therapies have the potential to provide a one-time treatment that cures or alleviates severe illness, improving quality of life and reducing health care burden.

There are multiple approaches to deliver therapeutic genes to treat genetic disorders or other diseases, depending on how the genetic information is delivered. For some diseases, the therapeutic genes are directly delivered into a patient's body (*in vivo* gene therapy), typically using a viral vector to transport the genetic material (DNA or RNA) to target cells or tissues. A key challenge of this type of gene therapy is ensuring that the therapeutic gene accurately targets the right cells within the correct tissue and is efficiently delivered to millions of these cells without disrupting the function of neighbouring cells. Equally critical is ensuring that the inserted gene produces an adequate amount of the required protein to effectively address the medical condition or genetic disorder. Additionally, the therapeutic gene also requires a delivery vehicle that can enter cells without provoking a harmful, and occasionally fatal, response from the immune system. These hurdles represent critical aspects of successful gene therapy implementation.

Tradename (generic)	Year approved	*ex vivo/ in vivo*	Indication	Therapy type
Imlygic (talimogene laherparepvec)	2015	*In vivo*	Precursor acute lymphoblastic leukemia (ALL)	Oncolytic gene-modified viral gene therapy
Spinraza (nusinersen)	2017	*In vivo*	Spinal Muscular Atrophy (SMA)	Antisense Oligonucleotides
Kymriah (tisagenlecleucel)	2018	*Ex vivo*	relapsed or refractory follicular lymphoma	CAR-T cell therapy
Luxturna (voretigene neparvovec-rzyl)	2020	*In vivo*	Leber's congenital amaurosis (LCA)	AAV Vector gene therapy
Yescarta (axicabtagene ciloleucel)	2020	*Ex vivo*	large B-cell lymphoma (LBCL)	CAR-T cell therapy
Zolgensma (onasemnogene abeparvovec)	2021	*In vivo*	Spinal Muscular Atrophy (SMA)	AAV Vector gene therapy
Tecartus (brexucabtagene autoleucel)	2021	*Ex vivo*	Mantle cell lymphoma (MCL)	CAR-T cell therapy
Evrysdi (risdiplam)	2021	*Ex vivo*	Spinal Muscular Atrophy (SMA)	RNA therapy
Leqvio (inclisirin)	2021	*Ex vivo*	Cardiovascular disease	RNA therapy
Carvykti	2023	*Ex vivo*	Relapsed or refractory multiple myeloma	CAR-T cell therapy

Table 1: List of therapies approved by the Therapeutic Goods Administration in Australia [1-3]

Generally, *in vivo* therapies tend to be best suited for diseases where the replacement of a protein is needed (e.g. Zolgenmsa for spinal muscular atrophy).

Alternatively, therapies such as the approved CAR (Chimeric Antigen Receptor)-T cell therapy, Kymriah, involve removing cells from a patient, genetic modification outside the body, and then the reintroduction of modified cells or tissues back into the patient. This type of cellular therapy is also known as *ex-vivo* gene therapy. The choice between these approaches depends on the specific disease being treated, the target tissues involved, and the safety and efficacy considerations for each patient. Both methods have shown clinical impact for treating a variety of genetic and acquired disorders.

The surge in approved therapies internationally is paralleled by a remarkable spike in global research and development efforts, with 3,905 therapies in development globally, ranging from preclinical through pre-registration[7]. Within the gene therapy pipeline, oncology and rare diseases maintain their prominence, both in the broader development landscape and within clinical trials.

Australia has a strong gene therapy research community that spans across the country and encompasses diverse diseases and therapeutic approaches. While Australian researchers are renowned for their excellence in discovery and preclinical cell and gene therapy research, it's crucial to acknowledge that gene therapy is still considered a relatively new field. Ongoing support and investment are imperative to nurture not only the research sector but the entire pipeline, ensuring continued growth and success of gene therapy initiatives in Australia which in turn make a significant impact worldwide.

3. National Consultation

In the first phase, 15 key informants were interviewed, including 12 gene-related therapy experts and 3 patient representatives, from across Australia. Interviews were aimed at capturing opinions on current challenges and barriers and future research priorities to progress the field. Thematic analysis was conducted to extract key themes from the interviews, which subsequently informed a broader consultation survey. An online survey was distributed nationally to various

Research Highlight

Australian researchers leading the development of gene therapy for Duchenne muscular dystrophy.

Three ground-breaking gene-patching drugs, granted FDA approval for treating Duchenne, emerged from the pioneering research conducted by Professors Sue Fletcher and Steve Wilton at the Perron Institute[4]. These drugs were licensed through The University of Western Australia and the researchers are currently affiliated with the Centre for Molecular Medicine and Innovative Therapeutics (CMMIT) at Murdoch University. Tailored to address distinct dystrophin gene mutations, each drug underwent rigorous testing in separate clinical trials. Successfully licensed to Sarepta, these three Duchenne drugs are now accessible in the United States, offering treatment to nearly 30 percent of individuals diagnosed with Duchenne Muscular Dystrophy.

stakeholders, including research institutes, universities, hospitals, industry stakeholders and consumer groups. The survey, based on the key themes identified in the first phase, covered topics such as recent advancements, challenges in gene therapy, research priorities, translational research, collaboration, and future perspectives. In total, 44 responses were collected during the three-week circulation period of the survey.

In this section we present the full breadth of stakeholder responses. The stakeholder consultation guided the formation of the specific GHFM recommendations (section 4) and areas of focus that are discussed in further detail (sections 5-10).

Areas of focus include:

- Manufacturing
- Workforce
- Funding
- Regulatory Environment
- Research Translation
- National Collaboration

See *Appendix 3: National Consultation Method* for full consultation methods, interview findings and survey summary.

Stakeholder Findings

Challenges and Barriers

The challenges and barriers to the successful development and implementation of gene therapy, as highlighted by both our key informants and survey respondents, form a complex landscape of critical factors. These include the financial constraints associated with gene therapy research and development arising from limited research funding, absence of a coordinated national approach to address these issues, as well as intricate challenges tied to research translation.

Consumers have expressed concerns about the considerable cost of treatment and its limited accessibility. Their concerns extend to the reimbursement of treatment, early diagnosis, safety assurances, and the long-term benefits of gene therapies. Additionally, consumers advocate for a mechanism to attract clinical trials to Australia and in the context of cancer, wanting gene therapy to be administered as a first or second-line treatment instead of the last-line treatment when patients are already in a compromised state.

Stakeholders and consumers alike acknowledge the need to enhance manufacturing capabilities, address workforce engagement and educational needs comprehensively, and foster effective collaboration with industry stakeholders.

Research Gaps and Funding Recommendations

In addressing the critical research gaps within the realm of gene therapy, stakeholders emphasised the need for strategic funding recommendations to drive progress effectively. First and foremost, they advocate for the establishment of grant opportunities that are tailored to support innovative and impactful gene therapy research, incentivising collaborative efforts across the scientific community. Alongside this, the creation of a Collaborative Centre or Coordinated Network that can foster synergy among researchers, helping to harmonise efforts and pool resources for more streamlined and productive investigations.

To ensure sustainable advancement, stakeholders propose a co-funding approach that involves both industry and government participation. This collaborative model can significantly bolster the financial support available for gene therapy research, allowing

for a more comprehensive and dynamic approach to address the identified research gaps.

Recognising the critical importance of infrastructure and manufacturing capabilities, stakeholders recommend investment in a dedicated production facility for gene therapy products. This facility can ensure reliable and efficient production processes, addressing a pressing need in the field. Simultaneously, funding directed towards preclinical studies can underpin the validation and refinement of gene therapy concepts, bringing them closer to practical applications.

In response to the workforce challenges within gene therapy research, stakeholders urge investment in workforce development, including training programs and infrastructure improvements. This ensures that the field can attract and retain top talent and foster innovation. Furthermore, allocating resources to the development of gene therapy delivery systems (e.g. vectors) is essential for enhancing the therapeutic potential of gene therapies, enabling them to reach their intended targets effectively.

Lastly, stakeholders call for funding support for proof-of-concept clinical trials. This was echoed by consumers and was suggested that funding promising gene therapy clinical trials would act as a catalyst to support the ecosystem. These trials serve as a crucial bridge between research findings and practical clinical applications, ensuring that promising gene therapy strategies can be tested and implemented to be used by patients who have no other alternative treatments.

Future perspectives

In envisioning the transformative impact of gene therapy on patient care and health in the coming years, key considerations emerged from stakeholders.

Risk prediction and early diagnosis through investments in carrier screening and newborn screening (NBS) promise to prevent diseases and enable timely interventions, fundamentally reshaping patient outcomes.

The implementation of expedited TGA approval processes could significantly enhance access to innovative treatments, improving prognoses for diseases ranging from rare conditions to solid cancers and chronic illnesses.

Stakeholders aspire to make genomics-enabled therapies to be more affordable and accessible, listed on the Pharmaceutical Benefits Scheme (PBS), recognising the potential to revolutionise health care systems and patient care and as a one-time intervention.

As bespoke and affordable therapies enter the market, Australia's proactive stance is crucial, particularly given the global landscape where international industry-led advancements in gene therapies dominate.

However, it's imperative to acknowledge that while gene therapy holds promise, its current availability is limited to a specific set of diseases, emphasising the need for broader inclusivity and ongoing advancement to benefit more extensive patient populations.

Stakeholders acknowledge that Australia is poised to play a pivotal role in advancing gene therapy, leveraging its world-leading basic and preclinical research. With robust government and industry support, this research is positioned to deliver end-to-end research-translation capabilities through a coordinated effort.

4. Recommendations

Research priority areas for implementation of gene therapies in Australia have been identified and developed based on stakeholder feedback and guidance from the incubator project working group. Three aims have been identified as priorities for research funding, reflecting different stages of development that would accelerate multiple projects simultaneously.

Aim 1: Accelerate the research translation of innovative, safe, and effective therapies.

Support translational research projects that are preparing for and conducting clinical trials to enable translation of novel therapies with clear commercialisation prospects. Applicants will need to articulate:

- A final product or therapy with strong commercialisation potential
- Enable an Australian clinical trial
- A feasible path to market
- An approach to regulatory affairs (TGA, FDA or other regulators)
- A competitive advantage over comparable products
- Appropriate consideration of the ethical, legal and social issues associated with therapies (consumer engagement)
- A strategy for enhancing sector capacity of key clinical, manufacturing and commercial skillsets (infrastructure)
- Potential funding leverage

The minimum amount available for a single grant is $5 million and the maximum amount available for a single grant is $10 million. Grants conducted over a period of 5 years.

Aim 2: Create a pipeline of potential therapies and platforms (enhancing IP development)

Support for feasibility studies of promising novel gene therapies and projects that are aimed at novel manufacturing methods to improve efficiency.

Projects may include:

- Novel gene therapy targets for diseases of unmet need
- Non-viral based gene therapy (e.g. RNA, CRISPR etc.)
- Reducing the cost of goods
- Improving efficiency of manufacturing processes
- Infrastructure projects will be considered if there is sufficient demonstration that this will expedite the translation of research (e.g. standardised manufacturing platforms, improved manufacturing methods).

Applicants will need to articulate to a phase appropriate level:

- A final product or therapy with strong commercialisation potential
- A feasible path to market
- An approach to regulatory affairs (TGA, FDA or other regulators)
- A competitive advantage over comparable products
- Appropriate consideration of the ethical, legal and social issues associated with therapies (consumer engagement)
- A strategy for enhancing sector capacity of key clinical, manufacturing and commercial skillsets (infrastructure)
- Potential funding leverage

There is no minimum amount available for a single grant and the maximum amount available for a single grant is $2 million over 3 years.

Aim 3: Build the gene therapy translational ecosystem - National Network

The establishment of a collaborative and cohesive network to ensure there is a united national effort in advancing research and providing an ecosystem to support research translation and clinical implementation of gene therapies. It is expected the network will bring together the gene therapy research and clinical communities, in particular investigators that are supported in Aim 1 and 2, to enhance collaboration and cooperation in the field to increase resource-sharing and avoid duplication of work.

The network will support:

- **Workforce development**: enhancing education and training for individuals across the gene therapy pipeline.
- **Consumer engagement**: to enable consumer involvement, understanding of unmet needs and barriers, education, and support.
- **Stakeholder engagement**: host events to bring all stakeholders together to discuss and progress key priorities.
- **Market Analysis**: enabling research to assess the gene therapy market for their work.

We recommend a total of $5 million dollars be allocated to Aim 3 over 5 years.

5. Manufacturing

Stakeholders and survey respondents have identified several manufacturing challenges, including the prohibitive cost of preclinical studies, limited vector availability, inadequate infrastructure and workforce skills and capacity gaps in both research and industry. One stakeholder emphasised the current challenges faced by academics who must turn to commercial partners for manufacturing because of a lack of infrastructure within Australia. The price tags to use commercial manufacturers often force academics to prematurely relinquish their programs to the commercial sector or cease development.

"You have to go and pay companies in the US. $5 million for a manufacturing campaign, which means you cannot afford it as an academic, which means you're going to sell your program to the commercial sector, that's going to develop it. So, we're giving up programs prematurely. But that's because there is simply no infrastructure in this country today." Stakeholder #11

A 2021 report on Australia's Regenerative Medicine Manufacturing Capacity and Capability noted that there were 11 facilities engaged in cell and gene manufacturing across 49 clean rooms[8]. Subsequently, the National Cell and Gene Manufacturing Blueprint reported expansions and increased capabilities in five facilities, along with the addition of three new facilities with manufacturing space[9]. However, as captured in the reports, facilities are predominately cell therapy manufacturing sites and Australia has no facilities with the capability to manufacture GMP-grade viral vectors.

As global demand for these therapies continues to surge, there has been an observable strain on manufacturing capacity, translating into considerable delays experienced by international contract development and manufacturing organisations (CDMOs) which has resulted in a significant focus on the development of local manufacturing capacity.

Recent funding announcements signify improvement in Australia's cell and gene therapy manufacturing sector. Notable developments include:

- The NSW Government has committed $134.5 million to establish the Viral Vector Manufacturing Facility, in the Westmead Health and Innovation Precinct[10]. This will become Australia's first commercial (GMP-grade) viral vector facility[11].
- Investments in the establishment of mRNA manufacturing in Victoria[12], New South Wales[13] and Queensland[14] which are anticipated to be operational by 2024.
- The Vectorology Facility at the Children's Medical Research Institute[10] and The School of Biomedical Science Viral Vector Core at The University of Queensland, both currently manufactures research-grade vectors for clients[15].
- An expanded cell and gene therapy manufacturing facility opened in July 2023 at Peter MacCallum Cancer Centre in Melbourne as part of a $105 million project. Operated by Cell Therapies Pty Ltd, it will be Australia's only biomedical manufacturing site where CAR-T cells and other "living" cancer therapies can be made at a commercial scale[16].

In addition, Therapeutic Innovation Australia (TIA) operates as a non-profit organization, receiving funding from the Australian

Department of Education through the National Collaborative Research Infrastructure Strategy (NCRIS) program. TIA plays a pivotal role in bolstering national translational research infrastructure by enabling access to a network of cell and gene therapy development and manufacturing facilities to enable development and production of advanced therapeutic products, catering to early to late-stage clinical trials and patient care.

As reported by the National Cell and Gene Manufacturing Blueprint, a united and well-coordinated strategy to boost Australia's sovereign cell and gene product manufacturing capabilities will be vital in positioning Australia as an Asia-Pacific hub[9]. This sovereignty empowers access not only to early-phase trials for Australian patients benefiting from locally developed products but also paves the way for participation in innovative and cutting-edge international trials[17]. Furthermore, the resilience of our manufacturing capabilities is indispensable in fortifying Australia against disruptions in the global supply chain.

"Although recent investment into the Westmead GMP facility is a significant leap forward for Australian manufacturing capacity, this is only one part of the puzzle. Greater capacity in scalable GMP-like manufacturing is needed, to ensure process development is optimised with reduced costs at early stages to ensure large-scale manufacturing is economically viable and production yields are maximised…. These capabilities require a workforce that is highly skilled in advanced manufacturing techniques, which is lacking due to Australia's limited manufacturing industry." Survey respondent.

In conjunction with manufacturing capacity, production efficiency represents a major contributor to cost and access to manufacturing facilities. Scaling up production for clinical trials in this field is a complex and costly endeavour, demanding specialised good manufacturing practice (GMP) capabilities, a highly skilled workforce, and intricate supply chains.

"Improving delivery systems/methods and immunogenicity will play an important role in reducing the amount of virus required for therapy, enhancing efficacy, causing fewer side effects, and drastically reducing costs. Collaboration between researchers, industry and facilities will play a vital role in fast-tracking development and improving manufacturing processes to translate therapies." Survey respondent.

While we have seen some improvements to viral vector production efficiency, additional optimisation has been identified to be a prominent challenge as well as a research priority for future investment. In addition, investment into the optimisation of production methods (scalability, safety and consistency) and the development of novel non-viral vector approaches are areas of high priority for immediate research that have the potential to impact the field.

Through collaborative efforts to establish essential infrastructure, Australia stands to create a sustainable ecosystem that attracts both local and international investments, ultimately maximising benefits to the whole gene therapy community, most importantly patients. These include the generation of employment opportunities, advancements in healthcare, and unwavering support for local research and development initiatives. The

level of funding required to address these infrastructure issues is beyond the scope of this funding call. Importantly, building Australia's manufacturing capability needs to be continually addressed at a national level using funds from the National Collaborative Research Infrastructure Strategy, State and Territory governments and the commercial sector. Furthermore, continuous collaboration with the commercial sector is imperative to establish global partnerships that will guarantee the sustainability of viable business models for manufacturing facilities.

6. Workforce

The development and implementation of gene therapy significantly affects the workforce across the entire pipeline, presenting a notable barrier to the technology's advancement and translation. Stakeholders have highlighted several associated challenges that underscore the importance of addressing them. Specifically, they noted the scarcity of individuals well-versed in modern gene therapy biology, resulting in a reliance on overseas recruitment to access the requisite expertise. Stakeholders emphasise the imperative of enhancing the development of a skilled workforce within Australia to reduce dependence on foreign talent.

The workforce requirements span various specialised areas involved in gene therapy development, including research and development, clinical trials, manufacturing, clinical practice, and post-market surveillance. Of importance, it will be crucial to address existing skill gaps, particularly in advanced therapy manufacturing and Good Manufacturing Practice (GMP) workforce skills to effectively support this industry[8].

"In addition to that basic stuff, there are some gaps, particularly in the workforce – manufacturing scientists who have the expertise to make a product for clinical use are very thin on the ground." Stakeholder #8

Process design expertise with an in-depth understanding of commercial-scale design and the knowledge of national and international regulatory requirements, both of which are important in developing efficient manufacturing processes whilst maintaining the quality and safety of products has been identified as a key skill gap in developing greater advanced manufacturing capabilities in Australia[18]. Adequate training programs and a robust workforce pipeline are essential for filling these gaps and promoting local manufacturing expansion [9]. A well-trained manufacturing workforce will not only enhance Australia's sovereign supply chain capabilities but also elevate its global reputation as a manufacturer of advanced medical products.

The Australian Government, through the Medical Research Future Fund (MRFF), initiated the Research Exchange and Development with Industry (REDI) program in 2020, a $32 million endeavour delivered by MTPConnect over four years. REDI collaborates with research, training, and industry organisations to address skill gaps in various themes, including advanced manufacturing and supply chain, clinical trials, and product development[19]. This initiative aims to enhance workforce skills and training in these critical areas. However, the future of this program is uncertain as the funding period for the program has now ended.

Additionally, partnerships and agreements, such as the collaboration between the Centre

for Commercialization of Regenerative Medicine Australia (CCRM Australia) and the Canadian Advanced Therapies Training Institute (CATTI), are playing a role in advancing cell and gene therapy training in Australia[20]. Access to online training programs is being provided, contributing to the development of a skilled workforce.

In March 2023, the Victorian Government announced a $10 million investment in the Monash Centre for Advanced mRNA Medicines Manufacturing and Workforce Training. This centre will provide highly specialised training for workers involved in all aspects of the mRNA manufacturing process[21].

Despite current initiatives, stakeholders express doubts about their ability to adequately meet the growing requirements of the field. Consequently, stakeholders emphasise the urgent need for the integration of cell and gene therapy topics into national science, technology, engineering and mathematics (STEM) education and outreach programs, encompassing all levels of education and training. This comprehensive integration is of paramount importance for nurturing and expanding future research and development, as well as the manufacturing workforce.

Within university curricula, stakeholders call for a substantial amplification of the focus on cell and gene therapy topics. They recommend moving away from the current practice of confining these subjects to broader fields such as molecular biology or microbiology and advocate for their inclusion in specialised courses. This progressive approach ensures that students receive focused and in-depth education in this cutting-edge field.

To create a workforce well-prepared for the challenges of gene therapy, stakeholders propose the establishment of opportunities like scholarships and training programs, with a particular emphasis on PhD students. This strategic investment in education and training is regarded as the path to developing the necessary expertise and skills required for the workforce.

"I think we need a more skilled workforce. I think there needs to be more emphasis in university curricula on these areas, instead of just being dealt with as part of a molecular biology course, or microbiology... There needs to be a lot of opportunities for scholarships, and training for PhD students. And that's where you get the workforce from. You can't bring it all from overseas. We have people that are trained of course, but if you really want an area to flourish, you probably need more of them. And also, attracting good people from overseas. There needs to be some way that would attract them to take and get something out for their careers."
Stakeholder #2

It is becoming increasingly urgent that the education and training of clinicians, pharmacists, nurses and other healthcare professional keeps pace with the growing number of preclinical, clinical and approved therapies. Internationally, countries like the United States, the United Kingdom, and Spain have recognised the importance of providing comprehensive training for healthcare professionals in the field of cell and gene therapy. In the US, the American Society for Transplantation and Cellular Therapy (ASTCT) offers a training and certification program[22]. The UK, through its Advanced Therapy Treatment Centre (ATTC) network, has taken a thorough approach by assessing

the training needs of the healthcare workforce. They have partnered with organisations like the Cell and Gene Therapy Catapult and Health Education England's e-Learning for Healthcare to create educational content for medical professionals, enhancing their understanding of advanced therapy medicinal products[23]. In Spain, the national action plan for advanced therapies mandates that designated centres provide training to health professionals[24].

In Australia, there is a noticeable shortage of educational materials available for health professionals in this field. While government-funded initiatives are underway to develop specific education programs for gene therapies, there is still much work to be done. The Sydney Children's Hospital Network (SCHN) is currently developing an educational initiative focused on Adeno-Associated Virus (AAV) gene therapy[25]. This program encompasses multidisciplinary team models of care and care standards for eligible gene therapy patients using recombinant adeno-associated virus (rAAV) vectors. The aim is to implement and evaluate this program at SCHN and eventually make it accessible to other healthcare services.

The lack of a nationally coordinated and consistent approach to health professional education in gene therapy is evident. There is a clear need for further efforts to establish a national workforce strategy that can adequately meet the growing demand for the development, manufacturing, and management of gene therapies.

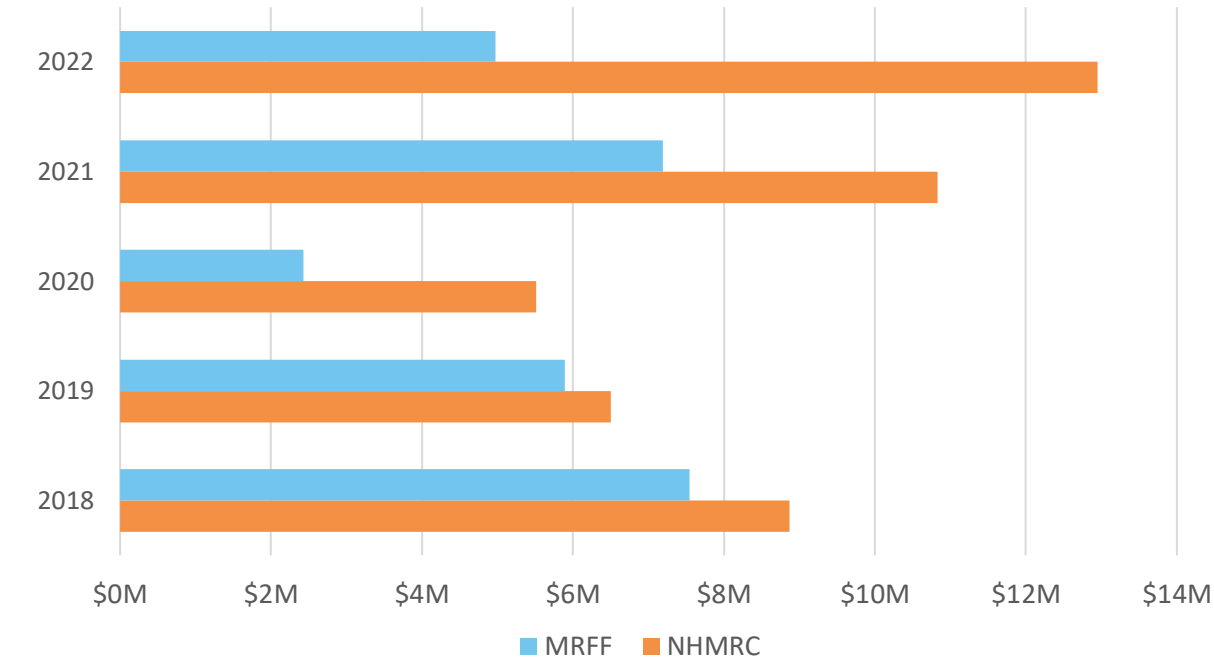


Figure 1: Government grant allocation for gene-related therapy research (AUD Millions)
Terms used to filter the funding: gene therapy/therapies, RNA therapy/therapies, genetic therapies/technologies, gene technology, cell and gene therapies, gene editing, gene-addition therapy, genome editing, gene silencing, adeno-associated viral vectors, Chimeric Antigen Receptor (CAR) -T, Antisense Oligonucleotide (ASOs), mRNA therapy/therapies.

7. Research Funding

Cell and gene therapy development is notably fragmented when it comes to research and translation efforts in Australia. Stakeholders have reported that this fragmentation is largely attributed to limited research funding and the competitive allocation mechanisms that drive competition between researchers instead of fostering collaboration and utilisation of existing capacities.

One stakeholder (#10) emphasised the issue of insufficient funding, stating, *"I genuinely do not think that Australia today has sufficient funding to do the important research we need to do. So I think that creates barriers in the way people work that are unhealthy in the sense that it's not allowing people to properly collaborate and share knowledge and then work together for a better health outcome. That's a structural problem. That is a challenge that needs to be addressed."*

Another stakeholder (#11) illustrated the impact of funding constraints on NHMRC grants, explaining, *"When someone approaches me with a collaboration opportunity, I can only offer my name as a collaborator because I can only afford two grants for myself. This limitation stifles collaborative spirit and prevents meaningful cooperation, as I cannot afford to share my grants."*

In Australia, the Commonwealth Government distributes funds towards gene therapy research through the National Health and Medical Research Council (NHMRC) and the Medical Research Future Fund (MRFF). NHMRC funding is investigator-initiated and is not directed by NHMRC to any specific disease, health, or research topic. However, a proportion of NHMRC funds is directed to specific topics primarily through Targeted Calls for Research and International Collaboration schemes, or priorities identified in the NHMRC Corporate Plan. To date, gene therapy research has not been listed as a Targeted Call for Research. Between 2018 and 2022, NHMRC invested $4.35 billion in 4,144 research grants, with only 1% ($44.67 million across 47 grants) allocated to investigator-initiated gene-related projects (Figure 1,[26]).

The MRFF, a $20 billion research innovation investment, supports research missions that address significant health challenges. Since 2018, $25 million has been allocated to gene-related therapy research through the MRFF (Figure 1), with a substantial portion channelled through the Stem Cell Therapies Mission[27]. However, gene therapy research has yet to emerge as a designated research mission.

In Australia, early-stage and preclinical research programs rely primarily on funding from government agencies, academic institutions, and philanthropic organisations. Although improvements have been observed, especially through MRFF funding, there remains an insufficiency of funding, particularly in the preclinical and early clinical research phases. Notably, compared to international counterparts like the United States and the European Union, Australia experiences a marked scarcity of venture capital investment and collaborative partnerships between industry and academia[28], both of which are vital for funding later-stage development and the translation/commercialisation of innovative therapies. Stakeholders frequently cited reliance on foundation funding and state government initiatives, but these funding sources often fall short of the financial resources needed for conducting necessary clinical trials, which are crucial for obtaining

regulatory approval for novel therapies. Furthermore, stakeholders have underscored the need for targeted funding for the development of gene therapies for ultra-rare diseases, which may not attract interest from the industry. This situation emphasises the crucial role of substantial government funding in advancing gene therapy for these conditions. The primary alternative seems to involve individual philanthropists who fund therapies tailored to specific diseases. Unfortunately, this leaves economically disadvantaged patients without access to potentially life-changing treatments, as they lack the means to finance research programs.

"There's no interest from industry on ultrarare disease gene therapy development. Without significant government funding, the only way to progress with gene therapy is individual philanthropists funding their own diseases to be developed for themselves. Poor patients who can't afford funding research programs will miss out." Survey respondent.

While there have been substantial past government investments in gene therapy research and development, there is an urgent need to ensure that funding covers the entire lifecycle of a product and is oriented toward providing patients access to innovative therapies. Stakeholders underscore the importance of better funding models, coordinated national and international research programs, and larger government investments, spanning all stages from basic research to preclinical and clinical trials. Additionally, it is crucial to prioritise funding for key hospitals involved in gene therapy trials and build their capacity, including staff education, gene therapy-specific staffing, and dedicated clinical facilities to facilitate clinical trials. The aim is to bridge the "valley of death" in gene therapy development and ensure that all patients can benefit from these innovative treatments.

Considering the substantial expenses linked to gene therapy research, including quotes of USD $5 million for manufacturing viral vector quantities essential for a phase I clinical trial on top of additional logistical cost and nonclinical testing, a critical requirement emerges for expanded funding opportunities to sustain Australian-led clinical trials. Relying solely on industry partnerships may not suffice. A more comprehensive approach, rooted in larger funding sources, is imperative. Such an approach not only addresses the financial challenges but also fosters increased local ownership and control over crucial research initiatives, ensuring a more sustainable and impactful trajectory for gene therapy advancements in Australia.

8. Research Translation

Research translation involves the transformation of laboratory-generated innovations into practical applications to be used in the real world. In the context of gene therapies, this entails taking a research project and ensuring its suitability for patient use. This encompasses the refinement of manufacturing processes to produce an adequate quantity while adhering to stringent quality standards for patient delivery. It also involves conducting toxicology assessments to ensure the therapy's safety, preparing a clinical trial protocol, collaborating with healthcare practitioners to facilitate therapy delivery, and coordinating with clinical trials teams to ensure the trial's feasibility. The successful journey from Phase I requires progression through Phases II and III before

the therapy can be submitted to a regulatory body for full approval to treat patients. This is a lengthy and costly process, typically extending over 15 years.

Stakeholders emphasised that the transition from research to therapy is fraught with significant challenges, and Australia's limited role in gene therapy development can be attributed to an emerging but still nascent research translation culture. Limited translation has been attributed to government funded grants prioritising the production of academic publications rather than activity facilitating the creation of intellectual property and maximising the return on investment through the commercialisation of these therapeutic interventions. This prevailing bias towards emphasising academic output significantly restrains our ability to fully exploit the substantial global investments witnessed in the field over recent years. Furthermore, stakeholders recommended the need for more experienced and specialised technology transfer officers and researcher translators, which oversee identification, protection and management of intellectual property (IP) created by researchers as well as access to funds to assist with IP development.

"When I compare ourselves to virtually any other country globally …there is much more movement between industry and research… we do not have tech transfer offices in big universities, our tech transfer offices are overwhelmed and under-skilled… We also need research translators in the genomics space. And it's those that need to be valued by the university system. We need people that can connect, engage with the industry, understand what that pathway looks like, and have meaningful conversations about both academic (and) commercial pathways."
Stakeholder #5

To successfully translate research into therapeutic products, the academic workforce needs guidance on conducting projects with the potential for translation. Providing training and education in translation research activities could greatly benefit the community, given that only 19% to 25% of survey respondents indicated having an excellent or good understanding of crucial aspects such as quality assurance, manufacturing, process development, and fund approval (Appendix 6: Consultative Survey Summary). Moreover, collaboration with industry stakeholders is crucial due to the expensive nature of advancing through clinical trials, but Australia's limited presence of industry presents obstacles in this area. Unlike the United States, which benefits from substantial venture capital banking, many research projects in Australia remain confined to the laboratory and do not progress to real-world applications.

"I'm not convinced that most of the academic grants in Australia have got the bandwidth to properly do this [research translation]. And they often segment the work to the stuff that they're comfortable with. Like the preclinical workup. But they're very reluctant to cover the true costs of conducting the trial."
Stakeholder #4

The primary focus of translational research is to deliver innovations to patients. It is imperative to start considering this objective earlier in the research process. While there is certainly a place for discovery research, which Australia excels at, the challenge lies in recognising when a research program should

transition into a development program. Development programs require different experiments aimed at preparing innovations for patient use, but the funding available often falls short as research programs tend to be shorter and less financially substantial. To encourage researchers in translating their work, academic institutions and funding bodies should begin recognising the creation of intellectual property alongside publication records when evaluating promotions and grant applications. Currently, these assessments heavily prioritise publication records.

There are effective approaches to support researchers in bridging this gap. This includes equipping researchers with knowledge of the therapeutic development process and providing guidance on how to engage effectively with industry. Additionally, there is a need to develop knowledge of gene therapies in commercialisation offices as the pathways (regulatory, manufacturing, market analysis etc) are different from standard small molecular therapeutics. This would allow researchers to collaborate with academic institutes' commercialisation offices to secure appropriate patents and identify potential partners to advance projects. The establishment of infrastructure within the academic setting will help drive projects forward and "de-risking" them, making them more appealing to external investment. It's important to note that public funds are unlikely to cover the costs of Phase III trials, and by that stage, a company should ideally be established, either through the researcher's decision to license the technology and establishment of their own company or through the interest of biotech/pharma companies in acquiring the technology license.

One significant challenge lies in the lack of understanding of the translation journey for researchers. There are not many who have successfully navigated this path. It would be immensely beneficial to have open dialogue with the industry, allowing them to share their experiences with academia to facilitate the journey for future innovations. Currently, the rapid movement of research overseas limits this culture of knowledge sharing.

The role of venture capital funding and biotechnology companies is key to translating science into new gene therapies. In Australia, as in the broader life sciences sector, several barriers to investment are commonplace. These include limited access to venture capital funding, geographical isolation from international investors, and significant gaps throughout the research translation pathway. However, in the realm of Australian gene therapy development, there are distinctive hurdles to surmount. These include the elevated costs associated with pre-clinical GMP-quality product development, regulatory uncertainties, and intricate questions surrounding health economics. Overcoming these unique barriers is essential for promoting increased investment in Australian gene therapy research and development.

9. Regulatory Environment

The undeniable innovation inherent in these therapies presents a substantial chance to enhance the health prospects of many patients. Nonetheless, it is recognised that the delivery of gene therapies will challenge the Australian healthcare system. Regulatory and health technology assessment (HTA) bodies play distinct but interconnected roles in the process of bringing gene therapy to patients.

Regulatory bodies like the TGA play a vital role in ensuring the safety, efficacy, and quality of gene therapy products and research. Globally, cell and gene therapies present unique regulatory challenges, given their unconventional categorisation (as drugs, devices, or procedures) and diverse data requirements. These therapies often feature a single application with long-lasting effects, introducing uncertainties in approval endpoints, dosages, and long-term efficacy. Limited patient populations, especially in rare disease trials, make recruiting for large clinical trials challenging. Ethical concerns and the lack of direct comparisons to control groups further complicate assessments and introduce clinical benefit uncertainties. Regulatory frameworks have evolved in many countries, including Australia, to streamline cell and gene therapy approvals and support developers. However, priority or accelerated review pathways, as seen in several other countries, are notably absent in Australia[24]. Regulatory bodies must balance fostering innovation and patient access while protecting patient safety.

Australia, with only 10 cell and gene therapies approved, is currently facing challenges in keeping pace with the implementation and adoption of gene therapies when compared to international counterparts. Globally, there are 26 approved gene therapies, 24 RNA therapies, and 63 non-genetically modified cell therapies available for clinical use approved in at least one country[7]. As of October 2023, the United States Food and Drug Administration (FDA) has approved 34 cell and gene therapy products, with 5 approved between Q1-Q2 of 2023, signifying a significant (and increasing) gap in approvals between the Australia and the US[7, 29]. The FDA is making substantial progress towards achieving its ambitious projection of granting 10-20 approvals annually by 2025. This projection seems attainable, especially considering the existence of 3,905 advanced therapies in various stages from preclinical to pre-registration[7]. Without significant changes, it is unlikely that Australia will be able to match this pace of approvals.

"Regulatory requirements for clinical trials of gene therapies in rare diseases have created many barriers. Accelerated approvals by the US FDA have not been consistently applied. Using surrogate endpoints and natural history data has not been accepted for accelerated approvals (which goes against the FDAs own guidelines) For rare neurological conditions, this has meant that the burden of demonstrating clinical efficacy has been too high and meant that the developers of many promising candidates have run out of cash and investment. More consistent application of regulatory guidelines would help to de-risk gene therapy development, enable more confident investment in GT programs and stimulate the field." Survey respondent.

Health Technology Assessment (HTA) bodies evaluate therapy value, clinical effectiveness and cost effectiveness, a crucial step in ensuring economic viability and accessibility within the healthcare system. Due to the high cost of gene therapies, public funding is essential for equitable access. Despite the steep price tag, the potential value of these interventions remains favourable when compared to lifelong treatments required by existing therapies. Both regulators and payers are compelled to embrace new decision-making approaches to navigate uncertainties surrounding the duration of therapy effectiveness. In Australia, the TGA approved nine cell and gene therapies, with seven receiving public funding under the National

Health Reform Agreement (NHRA) or the Pharmaceutical Benefits Scheme (PBS). The NHRA agreement involves joint funding by Commonwealth and State/Territory health departments, ensuring nationwide access for patients. Notably, in 2022, Novartis' Zolgensma® became the first gene therapy pharmaceutical listed on the Pharmaceutical Benefits Scheme (PBS) in Australia, providing substantial savings to patients. Unlike other countries, clinical uncertainty is not addressed via the regulatory process in Australia. In other countries, clinical uncertainty is overcome by establishment of a patient registry which can be accessed by regulators, payors and clinicals. Instead, clinical uncertainty is managed through the HTA process after one year of public funding with a full review conducted by MSAC of clinical effectiveness, cost-effectiveness and budget impact that informs decision making about continuing reimbursement and pricing of therapies. Stakeholders have raised valid concerns regarding the sustainability of current funding models. The existing funding primarily covers the cost of the therapy itself but does not extend to the extensive team required to implement and administer the therapy and provide ongoing monitoring. This poses challenges to the long-term viability and accessibility of these therapies. As recommended by "The New Frontier – Delivering Better Health for All Australians," an inquiry focused on approval processes for new drugs and novel medical technologies, a review is underway to simplify the assessment process for cell and gene therapies. This review seeks to establish a clear and certain pathway for these therapies within the HTA process [30, 31].

"The funding model for the approved gene therapy Luxturna is not sustainable…no funding is dedicated to clinician's time, coordination, SOPs. Pharmacy involvement, disease specific specialists, operating theatre scenario etc." Stakeholder #9

While regulatory and HTA processes are not directly involved in the gene therapy research and development pipelines, we need to continue to progress conversations on the evolving landscape of these innovative treatments. A transparent and well-defined regulatory framework is of paramount importance. Companies and investors are more inclined to channel resources and capital into gene therapy research when they have a clear understanding of the regulatory landscape. Clarity instils confidence, as it enables stakeholders to anticipate a fair return on their investment, further encouraging them to commit to the lengthy and resource-intensive process of gene therapy development. Ultimately, a well-structured regulatory environment incentivises innovation and investment, facilitating the translation of promising research into real-world treatments.

Efficiency in the HTA process is equally critical. A streamlined HTA process ensures that the value and clinical efficacy of gene therapies are rigorously and promptly assessed. By streamlining the assessment of these therapies, we can reduce delays and bottlenecks, guaranteeing swift patient access to established gene therapies. These processes constitute essential components of the gene therapy ecosystem, propelling the progress of medical science and the enhancement of patient care.

"Clear Government policy and a willingness to fund specific therapies would encourage greater research and industry collaboration." Survey respondent.

Through collaborative networks and active engagement with patients and stakeholders, we can collectively address ethical and societal implications, gain insights into payer perspectives, and consider the preferences of patients and healthcare providers. This collaborative approach enables us to navigate the complex landscape of gene therapies and work together to ensure their responsible development and accessibility through refined policies.

10. National Collaboration

Many of the challenges outlined in this report can be effectively mitigated through enhanced coordination and collaboration across the cell and gene therapy development pathway in Australia. Stakeholders noted the absence of a coordinated approach hinders progress, leading to isolated efforts and unnecessary competition. Replication is a common issue in the country, as various small institutions and groups vie for limited funds without the benefits of collaboration. To compete on a global scale, Australia needs a national collaborative group that genuinely prioritises working together.

The success of gene therapies, particularly for rare diseases, relies on a coordinated national approach due to the financial impracticality of establishing individual programs. Many stakeholders and survey respondents emphasise the need for a national "authority" that can drive the development of a nationally coordinated approach. The establishment of such a national collaboration network for gene therapy research holds immense potential. It can reduce redundancy, streamline research activities, and lead to significant time and cost savings. By connecting researchers and experts across the country, a national network can facilitate knowledge exchange, enabling the cross-pollination of ideas and skills, thereby accelerating innovation and effective problem-solving. Furthermore, it could assist in setting standardised protocols, facilities, and expertise. This, in turn, would facilitate the transition from preclinical research to clinical trials. The newly formed Cell and Gene Catalyst, from Ausbiotech and Medicines Australia, may represent the earliest form of a national network across the whole cell and gene therapy ecosystem. Key partners are

Ausbiotech, Medicines Australia, Cell Therapies, CSL, Novartis, Pfizer, TIA and Roche. However, strong engagement of academia within such a network is missing in Australia.

While we acknowledge successful international examples, such as the Bespoke Gene Therapy Consortium in the United States [32], it's essential to recognise that establishing such a network requires substantial, long-term investments from government, industry, and research institutes. This may extend beyond the scope of the current recommendations but a model that Australia should consider in the future.

To ensure Australia's continued growth in the gene therapy translation ecosystem, we recommend the establishment of a collaborative and cohesive network, fostering a united national effort to advance research and support the translation and clinical implementation of gene therapies.

The proposed network aims to bring together gene therapy research and clinical communities, promoting collaboration and cooperation to optimise resource-sharing and minimise duplication of work.

This network would specifically focus on:

1. Workforce Development: Prioritising the development and training of a skilled gene therapy workforce, encompassing researchers, manufacturing staff, and clinicians. Investment in education and training programs will ensure a sustainable supply of qualified professionals capable of driving innovation and translation to meet the growing industry demands.

2. Supporting Commercialisation: Comprehensive market analysis is crucial to understanding the potential for gene therapy products in both domestic and international markets. This analysis aligns research efforts with real-world health needs, informs strategic decision-making, and ensures that gene therapies can have a meaningful impact on patients' lives while being commercially viable within the healthcare ecosystem.

3. Consumer Engagement and Education: Involving patients, families, and patient advocacy groups in decision-making processes is essential for fostering transparency and alignment with individual needs while addressing concerns related to ethics, safety, and accessibility. Simultaneously, comprehensive consumer education initiatives are necessary to increase public awareness and understanding of gene therapy. These efforts build trust, alleviate concerns, and promote informed decision-making, creating a supportive environment for gene therapy programs in Australia.

4. Stakeholder Engagement: This includes promoting information sharing, mentoring, and networking opportunities among stakeholders to create a cooperative and well-informed ecosystem for gene therapy research and development.

The establishment of a collaborative and cohesive national network emerges as a pivotal solution to the challenges outlined in this report. The Cell and Gene Catalyst has strong industry engagement, aims to build the cell and gene therapy ecosystem in Australia and therefore provides a promising foundation for such a network. However, to ensure sustained growth and success in Australia's gene therapy research translation ecosystem, we recommend the formal creation of a network focusing on workforce development, supporting commercialization, consumer engagement and education, and stakeholder engagement. This comprehensive approach aims not only to optimize resource-

sharing and minimize duplication of work but also to foster innovation, transparency, and trust within the gene therapy research and development community. By embracing this unified effort, Australia can position itself as a global leader in gene therapy, contributing to advancements that benefit patients, researchers, and industry stakeholders alike.

11. Appendix

Appendix 1: Abbreviations

AAV	Adeno-associated viruses
ASTCT	American Society for Transplantation and Cellular Therapy
ATMP	Advanced Therapy Medicinal Products
ATTC	Advanced Therapy Treatment Centre
CAR-T	Chimeric antigen receptor - T
CATTI	Canadian Advanced Therapies Training Institute
CCRM	Centre for Commercialization of Regenerative Medicine
CDMO	Contract Development and Manufacturing Organization
CNS	Central Nervous System
CRISPR	Clustered regularly interspaced short palindromic repeats
EMA	European Medicines Agency
FDA	Food and Drug Administration
GHFM	Genomic Health Futures Mission
GMP	Good Manufacturing Practice
IRD	Inherited Retinal Diseases
MRFF	Medical Research Future Fund
mRNA	messenger ribonucleic acid
NHMRC	National Health & Medical Research Council
rAAV	recombinant adeno-associated virus
REDI	Research Exchange and Development with Industry
RMAT	Regenerative Medicine Advanced Therapy (RMAT)
SCHN	Sydney Children's Hospital Network
SMA	Spinal Muscular Atrophy
SSC	Scientific Strategic Committee
STEM	Science, technology, engineering, and mathematics
TGA	Therapeutic Goods Administration
UQ	University of Queensland

Appendix 2: Definitions

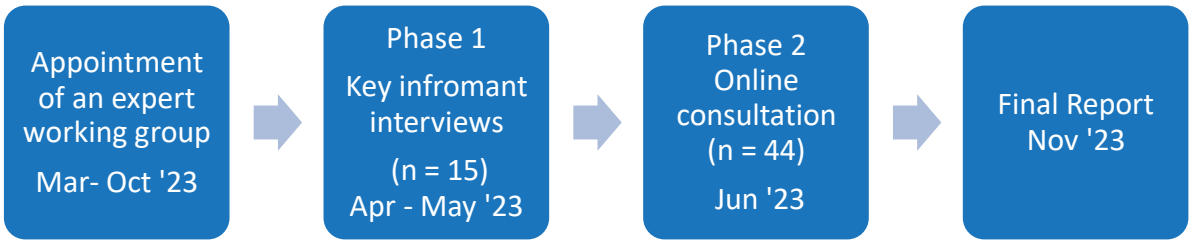
Gene therapy	Gene therapy is the introduction, removal, or change in the content of a person's genetic code with the goal of treating or curing a disease.
Ex Vivo Gene Therapy	Patient cells are harvested, cultivated in the laboratory, and incubated with vectors carrying a corrective or therapeutic gene. Cells with the new genetic information are then transplanted back into the patient from whom they were derived.
Gene	A segment of DNA found on a chromosome that codes for a particular protein. Humans have tens of thousands of genes that act as a blueprint for making specific enzymes or other proteins for virtually every biomedical reaction and structure in the body.
Genome	The sum of all genes that code for a particular organism and found in the chromosomes
Clinical Trial	A clinical trial is a research study in human volunteers and is designed to answer specific questions about a disease, new therapies, or new ways of using known treatments. Clinical trials (also called medical research and research studies) are used to determine whether new drugs or treatments are both safe and effective. Carefully conducted clinical trials are the fastest and safest way to find treatments that work in people. Trials are in four phases: Phase I tests a new drug or treatment in a small group to evaluate safety and toxicity. Some Phase I trials solely examine characteristics of a disease and provide needed background information for developing novel therapies. Phase II expands the study and begins to assess efficacy. Phase III expands the study to an even larger group of people and often compares the agent to a standard of care treatment. Phase IV takes place after the drug or treatment has been licensed and marketed.
Adeno Associated Virus	AAV are small DNA viruses that do not cause human disease. The nine distinct serotypes of AAV preferentially go to different tissues. AAV have been engineered to carry genes into dividing and non-dividing cells of the body.
In Vivo Gene Therapy	The administration of a vector carrying the therapeutic genetic material to a live animal. The vector can be delivered by a variety of methods, including direct injection into the blood (intravenous injection) or various organs by other physical means of administration (hypodermic injection, aerosol, intrathecal, etc.).
Lentivirus	Represents a class of animal and human viruses. Modifications of these viruses for vectors involve removal of the viral genes that cause disease and replacing the viral genes with therapeutic genetic material. In this way the lentivirus is engineered to insert the new DNA into the genome of the target cells which can then be used to treat disease.
Messenger RNA	Messenger RNA (mRNA) is a single molecule of RNA that works as a chemical map for a protein product
Mutation	A change in the sequence of DNA which alters gene function. Sometimes the mutation changes the gene so that the protein encoded by the gene is abnormal. In other cases, the protein may be normal, but the mutation causes the cell to make too little or too much of the protein.
Non-Viral Gene Therapy	While some gene therapy approaches utilize engineered viruses to deliver genetic material, there are a number of other methods available and have been referred to as non-viral gene therapy. More recently, these methods have been called synthetic gene therapy.

Vectors	Gene therapy delivery vehicles, or carriers, encapsulate therapeutic genes for delivery to cells. They include both genetically disabled viruses such as adenovirus or AAV, and non-viral vectors such as liposomes.

Adopted from American Society of Gene and Cell Therapy

Appendix 3: National Consultation Method

The national consultation commenced with the appointment of an expert working group. The working group provided oversight of the entire project, including developing the methodological approach which consisted of in-depth interviews with selected key informants (phase 1) and based on feedback received from key informants, a broader online consultation survey (phase 2). At each phase, the working group provided guidance and contributed and reviewed the final report inclusive of recommendations.



Method

Phase 1 - Key informants (n=15) were interviewed across Australia. Twelve (n=12) key informants were experts working in the area of gene-related therapies and three (n=3) were patient representatives with first-hand experience.

The interview questions were provided to both groups before the interview. The interview questions were tailored to suit the two groups and therefore differed from one group to the other. The interviews were 45 minutes in duration and were conducted by two Australian Genomics project coordinators. Participants provided verbal consent to participate in the interviews. The participants were informed that the aim of the project was to develop and submit recommendations to the Medical Research Future Fund (MRFF) to inform the design of future research priorities in Australia in the gene-related therapies space. Once all the interviews were completed, the interviews were transcribed and analysed thematically. The thematic analysis then informed a broader consultative survey.

Phase 2 - The online survey intended for a broader consultative group was developed based on the main themes that emerged from the key informant interviews and was circulated Australia-wide among research institutes, universities, hospitals, industry players and consumer groups. The survey was circulated for two weeks initially, and then further extended for a week. The survey concentrated on **current research** specifically the recent advancements in gene therapy research in Australia and international exemplars and current challenges and limitations in gene therapy development; **research priorities** how we could prioritise the research areas based on the current funding considering the current landscape and prospects taking into account Australian innovation; **research translation** the current understanding of translational research and how Australia can maximise research by creating intellectual property research; **collaboration and support** improving collaboration in the gene therapy research community; and finally future perspectives. A total of 44 responses were received from across Australia.

Appendix 4: Key Informant Interview Summary

Key informants (n=12) with diverse expertise across multiple roles were interviewed. 83% of key informants had research and development expertise, while 58% had international experience and 50% had experience working with industry, commercialising gene-related therapies, and clinical trials. Key informants with experience in leadership, academia, intellectual property development, licensing technology, manufacturing and regulatory approvals, clinical mission and philanthropic funding, translational process development and implementation were also interviewed.

Key Informant Experience	%
Research & Development	83
International	58
Working with Industry	50
Commercialising	50
Clinical trials	50
Leadership	33
Academic experience	33
Intellectual property (IP) development	25
Licensed technology	25
Manufacturing and regulatory approvals	25
Clinician	17
Mission and Philanthropic organisation	17
Translational process development	8
Implementation	8

The key informants interviewed held multiple roles. The table above reflects the different roles and responsibilities held.

The key informants were experts in the different delivery methods of gene-related therapies. While 33% were experts in AAV technology, 67% viewed AAV as the world's foremost commonly used gene delivery system due to its properties. 17% of key informants were also involved in delivery systems that involved lentiviruses, lipid nanoparticles, antisense oligonucleotides, and chimeric antisense receptor (CAR) – T. In addition, 25% of our key informants were involved in platform technologies while 17% were involved in developing stem cell-based organoid models.

Technologies developed and used by key informants	%
Adeno-associated viruses (AAV)	33
Lenti viruses (LV)	17
Antisense Oligonucleotides (ASO)	17
Chimeric Antigen Receptor (CAR) -T CAR-T	17
Clustered regularly interspersed short palindromic repeats (CRISPR)	8
Nonviral delivery methods (lipid nanoparticles)	17
Platform technologies	25
Stem cell-based organoid models	17

The key informants were experienced in many different technologies in gene-related therapies.

The interviews targeted the key research gaps, main challenges and barriers to implementation, Australia's niche capabilities in the international landscape, and opportunities to leverage current research/funding nationally and internationally.

Key Research Gaps

42% of key informants were concerned with the delivery methods of gene-related therapies. The need for better, safer and more efficient vector systems with less adverse reactions was highlighted. 33% stated that there is a need for more fundamental and rare disease research. While 17% felt the need for common platforms/pathways, diagnostics and gene therapy strategies. In addition, the key informants also mentioned the need for research into complex diseases, CRISPR-based diagnostics, molecular research, gene therapy screening methods and Health economics to name a few.

Key Research Gaps	%
Safety and effective delivery methods	42
Basic Research: identification of targets/pathways/pipelines	33
Rare Disease	33
Common platforms/pathways	17
Diagnostics	17
Gene therapy strategy	17
Complex diseases	8
CRISPR-based diagnostics	8
Molecular Research: promotors, genetic switches	8
Gene therapy screening methods (invitro methods)	8
Health Economics	8
Pathogen Genomics	8
Nanotechnology	8
Combination of stem cell therapies with gene therapies	8
Predictive tools for patient responses to therapy	8
Enzyme replacement technologies	8
Somatic cell and gene therapy	8

Main challenges and barriers to implementation

The top challenges and barriers to implementation identified by the key informants were the cost of the therapy, workforce skills, engagement with industry, research translation and lack of a coordinated national approach. All of these points were mentioned by at least half of the group interviewed and were key themes that were mentioned throughout the interviews.

Challenges and Barriers to Implementation	%
Cost (therapy/production)	83
Workforce skills	75
Engagement with industry	75
Research translation	75
Lack of a coordinated national approach	75
Funding (not adequate)	67
Patient population issues (safety, cohort size, accessibility)	67
Infrastructure (namely vector production)	58
Safety (long-term effectiveness, immune system response)	58

Researchers working in isolation/competition between research groups and institutions	50
Academic system/commercialisation knowledge	42
Education and engagement of healthcare providers and hospital staff	33
Support for intellectual property development	33
Clinician time/involvement	25
Availability of relevant models/large animal models	25
Regulatory requirements	25
Clinical Trial support (prior to commencement)	17
Funding models (not sustainable, only covering the drug)	17
Ethics Concerns in the Community	17
Diagnostics	8
Better global benchmarking	8
Australian Markets	8
Promotion of gene therapy	8

If you could write a grant opportunity in gene-related therapy, what would you fund?

42% of key informants stated that they would write a grant opportunity for a collaborative centre/ coordinated network and would like to see a co-funding approach between industry and government. And 25% stated that they would like to see a production facility while 17% requested grant opportunities for preclinical studies, looking into workforce issues related to skill and infrastructure, improving delivery platforms and developing proof of concept clinical trials.

Grant Opportunity	%
Collaborative Centre/Coordinated Network	42
Co-funding approach between industry and government	42
Production facility	25
Preclinical studies	17
Workforce issues - skills and infrastructure gaps	17
Delivery platform development	17
Proof of concept clinical trial	17
Stable packaging cell line	8
Novel viral vector capsids	8
Antibiotic resistance-free plasmids	8
Genetic switches	8
Gene therapy for the eye	8
Development of treatments (through one centralised facility) for single mutation recessive diseases	8
Gene therapy for complex disease	8
Education of paediatricians	8
Natural history studies	8
Health Economics Research	8
Rare disease and cancer	8
Cross-disciplinary research	8
Rare disease (sample collection, biobanks, registries)	8

Australia's niche capabilities in the international landscape

The top four niche capabilities respectively were the development of a collaborative network, improving clinical trial capability, developing preclinical and discovery research capability and development of novel delivery systems.

Niche capabilities	%
Collaborative network	42
Clinical trial capability	25
Preclinical and discovery	25
Development of novel delivery systems	17
Central facility (That is a global destination for Gene Therapeutics)	8
Patient registries for rare disorders	8
Manufacturing and translation capability	8
Pathogen genomics	8
Duchenne Muscular Dystrophy	8
Liver diseases	8
Eye diseases	8
Haemophilia	8
Rare disease	8

Opportunities to leverage current research funding/ nationally and internationally

58% of key informants stated that it would be important to leverage funding by partnering with industry and 33% stated that Australia is well positioned to bring clinical trials from overseas due to our R&D tax incentives, regulatory frameworks, clinical care, patient population and urban centres. One of the key informants reiterated that Australia should begin medical tourism and establish itself as a gene therapy centre for the world.

Leverage	%
Partner with industry	58
Clinical trials from overseas due to R &D tax incentives, regulatory framework, clinical care, and patient population and urban centres	33
Examine current investment and procurement models	25
NHMRC, ARC, MRFF	25
Collaborative process between stem cell people and gene therapy	25
Co-investment - match government funding with industry funding	17
Disease Foundations & Special Interest Groups	17
Australian Genomics networks and infrastructure	8
ReNew funding at MCRI and Stem Cell mission	8
Brain Incubator	8
Pathway to set up start-up companies	8
Austrade	8
Clinical researcher connection to big pharma	8
Genetic counsellors	8
IPSC human tissue models for high throughput drug screening	8

Appendix 5: Consumer Interview Summary

Three (n=3) consumer representatives were interviewed. The consumers included a parent of a child who has a genetic disease, head of research at a patient representative organisation who was experienced in raising awareness and advocacy and clinical trials access and limitations. The third consumer was involved in gene-related therapies related to the rare cancer space.

The main challenges with gene-related therapies

The two main challenges encountered by consumers are the cost of the treatment and the access to treatment. In addition, reimbursement of treatment, the need for early diagnosis, safety and long-term benefits were of concern. Finally, the consumers felt that there needs to be a mechanism to attract clinical trials to Australia. Consumer #3 (C3) commented that gene-related therapies for cancer are the third line of treatment and by the time the patients receive this treatment, they are very weak.

The future targeted research in gene-related therapies

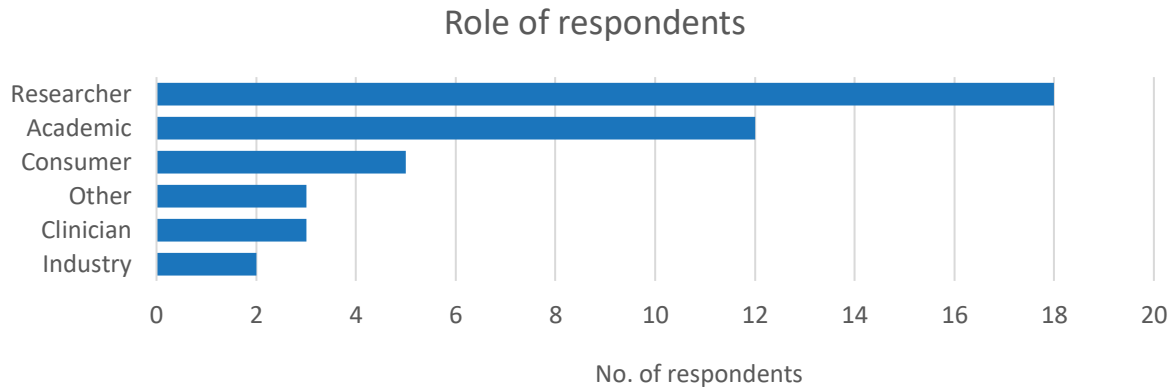
The consumer representatives agreed that the research undertaken should result in early diagnosis (i.e., newborn screening) and treatment. Using novel technologies (viral vector therapy, CRISPR, Pluro protein, CAR-T therapy) provides hope to consumers who had little or no hope previously. It is important for research to be channelled as widely as possible but not at the expense of a lot getting done with no results. Consumer #2 (C2) stated that the development of gene therapy in a platform, with a plug-and-play mechanism would result in therapy for more patients with varied genetic disorders while C3 hoped that gene related therapies would be the second line of treatment instead of the current third line of treatment. They all agreed that basic research to improve the delivery systems would be of utmost importance.

The future improvements in gene-related therapies

The top three improvements for the future were building on education to patients and encouraging community representation in research projects; providing equitable access to clinical trials as well as proven therapies and introducing better funding models.

Appendix 6: Consultative Survey Summary

Based on the key informant and consumer interviews the survey was developed for further consultation. We received 44 responses inclusive of 10 partial responses. The majority of respondents were researchers and academics while consumers were third respondents. In addition, a few clinicians, industry players and other categories responded. The other category included a consultant, core-facility manager and a person from the not-for-profit sector.



Others: consultant, core facility manager, not-for-profit

Section 1: Current Research

Question 1.1 In your opinion, what are the most significant recent advancements in gene therapy research in Australia? (n=35)

Common Themes	
Clinical Trials	• Newborn screening pilot for gene therapy clinical trial (SMA set precedent). • Being able to provide gene therapy to patients in Australia via clinical trials. • Preparation of commercially sponsored trials in disciplines outside of neurology.
Manufacturing	• Increasing capacity to deliver treatment locally.
Therapy Approval/Funding	• TGA approval of Luxturna, Zolgensma, CAR-T cell therapy. • Cost sharing between state and federal governments. • FDA approval of AAV-based products.
Technology	• Somatic cell CRISPR genome editing. • CRISPR, mRNA and lentiviral vectors. • Patient cell models (iPSC, organoid etc). • OmniCar – a universal CAR-T platform.
Manufacturing Capacity	• NSW Health investment in clinical grade vector production facility.
Research	• Preclinical development of therapies to treat cardiac and neurological disorders, which have been supported by recent infrastructure investment to establish the UQ Viral vector Core. • Next generation/engineered AAVs developed at CMRI. • Develop liver targeting AAV capsid variants. • Gene editing for cellular reprogramming in late-stage eye disease. • Gene therapy in patients with transfusion-dependent beta-thalassemia.

Question 1.2 Are you able to share an international exemplar in gene therapy development? (n=27)

The international exemplars could be summarised according to therapies for targeted diseases and the respective technologies used, organisations/consortiums targeting particular diseases and therapies, and international clinical trials.

Therapies for targeted disease
AAV gene therapy related developments
Zolgensma for Spinal Muscular Atrophy (SMA)
Luxturna for Leber's congenital amaurosis (LCA)
Elevidys for Duchenne muscular dystrophy (DMD)
Roctavian and Hemgenix for Haemophilia A & B
Lumevoq to improve vision loss in people affected by Leber hereditary optic neuropathy - a form of mitochondrial disease that affects 100 families in Australia
n of 1 (made to order therapies): spastic paraplegia type 50 (SPG50)
CAR-T therapy related developments
Yescarta for large B-cell lymphoma
Kymriah for relapsed or refractory follicular lymphoma
GD2-specific therapy in solid cancers
Antisense Oligonucleotides Synthesis (ASO)
Spiranza & Nusineren for SMA type I, II or IIa
Exondys for Duchenne Muscular Dystrophy (DMD) gene
n of 1 (made to order therapies): Batten disease, Ataxia-telangiectasia, KCNT1 epileptic encephalopathy
Various types of neuromuscular disorders such as fascioscapular dystrophy
CRISPR- CAS9
Sickle cell disease (clinical trial CTX001)
β-Thalassemia (clinical trial CTX001)
Lung cancer
Organisations/consortiums targeting particular diseases
Central Nervous System (CNS) diseases e.g. *Sanfilippo* from Lysogene (https://lysogene.com/our-technology/)
Bespoke gene therapy consortium from US - public private initiative to build standardisation into gene therapies (especially rare diseases)
Foundation fighting Blindness (currently Spark Therapeutics)
Children's Hospital of Philadelphia
SickKids Toronto
Start-ups funded by families (FAST) - e.g. for ASO therapies
Sangamo Therapeutics - https://www.sangamo.com/
UK Respirotory (Cystic Fibrosis) Gene Therapy Consortium: https://www.respiratorygenetherapy.org.uk/
International trials for the following diseases
SMA, and primary immunodeficiencies including RAG1 and RAG2 deficiency are current examples

Questions 1.3 What do you think are some of the current challenges and limitations in gene therapy development? (n=44)

Other: Hospital capacity, patient education and engagement for informed consent, public engagement and understanding

Question 1.4 Would you like to provide further details or comments about the topics you have ranked? (n=18)

Comments listed under key themes.

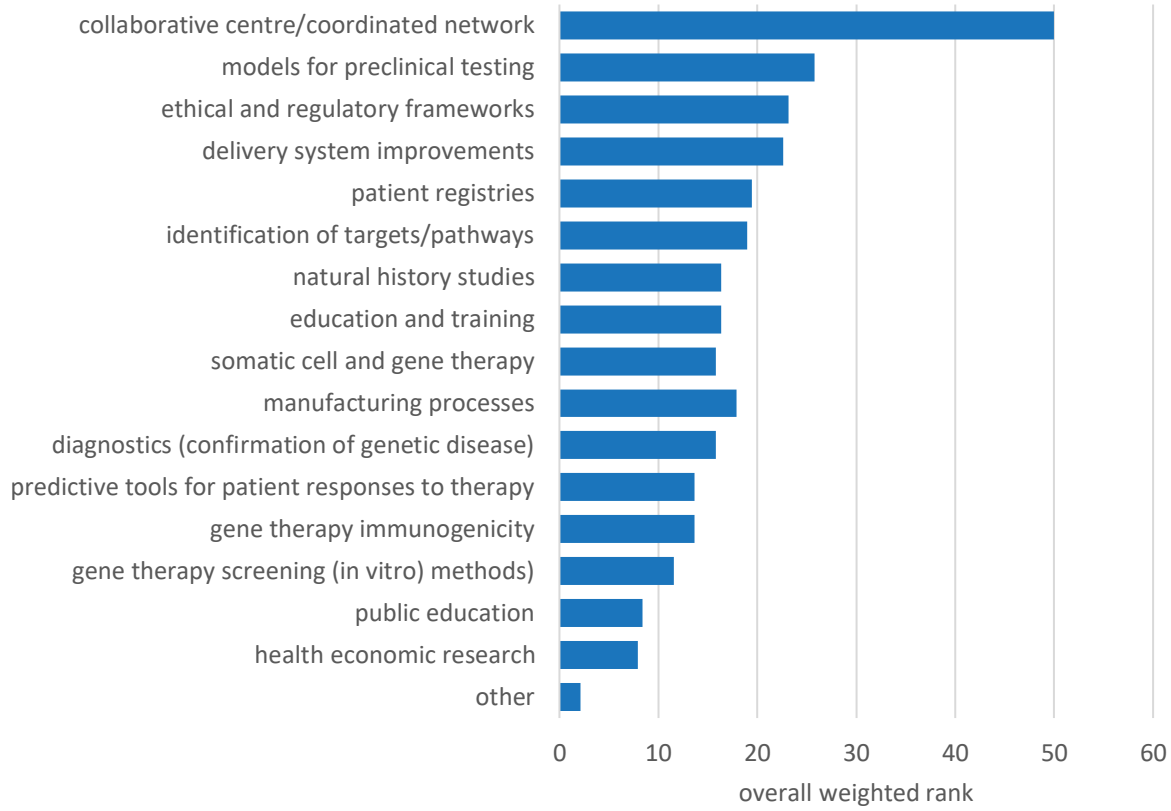
Regulatory requirements	• Health technology assessment processes. • Clear Government policy and a willingness to fund specific therapies which would encourage greater research and industry collaboration. • Major problems are infrastructural; need to first establish a health care system and translational models appropriate for genomic medicine. • Accelerated approvals by the US FDA have not been consistently applied. Using surrogate endpoints and natural history data has not been accepted for accelerated approvals (which goes against FDAs own guidelines). For rare neurological conditions, this has meant that the burden of demonstrating clinical efficacy has been too high and meant that the developers of many promising candidates have run out of cash and investment. More consistent application of regulatory guidelines would help to de-risk gene therapy development, enable more confident investment in GT programs and stimulate the field. However, before therapies reach this commercial investment stage there are also barriers to the translation of laboratory research into gene therapies into pre-clinical and clinical research. Better funding models and

	coordinated programs of research (not just national, but international) are needed to bridge the 'valley of death' for these candidates.
Manufacturing	• Recent investment into the Westmead GMP facility is a significant leap forward for Australian manufacturing capacity, this is only one part of the puzzle. Greater capacity in scalable GMP-like manufacturing is needed, to ensure process development is optimised at with reduced costs at early stages to ensure large-scale manufacturing is economically viable and production yields are maximised. • The UQ Viral Vector is aiming to develop these capabilities to support streamlined transfer to larger GMP manufacturers. These capabilities require a workforce that is highly skilled in advanced manufacturing techniques, which is lacking due to Australia's limited manufacturing industry. • Skilled manufacturing workforce resourced with appropriate information on trials and emerging therapies. Increased capacity for clinician/researchers to enable clinical trials.
Research Translation	• The bridge from research to therapy is huge with many challenges
Delivery systems and therapies	• CAR-T cell therapy is burgeoning internationally but is at an embryonic stage in Australia despite significant clinical activity and preclinical innovations. We are missing out as a nation. • Types of therapies: mRNA, viral vectors, CAR-T. • Significant attention has been given to mRNA therapies, viral vector-based therapies, including gene therapies have been quietly building in the background, yet capabilities remain limited.
Nationally coordinated approach	• Because gene therapies are often in rare diseases, a coordinated national approach is vital to the success of any program. It is not financially viable to establish every program at every hospital (especially when doing trials). • Ideally having an attractive coordinated healthcare system that records details about relevant patient groups ready for an industry representative. This is particularly relevant for those with rare diseases but there is no critical infrastructure supporting this and as such trials are preferentially run in Europe/USA. • One of the biggest issues is the lack of a national 'authority' that could drive development of a nationally coordinated approach to addressing the main issues. Had the AHMAC structure not been dissolved due to COVID, states and territories would have progressed with this activity, which would likely have been modelled on the National Health Genomics Policy Framework. While the Health Technology and Genomics Collaboration has been recently stood up, it will take time to understand its role and get folk engaged, let alone get across such issues, especially given the departure of policy officers with relevant content expertise across governments in recent years. Of note, the cost of gene therapies is not an issue if PBAC approved and PBS-funded the

	Commonwealth will pay and if MSAC-approved and NHRA- funded all gov will pay as per the NHRA.
Cost	• Cost/availability of manufacturing vector for preclinical studies is prohibitive. • The issue of cost relates to implementing these therapies, which is borne by the public.
Technology Improvement	• Technology improvements in - tools for delivery and expression- remain critical. • Research should include the development of improved preclinical models. Many gene therapies that work in rodents do not translate to humans, meaning years of time and money are wasted.
Australian landscape for gene therapy	• Australia is not seen by international clinical research consortia or pharma as a place to "do business" for gene therapy research, clinical trials and therapy. • Australia doesn't have a leading role in gene therapy development - this may be linked to a developing but still limited research translation culture. However, Luxturna is a positive example of gene therapy development and implementation in Australia. • Due to the state of the field of gene therapy, scientists leave Australia in search of opportunities in other countries in both academia and the private sector for gene therapy research.
Education and Engagement programs	• Gene therapy health literacy in the patient community is low. Education and engagement programs need to be developed to improve health literacy in this complex and evolving field to enable informed consent. The onus should not fall on individual patient organisations to provide these resources, but rather it would best be through a coordinated national approach.
Funding	• Limited industry funding for rare diseases without significant government investment. Philanthropic funding will progress gene therapy which could lead to a lack of equitable access in certain cases. • Development of gene therapies requires significantly more investment from the government for all stages from basic research, preclinical to clinical trials. This research should include development of improved preclinical models. Many gene therapies that work in rodents do not translate to humans, meaning years of time and money are wasted.
Clinical trial sites	• Setting up trial sites is more complicated and time-consuming than for drug trials as ethics and governance is complex and protracted. Need to balance safety concerns that will never be 100% known. • Access for Australian patients to gene therapies in clinical trials without a site in Australia. Limited number of participants in clinical trials - i.e., more eligible patients than slots available (due to cost and safety concerns). • Inadequate clinical trial readiness, including a lack of rare disease patient registries to assist with planning and recruitment to trials.

Section 2: Research Priorities

Question 2.1 If $2-5 million grants became available, how should we prioritise the following research areas in terms of funding and resources? Please consider the current landscape and future prospects as well as areas that can capture Australian innovation. (n=38)



Question 2.2 Would you like to provide further details or comments about the topics you have ranked? (n=15)

Comments listed under key themes.

Collaborative centre/ coordinated network	• As Australia is very small in comparison to other competitors and it is important to set up a collaborative gene therapy centre/network to enable education and collaboration between researchers and sites. • Building on existing strengths. • Collaboration between researchers, industry and facilities will play a vital role in fast-tracking development and improving manufacturing processes to translate therapies.
Research	• More attention to rare disease. • Diagnostics (n=4) • Important to identify rare diseases in Australia. • To build critical infrastructure to record this information via registries. • Early diagnosis ideally pre-symptomatically through newborn screening. • Preclinical research into diagnosis.

	• More Indigenous genomics research and engagement/leadership with Aboriginal and Torres Strait Islander peoples. • Natural history studies (e.g. neurodevelopment disorders) to prioritise which diseases should be treated with gene therapies.
Clinical translation	• Developing human preclinical models to test gene therapies to significantly improve the likelihood of successful translation. • Gaps in translation, including an easy and coordinated pathway to navigate regulatory framework and clinical translation/implementation. Facilitating and investing into joint industry-academic research with clear translational objectives. • Clinical trial readiness and building networks in collaboration with other partners.
Delivery systems and therapies	• Improving delivery systems/ methods and immunogenicity will play an important role in reducing the amount of virus required for therapy, enhancing efficacy, causing fewer side effects and drastically reducing costs. • CAR-T cell therapies for solid and liquid cancers. • Typically, clinical/hospital focussed. Although translation will be seen only if hospital system is prepared.
Education and Training	• Need for workforce training for manufacturing. • Lack of funding for clinical researchers/scientists which then results in a gap of translating clinical trials and clinical practice.

Question 2.3 Are there any specific diseases or conditions where the potential of gene therapy remains largely untapped? (n=33)

Rare Disease	Rare monogenic disease (n=4)
	Ataxia telangiectasia, hereditary spastic paraplegia, white matter diseases
	Rare neurodegenerative diseases
	Childhood dementia group of disorders - severely unmet level of urgent need (n=2)
	Childhood neurological conditions
	Leukodystrophy - lots of potential and interest from industry
	Multiple neurodevelopmental disorders
	Centronuclear myopathy (DNM2)
	Motor neurone disease is a late onset condition with 15% that carry a monogenic form - whole families are affected - it causes early death (<=5 years from onset)
	Mitochondrial diseases (n=2)
	Congenital mismatch repair deficiency
	Duchenne muscular dystrophy
	Fanconi anaemia
Retinal	Inherited retinal diseases
	ocular diseases: there are many recessive, loss of function, retinal dystrophies which will benefit from gene therapy
Cancer: Solid Tumours	CAR-T cell therapies for solid cancers (n=3)
Rare Cancer	Rare and less common Cancers
Other	Kidney Disease and many of the other more adolescent/adult-onset monogenic disorders
	Cardiovascular disease remains the biggest contributor to human mortality and yet gene therapies targeting heart disease have remained elusive. This, in my opinion, is due to the lack of adequate vector targeting to the heart.
	Cystic fibrosis (n=2)
	Many blood cell diseases "easily" conceptualised compared to others. Bone marrow failures. Immunodeficiencies etc
	Metabolic disorders

Question 2.4 Are there any particular aspects or technologies within gene therapy that require focused attention and advancement? (n=27)

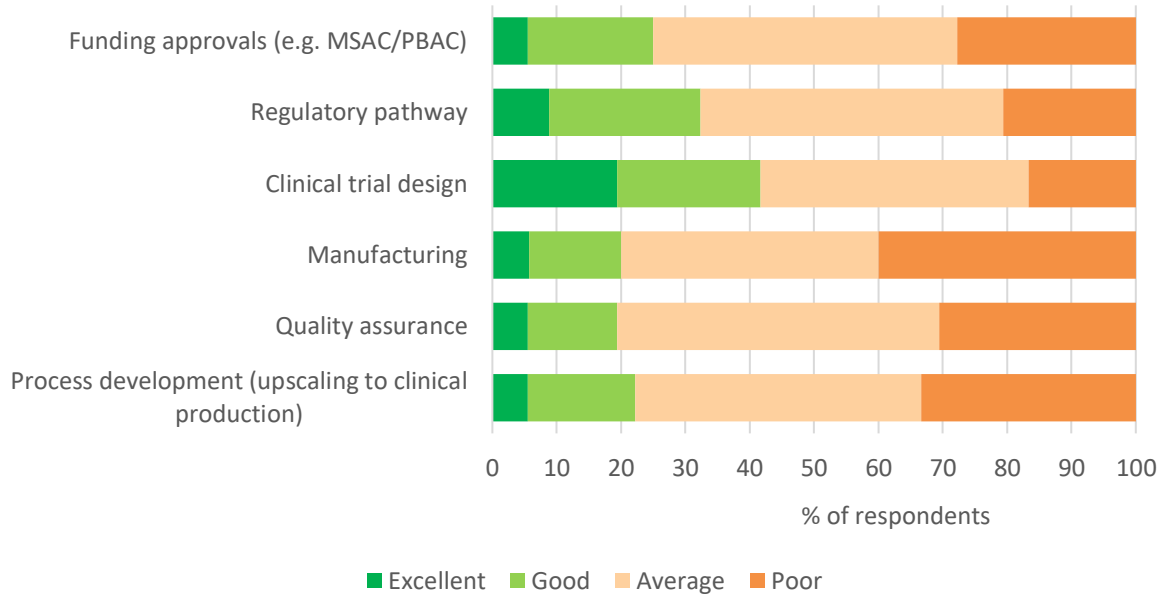
Delivery/Safety	Improved delivery systems.
	Delivery mechanisms.
	Delivery to the relevant cell-types affected and expression.
	Delivery of larger genes.
	Components of capsid and content construct to improve efficiency.
	Unwanted immune system reaction.
	Gene delivery into the eye needs further refinement to reduce risks. Technologies that can be improved include affinity of vectors to certain target cells in the retina, penetration through layers of the retina, use of antisense molecules rather than viral vectors carrying the entire gene.
	AAV capsid variants with altered tropism and the interaction of these with the host immune system.
	Safer vectors to deliver gene therapy. Ensuring persistence.
	Research to enhance the effectiveness and safety of gene therapy - novel capsids, non-viral vectors, improved CNS targeting, reduce immune responses.
	Immunogenicity, and ways to limit this.
	CNS targeting of vectors for safe and efficient delivery to the brain via peripheral delivery routes. Rapid advancement into clinical use of technologies such as Imlifidase and similar to enable the delivery of gene therapy to individuals with pre-existing antibodies to gene therapy vectors. Biomarkers for prognostication and treatment effect.
Manufacturing/ Infrastructure	Upscaling of viral vectors is a bottleneck preventing the advancement of viral-mediated gene therapy. I have seen firsthand the work to overcome this in centers in the UK and I do not see that there will ever be the funding resources to deal with this here in Australia. We will continue to rely on other countries to get past this obstacle.
	Unlike other advanced therapies (e.g. protein), manufacturing of viral vectors is in its relative infancy and is not standardised. A co-ordinated effort from industry and academia is required to improve manufacturing efficiency and reduce costs. Developing ways to improve transgene expression can also be improved, e.g. greater virus uptake into cells, less degradation, improved nuclear localisation.
	Capital city-based infrastructure for clinical trials of CAR-T cell therapy.
Clinical translation and approval	Outcome measures and endpoints for clinical trials.
	Outcome measures that are meaningful and measurable.
	Regulatory changes that allow evidence from human in vitro models to be accepted as evidence.
	translation into clinical care / access for patients.
Technologies	Gene editing.
	More attention in genome editing.
	mRNA therapies.
Education and Engagement	Health literacy for informed consent.
	Public and clinician engagement and education is key.
Other	Target tissue access, and safety switches if appropriate.
	Efficiency of primary haematopoietic stem cell editing, transduction.
	Understanding tissue specific isoforms.

	Viable models of care for rare and ultra-rare diseases, including novel collaborative approaches for patient care.
	Lack of any nationally coordinated approach for both research and development and policy/funding/implementation.
	We could look at our role in progressing existing gene therapies currently under development overseas. I think sometimes it's easier to focus on side questions, like community education and ethics. While this is without a doubt important, we shy away from investing into risky but promising gene therapy development that could benefit people now. Because of this, patients are already accessing risky experimental treatments overseas that are not well regulated.

Section 3: Research Translation

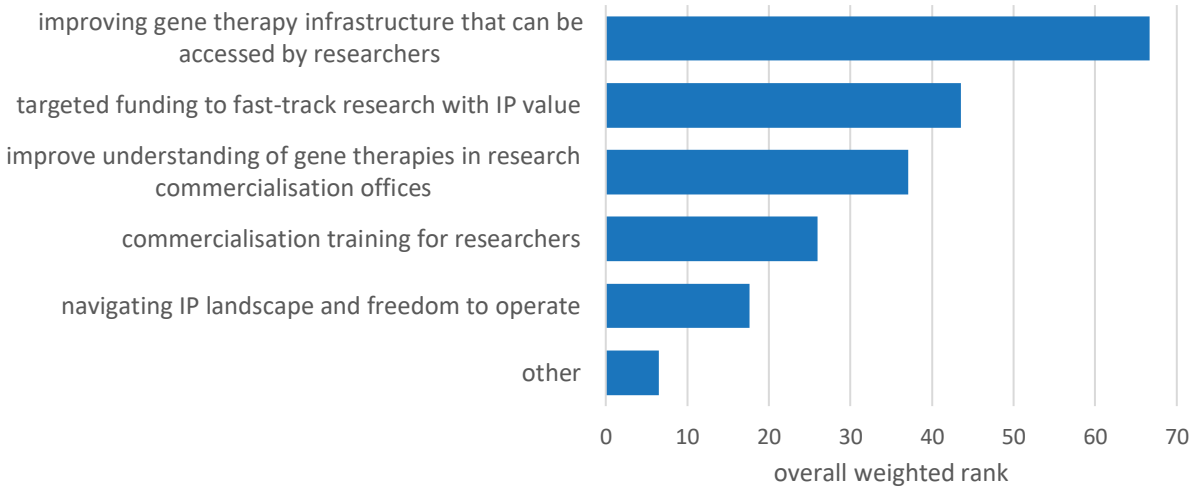
Question 3.1 What is your level of understanding of the following translational research activities (preclinical development to phase I trials)?

Key:
Excellent = "My product is in Phase I and I have had to navigate this already"
Good = "I have started to become aware of this as my project matures"
Average = "I know that I need to do this but don't really have much knowledge of how to do it"
Poor = "My research is too early to consider this"



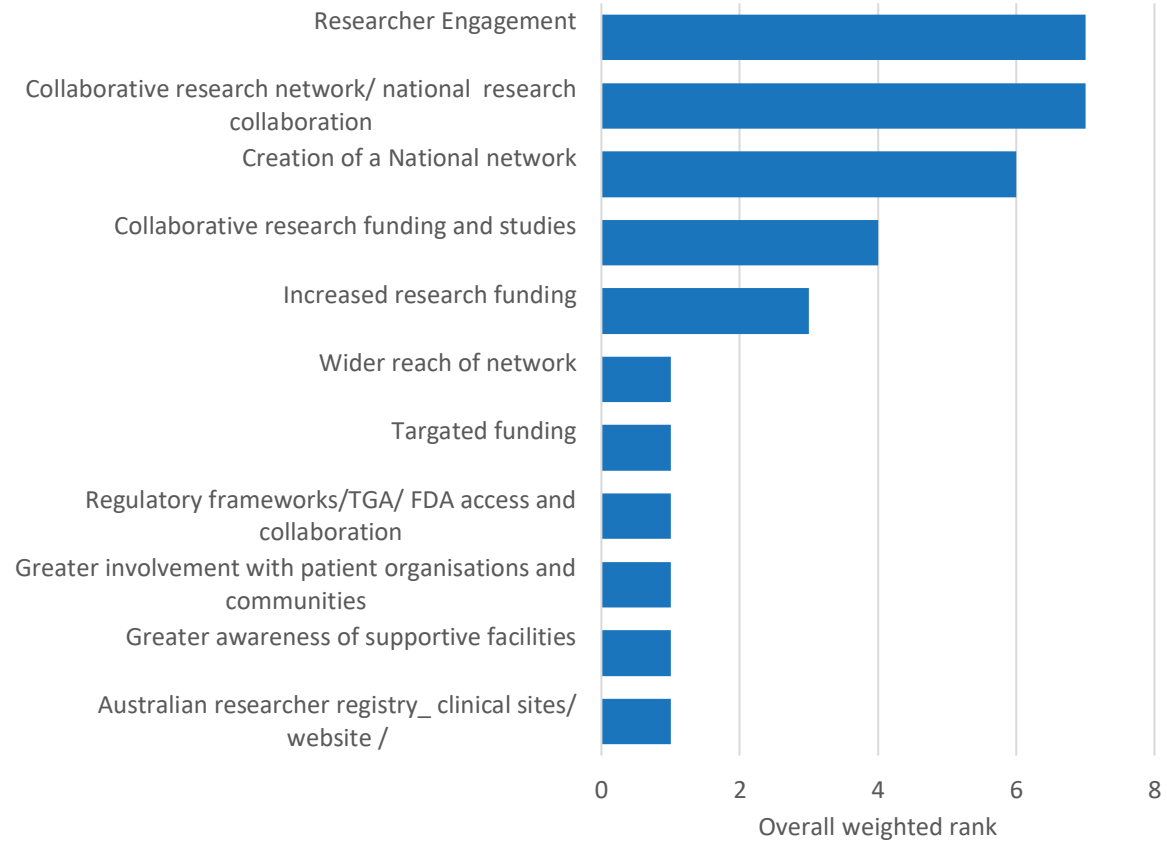
The level of understanding for research translation activities in areas of process development, quality assurance, manufacturing, clinical trial design, regulatory pathway and funding approvals (e.g. MSAC/PBAC) generally received a 20 – 30% response of 'excellent' and 'good', while the majority (~50%) stated they had an 'average' understanding of the research translation pathway.

Question 3.2 How can Australia maximise the value of the research throughout the creation of intellectual property research? (n=36)



Section 4 Collaboration and Support

Question 4.1 What measures do you believe could improve collaboration and support within the gene therapy research community? (n=20)



Examples of research engagement suggested: webinar series to share experiences across ecosystem/ local international talks/ national conference/ state-based hubs and events/ promote sharing of knowledge/training workshops.

Section 5 Future Perspectives

Question 5.1 In your opinion, what major breakthroughs or advancements do you foresee in gene therapy research in the next 5-10 years? (n=30)

The following common themes emerged from the responses.

Improved delivery systems and advancements in technologies	• CRISPR and other gene editing technologies. • Cell-based gene therapies/CAR-T cell therapies - solid cancers. • mRNA technologies. • Viral gene therapies - improved delivery systems with safer vectors, AAV capsid variants with more specific organ tropism, understanding the immune response to AAV and how this can be managed in the clinical setting. • More precise delivery and engineered cell state-responsive gene expression. • Use of technologies to overcome pre-existing antibodies to gene therapy vectors that are a barrier to treatment access. • Platform technologies adapted for many diseases. • Increase in the number of available gene therapies especially for rare disease. • Effective delivery of gene therapy to the brain and adequate expression in relevant cell types of the brain. Circumventing pre-existing anti-AAV antibodies and the development of anti-transgene antibodies after gene therapy. Understanding of benefits of autologous HSC gene therapy vs AAV gene therapy. Biomarkers/outcome measures to accurately measure effectiveness of gene therapies in a short period of time.
Effective treatment/therapies for more diseases.	• Cardiovascular disease and diabetes as priorities e.g. atherosclerosis, heart failure. • Neurodevelopmental disability. • Existing incurable diseases. • New ocular gene therapy treatments. • Monogenic diseases. • Rare diseases e.g. haemoglobinopathies, cystic fibrosis. • Solid cancers. • Musculoskeletal disease e.g. Duchenne Muscular Disorder.
Streamlined regulatory pathways leading to better outcome measures	• Equitable access through a coordinated approach. • Early genetic diagnosis + gene therapy for some disorders leading to better patient outcomes. • Improved collaborations and industry-supported studies to promote translation of new gene therapies. • Increased number of supported researchers. • 'mainstreaming' of gene therapies for specific genetic disorders; opportunities for truly personalised interventions for de novo conditions. • Diagnosis early by gNBS - particularly when incidence is reduced as expanded reproductive genetic carrier screening is more broadly available.

	• Improved manufacturing efficacy (less loss of vectors during upstream and downstream processes) improved organ-specific targeting possible expansion of RNA for gene therapies. • Bespoke and affordable proven therapies entering the marketplace. • Gene therapy will become the 'norm' in therapeutics. • Research will be expanded to long term outcomes and complications of gene therapy in the real world.

Question 5.2 What role will Australia play in these advancements? (n=29)

While some believed that Australia had potential to advance in the field of gene therapy, some were of the view that Australia had many drawbacks and changes were required to advance in the field of gene therapy.

Potential to advance	• Australian basic & preclinical research is world-leading, and with support from government and industry, this research will be translational and transformative. We have the potential to offer end-to-end research-translation capabilities in Australia with a coordinated effort. • Melbourne is a centre of excellence for ophthalmic gene therapy. We are already a site for many trials, including Novartis and Janssen. Ability to make advances in the space of outcome measure development. • Australia will be proactive in considering systemic implications of gene therapy adoption/uptake. It remains to be seen what proportion of gene therapies are derived from Australian innovation, the volume of international industry-led advancements are just overwhelming. • Clinical and preclinical innovation and breakthroughs are and will continue to develop in Australia e.g. CAR-T cell therapies for solid cancers. • To have an impact Australia's role will need to be focused to a few types of disorders e.g. neurometabolic, cancer, immunodeficiency. • Leading research and clinical trials. • Australia is engaged in trying to reduce the burden of rare diseases and will continue to do so. • Contributing to R&D
Drawback and required change	• Overseas, the industry is already working on the next generation gene therapies, for example Kate Therapeutics. Australia is lagging with only nine approved gene therapies. • Australia is not publicly funded, thus limiting access. Role of Australia unsure due to risk aversion. • Based on current infrastructure, capabilities and capacities, very little. However, once AAV manufacture is established and the above issues addressed/funded, and with 'right' funding (gov, industry), Australia could play a significant role, although the short-term roles are likely to be in terms of basic R&D and clinical trial recruitment. • Australian researchers to contribute towards global efforts to improve disease diagnosis. More industries bringing trials to Australia in addition to

	the USA and Europe, and natural history studies improving the characterising the population in Australia (rather than based on overseas estimates). • Adapting technologies developed elsewhere and repurposing these technologies for different diseases/individuals. • Developing a supportive healthcare system to roll out SNP array for everyone (polygenic risk scores for common diseases), and whole genomes for rare diseases. • Allocation of adequate funding and resources we can dedicate to progressing gene therapy in Australia.

Question 5.3 How do you envision gene therapy transforming patient care and healthcare in the coming years? (n=31)

Most participants were of the view that gene therapy will transform the healthcare system. Some suggested ways to transform patient care and therefore the healthcare system.

Early Diagnosis and treatment	We will be able to diagnose early through genomic testing and treat earlier through gene therapy.
	Genetic diseases will be treated at birth and as the babies grow they won't even know there was a gene defect.
	Better access to diagnosis of rare diseases through more widespread genetic testing programs.
	Currently in ophthalmology, only around 10% of patients with inherited retinal disease have had testing (1), but there is a huge campaign on presently to change this. I expect that in the near future, all patients will know their genotype. This will be added by programs like, the VENTURE IRD registry (2). Then, targeted gene therapy options will be available to all, as they are developed. (1) Gocuk SA, Jiao Y, Britten-Jones AC, Kerr NM, Lim L, Skalicky S, Stawell R, Ayton LN, Mack HG. Genetic testing of inherited retinal disease in Australian private tertiary ophthalmology practice. Clinical Ophthalmology 2022; 13(16): 1127 - 1138. (2) https://www.cera.org.au/venturing-forward/
	Gene therapy has the potential to provide a curative treatment for degenerative neurological paediatric diseases in the future, but only if gene therapy development goes hand in hand with a newborn screening landscape that facilitates clinical trials in pre-symptomatic individuals
	Gene therapy will have potential to modify diseases - I'm not sure will be a cure in long term- more likely modifying morbidity and mortality there will be a need to diagnose diseases earlier disease course will change and with that there will be a change in need for ongoing healthcare to assess and cope with these.
Increase in approvals and increased availability	There will be more TGA approvals, potentially having a huge impact on the lives of individuals
	Selective initially - before becoming more widely available / common-place.
	More bespoke and affordable proven therapies entering the marketplace
	Cheap, genomics enabled therapies that become affordable and are PBS listed

Improved outcomes for patients	Transformative for several chronic and acute diseases
	I think it will be transformative, the closest prescription to a cure yet
	Treatment options available for currently untreatable terminal conditions.
	Potential to change prognosis for rare diseases
	Gene therapy giving access and hope of treatment to previously untreatable eye diseases
	For solid cancer patients, CAR-T cell therapies will provide a treatment modality not addressed by current immunotherapies including immune checkpoint inhibitor therapy
	More precision medicine for rare and less common diseases.
	Gene therapy will transform patient's quality of life and extend life for a range of diseases that currently have no cure.
	This will hopefully move some debilitating or fatal early onset disease into managed/treated states allowing experience of a full lifespan. It will also hopefully begin to minimise some chronic disease, though the cost of wide scale delivery (i.e., short term costs) needs to be balanced against short-term fiscal reality and long-term health cost benefit.
	I think gene therapy will make an important impact in the care of patients with monogenic diseases which currently lack an effective therapy - it already has for an important handful. This group of conditions will continue to grow. Acquired diseases, while significantly more common, are a more challenging target for gene therapy.
	Clinical trials demonstrating effectiveness of new cell-based gene therapies.
Cost saving to the health system	Current approaches, such as bone marrow transplant/hematopoietic stem cell transplant do not usually address the underlying genetic disorder but correct the haematologic abnormalities such as for Fanconi Anaemia. Gene therapy will significantly reduce the lifelong risks of cancer. Moreover, gene therapy will be safer than bone marrow transplants and reduce the risks of graft versus host disease, thrombotic microangiopathies, etc. Ultimately, gene therapy will save the health care system significant funds.
Challenges to overcome	Given the possibility of treating inherited retinal diseases, there will be increased patient demand on genotyping and natural history tracking. Dedicated ocular genetic clinics will be in high demand. Clinical geneticists and genetic counsellor will be even more stretched in their time. Pathology labs won't be able to cope with the requests for molecular diagnosis in ocular genetic diseases.
	I think it will be transformative, but I am not sure it will become easily accessible in Australia any time soon.
	This may become a matter of course but will need significant clinical funding to support developmental clinical care to this level otherwise risks significant health equity issues
	The aim will be to improve patient care, and reduce the burden of rare diseases, but we also need to be mindful of limitations such as the possibility of harmful side effects.
	Will eventually become 'another tool in clinicians' toolkit' but that's a very long way off. Just making some accessible doesn't mean it's used/useful. Lots of implementation research needs to occur to ensure gene therapies are useful to clinicians and patients.
	Will only be available for a limited number of diseases. Great for those but many will miss out. Greater investment in carrier screening/ genetic NBS to prevent disease/enable early intervention is needed.

	Absolutely. The potential impact of gene therapy on patient and family [care/impacts, longevity, morbidity], health system utilisation, funding is HUGE, but likely to be cost effective at the end of the day. Unfortunately, our current R&D policy/government and hospital systems (both public and private) are not prepared to take advantage of opportunities at the moment. Much work needs to be done.
	I think Australia will be proactive in considering systemic implications of gene therapy adoption/uptake. It remains to be seen what proportion of gene therapies are derived from Australian innovation - the volume of international industry-led advancements are just overwhelming.

Section 6 Additional Comments

Question 6.1 Do you have any additional comments, suggestions or insights regarding gene therapy research (intentionally or nationally) that were not covered in the previous sections?

- Australia is an excellent place for gene therapy research but not for translation.
- Better support for rare diseases across the board e.g. centres of excellence in each capital city.
- A system to make patients aware of trials and possible therapies.
- Antisense molecules to be labelled "gene-based" therapy.
- Australian R&D landscape to lend itself to attracting industry/international interest/funding.
- The gene therapy pipeline indicates an impending fiscal and health system tsunami with no solution to understand the impacts facing Australian budgets and health systems and least of all the economic opportunities that are to be had.
- Be mindful of possible limitations and alternatives.

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