LUMINESCE
Alliance
Innovation for Children's Health

Parliamentary Inquiry Submission

Inquiry into Approval Processes for New Drugs and Novel Medical Technologies in Australia with a particular focus on those for treatment of rare diseases and conditions where there is high and unmet clinical need

So it turns out that I could easily write an entire essay about the impact that having a child like Jerry has on the family.

Here is what I have, in a few paragraphs.

As a family the impact of having a child with Jerry's needs is very significant. Priorities shift for everyone and there is an all-consuming focus on Jerry. We are fortunate our children will grow up to have important qualities, such as caring, empathy, resilience and a social conscience.

Although as parents, we feel a lot of guilt in not showing our other children as much attention as Jerry.

Jerry's future is a daunting prospect. The worry surrounding his ongoing care needs and his physical suffering is immense. We face enormous pressure in building a secure financial future for all of our children, and feel this must be done urgently so one parent is able to care for Jerry full time.

I worry about how our family will be affected as Jerry deteriorates and the stress and sadness this will bring all of us.

Jerry has been diagnosed with an extremely rare condition Spastic paraplegia 50 which is a slowly-progressing neurodegenerative disorder that generally presents with global developmental delay, moderate to severe intellectual disability, impaired/absent speech, small head size, seizures, and progressive motor symptoms.

Their only wish is that a strategic and appropriate policy and regulatory setting be considered to pave the way for supporting and funding precision medicine therapies and technologies for children like Jerry; and which will undoubtedly also lead to future access, equity, efficiency and sustainability of the health system.

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About Luminesce Alliance

Luminesce Alliance is a paediatric research hub that galvanises and accelerates NSW led paediatric research, harnessing Partners' strengths to unlock future prevention, treatments and cures for childhood illnesses.

Our Vision

Our Vision is to create Australia's most ground breaking, innovative and translational paediatric research hub that will change children's health around the world.

Our Mission

Our Mission is to have a voice on a national and international platform so that our research is disseminated and implemented to directly improve the health of children.

Our Purpose

Our Purpose is to empower our partners to work together in changing the global landscape in paediatric research.

Luminesce Alliance works bedside to benchtop to bedside

As an alliance between clinical and research organisations, Luminesce Alliance enables clinicians to drive the research agenda - bedside to benchtop - and for researchers to support rapid clinical translation of their work - benchtop to bedside. Luminesce Alliance provides a working demonstration of translational research in paediatrics.

Luminesce Alliance has critical mass

As an alliance we have access to Australia's largest and most ethnically diverse paediatric patient population, with the Sydney Children's Hospitals Network providing care to over 35% of the sickest children in Australia. This critical mass supports the clinical and scientific expertise for examining new models of care, their costs and benefits, and processes of effective integration into our healthcare system.

Luminesce Alliance partners have interlocking and reinforcing specialisations

Luminesce Alliance partners cover a wide range of paediatric health issues, from cancer and rare diseases to neurosciences and mental health. They also share approaches to healthcare including significant expertise in "omics", disease modelling, clinical trials, psychosocial impacts; application of new technologies, and, increasingly, a focus on population health, health economics and health services implementation.

Our Partners

The Sydney children's Hospitals Network
care, advocacy, research, education

Children's Cancer Institute

CHILDREN'S MEDICAL RESEARCH INSTITUTE
Jeans for Genes®

THE UNIVERSITY OF SYDNEY

UNSW SYDNEY

Commonwealth Inquiry into Approval Processes for New Drugs and Novel Medical Technologies in Australia with a particular focus on those for treatment of rare diseases and conditions where there is high and unmet clinical need

Terms of Reference

1. The range of new drugs and emerging novel medical technologies in development in Australia and globally, including areas of innovation where there is an interface between drugs and novel therapies;

2. Incentives to research, develop and commercialise new drugs and novel medical technologies for conditions where there is an unmet need, in particular orphan, personalised drugs and off-patent that could be repurposed and used to treat new conditions;

3. Measures that could make Australia a more attractive location for clinical trials for new drugs and novel medical technologies; and

4. Without compromising the assessment of safety, quality, efficacy or cost-effectiveness, whether the approval process for new drugs and novel medical technologies, could be made more efficient, including through greater use of international approval processes, greater alignment of registration and reimbursement processes or post market assessment.

Introduction

Luminesce Alliance is pleased to provide a submission to this important Parliamentary Inquiry into approval processes for new drugs and novel medical technologies in Australia; and, it is pleasing that the Inquiry will include a focus on access to treatment for rare diseases and conditions where there is high and unmet need.

Thousands of rare and ultra-rare disorders exist. Some are so rare that they don't even have a syndromic name attached to them. While individually uncommon, these rare diseases, including cancers, affect around 400,000 Australian children, with many requiring lifetime care.

The impacts on the health and quality of life for these children, as well as, for their families and the health system as a whole are significant. Children with these disorders typically display a high level of symptom complexity and have significant ongoing health and psycho-social challenges. The burden on the family, the Australian health care system and society is immense.

As a non for profit cooperative joint venture between the Sydney Children's Hospitals Network, Children's Cancer Institute, Children's Medical Research Institute, the University of New South Wales and the University of Sydney; we are at the front line for children living with rare diseases and their families. We are confronted daily with the health, psychosocial and financial impacts on families caring for a child with a rare disease. We also share alongside these families, the challenges and ramifications of barriers that currently exist in accessing new therapeutic and technological responses that are at hand. To demonstrate the obstacles and limitations, we present six Case Studies, they include: three year olds Lucia and Jerry, baby K, ten year old JD, 4 year old Ellie; and 6 year old Cooper.

What the Case Studies validate is there is no more exciting time for Australia to capitalise on the full value of our country's health system and research in collaboration with the entire sector. The gains to be made in enhancing the research, development, trialling and implementation of novel therapies and medical technologies for the treatment of rare disease in the paediatric setting in particular, are enormous. With appropriate levels of support, strong collaborative approaches and implementing a suite of measures, we can reduce the current hurdles facing our community.

To take full advantage of these transformative capabilities, we commend the Parliamentary inquiry to consider the recommendations listed at the end of this submission.

Finally, Luminesce Alliance would like to offer their support to a platform of discussions among relevant stakeholders to discuss views and develop consensus statements to reflect state of the art practice; and, how to integrate, in an equitable manner, powerful new approaches to addressing access to new therapeutic and technological responses for rare diseases and conditions.

Case Study 1 – Lucia diagnosed with WOREE Syndrome

Case Study 1 responds to Terms of Reference 1, 2 and 3

I am the father of a little 3-year-old girl called Lucia who was born with an ultra-rare and devastating genetic condition called WOREE (WWOX-related Epileptic Encephalopathy) Syndrome. I am writing to you as it has come to my attention that you are heading up a new parliamentary inquiry related to the development of new drugs and novel medical technologies.

During our pregnancy with Lucia, an ultrasound scan detected that she had a "thickened nuchal fold" which could be indicative of a genetic problem. A prenatal genetic test was carried out which looked for many known genetic syndromes but no mutations of clinical significance were detected.

Lucia was born in August 2017 via caesarean section and she appeared to be completely normal and healthy even though she did not have a strong cry.

We were discharged from hospital after three days to start our life as a new little family. During the first couple of weeks at home, some signs started to emerge that something wasn't right with Lucia.

She had a really tough time sleeping and would constantly awake with a startle. She also had some difficulty coordinating her swallowing when feeding. Nevertheless, these issues were not enough of a concern to suspect something much more sinister was afoot and we genuinely believed things will settle down. It was on day 18 after Lucia's birth when everything changed. Lucia had her first seizure and she was rushed to hospital for the first admission of more than 30 in her short lifetime.

The first year of Lucia's life was mostly spent in hospital while she was fighting dozens of seizures each day. It was also clear that she was not developing normally, and she did not achieve any of the expected milestones. My wife, who was on maternity leave, had to give up her career after it become clear Lucia will not be able to go to day care and will require around the clock support. During this period, diagnostic after diagnostic could still not provide us with any clue what is underlying Lucia's illness.

On Lucia's first birthday, we finally received a diagnosis following another round of genetic tests which explained everything that has been happening with Lucia. We were told that Lucia has WOREE Syndrome as a result of an extremely rare mutation of the WWOX gene. It was further explained that a deficiency of the WWOX protein has a severe impact on brain development and results in a severe epileptic encephalopathy which is refractory to standard anticonvulsants. Heartbreakingly, we were informed that most children with WOREE Syndrome had an average life expectancy of 4 years. But it was the final piece of news which devastated us - there is no treatment or cure. It was the worst day of our lives and the inevitability of losing our little girl was unbearable.

Since that fateful day 2 years ago, we have been doing all within our capacity to give Lucia the best possible life we can. Unfortunately, Lucia is not able to walk, talk or sit unassisted. She is not capable of crawling or rolling over. She is also progressively losing her vision. Despite these

limitations she receives weekly occupational therapy and physiotherapy to keep her senses stimulated and muscles engaged as much as possible.

Lucia is continuously fed into her jejunum for 22 hours a day via a gastrostomy attached to a feeding pump as she is unable to swallow safely and is at risk of aspirating liquid into her lungs.

Lucia is on a cocktail of 5 different anticonvulsants to try and keep her seizures under control and was previously also on the ketogenic diet, but sadly nothing is helping. Lucia has upwards of 15 seizures per day and suffers terribly as a result. She has had to be resuscitated on a number of occasions after she stopped breathing and has been admitted to hospital more than thirty times, including periods intubated in intensive care.

We take turns to sleep next to Lucia at night as her position needs to be changed every few hours and her secretions cleared using a suctioning machine. We are on guard 24/7 as she chokes frequently which requires immediate intervention. She also requires the use of a respirator at night as she suffers from sleep apnoea.

Now that Lucia is getting a bit older and heavier, my wife is struggling to lift her to put her in her stroller or into the bath and already starting to have significant back problems.

Lucia has weekly hospital visits for blood tests and to see specialists as she is closely monitored. Getting her in and out of the car is becoming challenging and without any immediate family support to assist with this process, we are struggling. Needless to say, we are extremely exhausted.

The only thing worse than the exhaustion is the constant stress and anxiety caused by seeing our little girl suffer so much on a daily basis; and, the prospect of losing her to this horrible disease. It is the first thing on our minds when waking and the last thought before heading to bed for a broken sleep. It is taking a massive toll on our emotional welfare.

Since Lucia's diagnosis we became aware of new interventions such as gene therapy which could potentially save our daughter's life and significantly improve her quality of life. Lucia suffers from a monogenic loss of function disorder which we now understand could be treated by gene therapy.

However, when we asked Lucia's geneticist and neurologist about the prospects of such a treatment, we soon came to realise that this does not appear to be a reality here in Australia. Furthermore, after reading some more, it became apparent that only large pharmaceutical companies are investing and developing gene therapies and the ones which have made it to market are sold at an astronomical cost.

Our initial excitement that a treatment could be developed which could cure our daughter was soon replaced by despondence.

I was therefore so heartened to learn about the parliamentary inquiry you will be heading which will take a closer look at expediting the development and approval of such therapies here in Australia. Our daughter is a prime example of a child with a rare disease which could greatly benefit from the type of novel medical interventions you will be investigating. Even though time is our biggest enemy and my daughter's disease relentless, I have no greater wish and hope that she may somehow be able to benefit from the developments here in Australia, within her lifetime.

I will be happy to provide you with further information and details surrounding our daughter's case and would welcome the opportunity to discuss further with you. I am willing to do anything and everything to assist with the inquiry and I thank you with all my heart for taking a closer look at this issue which is so important not only to me but also to so many other parents with children who are suffering terribly from a wide range of rare diseases.

Johann, Lucia's Dad

Case Study 2- Jerry diagnosed with an extremely rare condition SPG50

Case Study 2 responds to Terms of Reference 1, 2 and 3

This is my second son Jerry. He's curious, loving and sweeter than you could imagine. He loves to make you laugh, and while he can't talk, he has an amazing ability to communicate with his soulful, chocolate brown eyes.

His laugh is infectious and regular – a contagious mixture of joyful squealing and a deep hearty cackle.

His favourite things are cuddles with his family, tearing down the corridor on his wheelie walker and listening to his dad play guitar. He delights in thinking he's being naughty, squealing and laughing if he gets into trouble for splashing in the bath.

As his parents, Dave and I are besotted. His sister and brothers, Betsy, Otis and Alfie, love him to bits.

Our Jerry is a special little boy and he has special needs. He needs your help to help him to survive and thrive against the odds.

Jerry has an incredibly rare genetic condition that will take away everything he loves. A cure is close – it's a matter of when, not if.

But the clock is ticking for Jerry, and other children like him, and Australian researchers desperately need money to support a clinical trial that might help him.

Jerry's story began fairly typically, an easy pregnancy followed by a trouble-free birth, caught by his dad as he entered the world. It was so easy to love our beautiful, placid boy.

It was only as months wore on that we started to feel uneasy. The usual childhood milestones didn't come easily to Jerry and even simple things, like smiling, seemed like hard work.

At six months he was loosely diagnosed as having a 'global developmental delay'; he wasn't developing the way other babies did.

An MRI scan of his brain at 14 months revealed why. Jerry has a very thin corpus callosum, enlarged ventricles, which means decreased brain volume, and decreased myelination.

We loved him even more fiercely, cherishing the beauty in human diversity and feeling blessed that we'd been chosen as Jerry's defenders and parents. We imagined his future as our perfect son, our son with special needs. We were positive and strong, and determined to give Jerry the best shot at life. We could never have imagined his diagnosis could be worse, so much worse.

Just shy of Jerry's third birthday, we received devastating news. Genetic testing had led to the formal diagnosis of an extremely rare condition known as SPG50 – associated hereditary spastic paraplegia – a mutation of the AP4M1 gene.

Our geneticist delivered the news with an expert combination of compassion and bluntness. Jerry will soon lose his ability to crawl and to walk, things that give him joy and that he's fought so hard to achieve. Gradually spasticity will take over his limbs until he's confined to a wheelchair or his bed. He may never talk. He may have seizures. He may go blind. His brain will continue to deteriorate.

With the disease only recently discovered, his prognosis is unclear. He may reach early adulthood. He may not.

It was a devastating blow. How could our sweet, loving and innocent boy face so much suffering in his future, so different to the fate we had imagined for him?

Guided by our geneticist, we took him home, focused on his therapies, read scientific literature and researched online.

Then one sleepless night I discovered a Canadian website, CureSPG50.com, set up by Terry Pirovolakis. Terry and his wife Georgia are moving heaven and earth to find a cure for their two-year-old son, Michael, who has the same ultra-rare diagnosis.

Their fundraising focuses on gene-therapy technology, which may one day treat this insidious disease by halting the disease process and preventing the faulty gene from further damaging young brains and bodies. The research has turned up exciting results, and clinical trials are possible.

Even better for Jerry, the work is being led by Australian gene therapy experts at the Translational Vectorology Research Unit at Children's Medical Research Institute in Sydney. It is the only lab of its kind in Australia and one of the few in the world. The research aims to correct the mutations, delivering gene therapeutics into patient's cells affected by the disease. The hope is to deliver this treatment within two years of starting clinical trials, possibly sooner.

But the trial's expensive and health dollars are stretched, no more so than during an international pandemic.

Bess, Jerry's Mum

Current Challenges

The case studies of Jerry and Lucia demonstrate that rare diseases pose many challenges - from the person living with a rare disease, to their family and carers, rare disease organisations, the wider community, health professionals, researchers, the pharmaceutical industry and governments. It can be difficult for health professionals to gain deep, specialised knowledge and experience when seeing low patient numbers in comparison to more common diseases. Researchers face an uphill battle in securing funding and in coordinating statistically robust studies. Pharmaceutical industry interest in rare disease research and development can be low due to the relatively low demand.

Australia, however, is well placed to offer treatment to children who have are conditions like Lucia and Jerry.

New South Wales (NSW) in particular, has globally recognised gene therapy and viral vector experts who believe the future of medicine for children with rare diseases who often "slip through the cracks'' is in personalised treatments.

At Children's Medical Research Institute in Sydney, work is being done to create microscopic delivery vehicles, called vectors, which make gene therapies possible. The vectors deliver gene therapeutics into patient's cells affected by the disease. The therapy adds a working copy or replaces the faulty copy of a gene with a functional version.

In the case of Jerry, this innovative and novel research aims to use a viral vector to deliver a functional copy of the SPG50 gene to the patient's brain. This would be followed by making pre-clinical models, using organoids (mini human organs) developed by the Stem Cell and Organoid Facility at Children's Medical Research Institute. Organoids are mini organs that are grown in labs to test out therapies. The team at Children's Medical Research Institute will then use brain cells produced in this way to test their therapy before trials can begin.

What these case studies illustrate is that while the knowledge and diagnostic power around genetic disease has grown exponentially, the progress in disease prevention and treatment has been slower. Gene therapy has the power to fill the gap, and to bring real benefits to patients.

Australia is well placed to be a globally recognised leader in developing and delivering gene and gene-modified cell therapies, within an ecosystem that spans from discovery through to clinical trials in both paediatric, and adult settings. In order to realise this, a strong collaborative approach is required to put in place appropriate levels of regulatory, legislative and funding support.

Case Study 3 – Baby K diagnosed with Spinal Muscular Atrophy

Case Study 3 responds to Terms of Reference 1, 2, 3, 4

The therapeutic landscape for spinal muscular atrophy (SMA) has changed in Australia over the last four years. Known historically as a devastating neurodegenerative disease, characterised by irreversible death of spinal motor nerves, the condition had the unenviable title as the leading genetic cause of infant mortality.

In 2016, a pharmaceutical sponsored compassionate access program for nusinersen, a disease-modifying agent, was underway. Pharmaceutical Benefit Scheme listing for the medication ensued in 2018. Whilst this novel agent alters the often-fatal natural trajectory of the disease, the invasive, life-long nature of administration to maintain efficacy has significant implications on tolerability (especially in paediatric patients), psychosocial implications to caregivers and cost-effectiveness to healthcare services.

In 2017, an early phase clinical trial using a genetically engineered virus to deliver healthy copies of the gene for SMA showed stunning results. In clinical trials, this one-time intravenously administered agent is showing achievement of early developmental milestones as expected, in infants treated before symptoms are apparent. Gene therapy for children aged less than 2 years with SMA was approved by the Federal Drug Agency in May 2019 at a price of USD2.1M. In Australia, families with children with SMA younger than 2 years appealed for urgent access and commenced fundraising efforts, to circumvent a lifetime of invasive intrathecal injections and sedation, causing conflict and emotional distress in a rare disease community. Currently, there are no provisions for equitable and transparent pre-market compassionate access or a timeline to reach market for SMA gene therapy.

The case of Baby K illustrates current limitations, inequities of access and necessity for change in the regulatory landscape in Australia. This is particularly pertinent to a time-critical disease such as SMA, where benefits of therapeutic intervention are seen when infants are treated before symptoms begin, within a narrow therapeutic window where motor nerves are deemed salvageable.

Born in NSW, Australia in 2018, Baby K was diagnosed with SMA through a pilot state-wide newborn screening program for the condition. Current restrictions in Australia limit access to disease-modifying therapy to children presenting with signs of disease-onset. Thus, as a baby with initially no clinical symptoms of SMA, Baby K was faced with limited choices for intervention; and, the parents were placed in the unenviable scenario of watching and waiting for deterioration to occur.

Due to the insidious nature of motor nerve loss in this condition, Baby K started to exhibit symptoms of disease-onset within four weeks of life. Disease-related deterioration was stabilised with initiation of nusinersen. During the first year of life, Baby K required six doses of this medication, administered directly into the spine, with increasing need for sedatives and general anaesthetics to facilitate this invasive method of drug delivery. Considered a life-long therapy, the physical ramifications of repeated lumbar punctures, the emotional sequalae on parents associated with managing distress caused to their child and the considerable cost to healthcare services over a life-time of $110,000/dose, triggered a pursuit for an alternative, efficacious therapeutic avenue.

Secondary to limitations of access to gene therapy, the only recourse of action for the family remained self-funding the AUD3 million price tag for this agent, or entering a random health lottery run by industry, to facilitate access. Due to safety and dosing considerations after the first year of life, time was also running out for Baby K to remain eligible to receive this medication.

Baby K was 'picked' from the international lottery in June 2020 and dosed within two weeks of 'winning' access.

The clinical benefits are evident with attainment of independent walking within a month of dosing. The perhaps more subtle quality of life measures to Baby K and their family are innumerable. The differences in burden of treatment (>200 intrathecal injections and

anaesthesia at $110K per dose vs a single infusion) and cost savings over a lifetime are also emerging between these interventions.

Current Challenges

Baby K represents one of ten cases per year, detected by New Born Screening (NBS) for SMA in NSW alone, who travel on the same journey. Outside of NSW, 20 children with SMA will be born per year in Australia and experience delay in diagnosis without NBS for SMA.

Results from the NSW/ACT SMA newborn screening pilot have demonstrated its accuracy, efficiency and benefits arising from short-term health outcomes, alongside its acceptability, sustainability, and utility. SMA NBS programmes are being considered and implemented worldwide. However, Australians with SMA perceive health disparities and inequities due to a national lack of diagnostic capacity in newborn screening. An application for inclusion of SMA in national the NBS programme to the Standing Committee of Screening was submitted in November 2019, yet progress in the review and timelines are not known. A further potential barrier to the implementation of a positive recommendation is establishing funding from individual states and their health implementation readiness.

Whilst Baby K was deemed 'lucky', this case study highlights significant and unsustainable inequities of national screening and access to a rapidly evolving therapeutic landscape amongst children with rare neurological disease. If ongoing, health disparities will arise both within our population, and across international lines.

The case study has also illustrated that NBS and clinical trials have realised a significant paradigm shift and major change in health outcomes. The challenge for SMA is to now move from research to health practice and policy, to enable early and equitable access to diagnosis and treatment that is sustainable and cost effective across Australia.

In order to provide SMA treatments and optimise outcomes for patients, families and the community, it is important that policy and regulatory pathways support timely, equitable and sustainable access to life changing drugs and models of care, aligned with international practices. This can only be achieved if a strong collaborative approach is adopted across government, regulators, industry, clinicians and researchers.

The success in the treatment of SMA has also served to heighten awareness of the growing impact of gene therapy; and, the readiness of the Australian healthcare and biomedical research sectors to meet the challenge of making a burgeoning number of similarly ground-breaking therapies available to Australian patients at the earliest opportunity.

One critical challenge is the manufacture of gene transfer vectors, similar to that used for SMA, with current global demand dramatically exceeding supply. The NSW Department of Health has recognised this challenge, and the world-leading expertise in vector development within Sydney Children's Hospitals Network and Children's Medical Research Institute by providing $25 million in funding towards the establishment of a nationally significant advanced manufacturing capability.

The facilities under development at the Westmead Health Precinct will manufacture specialised gene therapy tools (vectors) at the scale and quality (Good Manufacturing Practice (GMP) code) needed for clinical trials in both paediatric and adult patients across Australia.

The facility will be led by global experts who have over 35 years of collective experience across a range of viral vector and plasmid systems, including lentiviral vectors, gamma-retroviral vectors, adenoviral vectors, rabies vectors, with primary expertise in adeno-associated viral (AAV) vectors. They are also global experts in genome editing, recently the first in the world to successfully correct a disease-causing mutation at single nucleotide resolution in patient-derived liver cells in vivo, at clinically relevant efficiencies.

This new capability will have a transformative effect on the Australian gene therapy sector, shortening the timeline from bench to beside research, with profound impact on families affected by rare genetic diseases.

The initial disease pipeline will include single gene disorders causing blinding eye disease, metabolic liver disease and childhood dementia as well as innovative CAR-T cell therapies.

It will also act as a catalyst for investment, attracting national and international biotech and pharma with the potential to seize a local share of what is anticipated to be a global market of around $20B annually within the next five to eight years. Based on overseas experience,

concomitant jobs growth would be in the order of 200% over the next five years to support the technical, manufacturing and regulatory requirements of these emerging technologies.

One key challenge will be reducing the current regulatory hurdles. Improved regulatory frameworks surrounding product development for rare and ultra-rare indications from bench to bedside are critical in saving time, money and precious lives. Improved regulatory frameworks and financial support are required to:

- expedite the evaluation process on safety and efficacy of new therapies;
- create clear preclinical requirements for Clinical Trial Exemption applications;
- improve and shorten the approval process;
- address reimbursement schemes faced by commercial entities and families;
- reduce treatment costs;
- address clinical manufacturing bottlenecks; and,
- dedicate efforts in monitoring the technology and reviewing the regulations of gene therapeutics to keep up with fast moving technologies.

The world is rapidly shift towards a precision medicine approach to healthcare and Australians must move with global strategies, policies and regulatory measures to enable timely, streamlined care to improve health outcomes for our children.

Case Study 4 – JD a boy with Cystic Fibrosis

Case Study 4 responds to Terms of Reference 1, 2, 3, 4

JD is a 10-year-old boy with cystic fibrosis (CF). He has two copies of a very rare mutation 5T;TG12. There are only 80 patients around this world with this mutation and he has two of them which is even rarer. Recently, there has been a paradigm shift in the treatment of CF with the availability of new disease modifying drugs available to Australian patients called Kalydeco, Orkambi and Symdeko which are the only drugs that treat the cause of CF by targeting the specific gene abnormality. Currently 50% of the ~3,500 patients with CF in Australia have access to these drugs. The current cost is ~$250,000 per patient per year. Another drug called Trikafta, has been submitted to the Therapeutic Goods Administration for consideration, and if approved, 90% of all patients will have access to treatment.

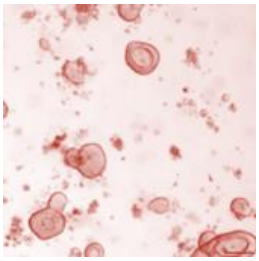
However, 10% of patients with a rare mutation, like JD, will not have access through the current regulatory pathways. One main reason for this is that clinical trials are not able to be powered sufficiently to demonstrate currently accepted clinical endpoints.

CF is the most commonly inherited disease in Australia, with chronically debilitating morbidities and reduced life expectancy, which currently stands at only 38 years. CF sufferers require intensive, ongoing medical treatment and physiotherapy. The significant healthcare burden costs our economy >$190 million per year. There are ~400 genes causing CF to be divided into 6 classes. The abnormal genes lead to a defect in a salt channel that affects the lining of the lung airways which leads to lung infections and ultimately lung failure and premature death. The various new disease modifiers prescribed to people with CF are targeted at specific genes enabling personalised or precision medicine and directly correct these defects; they have significantly improved the health outcomes of people with CF, by all measures.

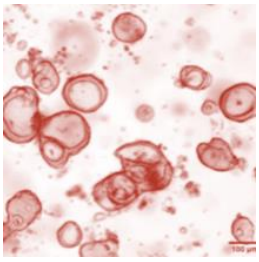
Current Challenges

Specifically for CF, a major breakthrough has been the use of stem cell cultures to grow laboratory models of a patient's organs (called organoids) using tissues from individual patients which are called CF Avatars. In organoids from healthy individuals, activation of the salt stimulates influx of water into the inside of the organoid, causing it to swell. Organoids from CF individuals will only swell if the exposure to a modulator drug corrects their defect. This swelling response is able to predict a patient's clinical response to the new treatment. This is exemplified as follows: we treated JD's CF Avatar with the drug modifier Orkambi. The figures below show the swelling of the organoids after treatment meaning the underlying defect has been corrected by the drug. While evidence in a laboratory show JD will respond, he will never be able to have access to the drug given the current regulatory Health Technology Assessment pathway.

Before Treatment



After Treatment



The CF Avatar platform will help clinicians develop personalised treatment programs, ensuring children receive best value healthcare, with the best drug for their CF. The platform revolutionises the way clinicians treat CF patients, reducing the "trial-and-error" phase and costs from the treatment process, and helping to develop personalised medicine. Similar platforms have shown remarkable success in other areas of healthcare, such as cancer, Europe has adopted a program to utilise organoids for access to drugs for rare mutations in CF. Moving away from a one size fits all model of care is vital if we are to improve the health and life expectancy of individuals with CF.

There needs to be a paradigm shift in the Health Technology Assessment pathway to allow patients with rare diseases, such as CF, to have equitable and timely access to approved life changing drugs that could benefit them through the use of innovative platforms to allow for best choice of drug for patients; and, repurposing of drugs already approved. Equally, such a paradigm shift will lead to potential cost effective and efficient health care treatments and outcomes.

Case Study 5- Ellie diagnosed with infantile fibrosarcoma, a type of soft tissue sarcoma

Case Study 5 responds to Terms of Reference 1, 2, 3, 4

Ellie was just eleven months old when she was admitted to Sydney Children's Hospital, Randwick, having been unwell for a couple of weeks. A scan revealed a tumour in her chest so large it was pushing her tiny heart and lungs to one side. Within days she was in the Intensive Care Unit on life support because she could no longer breathe unaided.

'We waited 8 years for Ellie to arrive. To be told she may not survive broke my heart. I wanted to take the cancer away from her and would have taken it on myself rather than see her suffer as she did,' says Ellie's mum,

Ellie was in a critical condition. She went on chemotherapy but after two weeks, the tumour showed no signs of responding. In fact, it continued to grow bigger. Nothing seemed to be working and time was running out.

Ellie was enrolled on the Zero Childhood Cancer (ZERO) clinical trial, led by Children's Cancer Institute in partnership with the Kids Cancer Centre, Sydney Children's Hospital. Her tumour biopsy was subjected to detailed analysis, with the ZERO team working around the clock to get results as soon as possible. Following sequencing of the tumour's entire genetic material through Children's Cancer Institute's partnership with the Lions Kids Cancer Genome Project, the ZERO team identified Ellie's cancer as infantile fibrosarcoma, a type of soft tissue sarcoma. They found a rare genetic mutation likely to be driving its growth, and identified a drug in the USA designed to specifically target that genetic mutation. The US drug company agreed to provide the drug on compassionate grounds and treatment began immediately. Within four weeks, the cancer had shrunk to a point where Ellie could be taken off life support, and within six weeks she was moved out of Intensive Care.

Ellie's parents couldn't believe the amazing results — they had their little girl back. No words could express their gratitude.

Today, Ellie is a lively 4 year old with an outgoing attitude. Ellie has started pre-school - a milestone that she, and her parents, are very excited about

Mina, Ellie's mum

Current Challenges

Over the past 30 years there has been virtually no industry driven new therapeutics development for paediatric oncology.

Childhood cancers are classified as rare diseases, a status that is further compounded by the increasing understanding of their heterogeneous nature, resulting in a continuously growing number of even rarer, distinct therapeutic sub-types. Childhood cancers also differ considerably from adult cancers in that they exhibit low mutational rates compared to adult cancers but feature a higher frequency of structural rearrangements in the tumour genomes.

Given the small patient population, the traditional drug development business model that is dependent on economies of scale has seen only a few cancer drugs being developed for, or being tested in children.

Classically, the inconvenience, expense and time associated with a paediatric clinical trial means that a pharma company will not consider such an exercise until after the drug has proved to be safe and effective in adults. This process can take decades, leaving children with therapies that are sometimes almost obsolete.

Paediatric clinical trials are further complicated by the fact that children metabolise drugs in very different ways to adults, meaning that it is often difficult to predict from adult or animal studies whether a drug will be more or less toxic in a child, and at what dose.

While some novel agents are available to children with cancer in Australia under compassionate access provisions, such access is usually granted on an ad-hoc basis, is reliant on the good will of individual pharma companies and does not generally extend to experimental agents.

Both the US and Europe have put in place legislative frameworks (The Paediatric Regulation, EU, and the RACE for Children Act (Research to Accelerate Cures and Equity Act) aimed at addressing the drug access challenges within the paediatric cancer field by mandating pharma companies to extend development activities to include paediatric use under certain circumstances, wherever meaningful and or possible; and, by introducing incentives including extension to exclusive marketing rights, as well as, vouchers for fast tracking approval in the US.

Most recently, the RACE act has come into effect in the US, which further increases the onus on pharma companies to produce paediatric development plans for new cancer drug candidates, making it mandatory to include paediatrics in the development pipeline where there are underpinning genetic targets present for both adult and paediatric populations. Early indications are that the new legislative provisions will have a significant impact on the willingness and level of engagement of pharma in paediatric drug development, although it is yet to be seen whether this growing engagement will actually extend to molecular targets specific to childhood cancer; rather than, adult cancer molecular targets that are also present in child cancer.

Drug access is one of the key challenges within the Children's Cancer Institute/Kid's Cancer Centre's ZERO Program, as currently the advanced diagnostics capabilities cannot be fully matched to a similarly sophisticated therapeutic response.

Another challenge is the fact that traditionally drugs have been licensed in Australia for a disease, not a molecular or genetic indication – in an era of molecular and genetic targeted drugs this creates artificial access restrictions. There is an opportunity to change regulatory provisions to facilitate the broadening of indications sharing the same molecular drivers of disease. A recent example from the US approval regime is Larotrectenib, the first drug approved for patients with a shared disease driver (NTRK fusion).

Luminesce Alliance partner Children's Cancer Institute, has been actively working with industry to develop a more efficient and open drug access framework. More recently, it has been working with international partners under the ACCELERATE initiative, which is a global alliance of government regulators, industry, clinicians and researchers to fast track the development of; and provide access to, novel therapies for children with cancer.

This international initiative clearly demonstrates there is also a role for a national alliance of government regulators, industry, clinicians and researchers to develop a strategic approach that is able to transcend the barriers that currently exist in accessing new therapies and pathways, across both paediatric and adult populations.

Case Study 6 – Cooper aged 6 and diagnosed with Aicardi-Goutieres Syndrome

Case Study 6 responds to Terms of Reference 1, 2, 3, 4

"Cooper was a happy baby and in the first six months of his life, his only fear was being smothered by kisses and hugs from his big brother, Harrison", says Cooper's mum, who recently shared this story with us.

By about eight months of age, Cooper had just about mastered the art of sitting. But one day he lost his ability to sit. For no apparent reason, he became irritable and started suffering high temperatures. He developed a tremor in his foot and spasticity crept into one side of his legs and eventually into all four limbs. He regressed and lost skills, including head control.

He was referred to a neurologist at Children's Hospital at Westmead. Initially it was suspected that Cooper had brain inflammation, and he was treated with a high dose of steroids. This gave him a lift in skills which he had lost in the past eight months, but they regressed again when he was weaned from the medication. It was then suggested he had Aicardi-Goutieres Syndrome (AGS) a genetic form of brain inflammation, based on the lumbar puncture findings and clinical picture. Genetic testing found a variation in his IF1H gene causing severe, potentially fatal brain inflammation (Aicardi-Goutieres Syndrome type 7). The diagnosis came 14 months after his symptoms began.

With no current treatment for such a rare disease, Cooper was faced with limited options for managing his condition. By understanding the genetic variation, and how this causes brain inflammation, it was proposed that blocking immune activation with a 'targeted' drug called a JAK inhibitor could work. Ruxolitinib is a JAK inhibitor which has been used against some forms of cancer and for adults with rheumatoid arthritis and Cooper was the first child in Australia to try it. Cooper's neurologist convinced the Children's Hospital at Westmead to pay for Ruxolitinib and 'repurpose' it for AGS.

Amazingly, it quickly lowered the inflammation in his lumbar puncture tests; and, as time has gone, there has been great clinical improvement. Cooper has not had high temperatures; he is happy, and he is progressing with skills rather than regressing. Spasticity has decreased a little in some limbs, and his latest MRI shows myelination has improved with no atrophy.

Now nearly six years' old, Cooper has the opportunity to put in a lot of hard work in physical and speech therapy and to relish everything he conquers. He has gone from limited head control to driving his motorised wheelchair, navigating an iPad, and smiling while he learns more every day.

Current Challenges

The treatment of Cooper was a world first and published in 2018 in the journal Neurology. A recent paper in the New England Journal of Medicine reported 35 children in US and France and showed that children with AGS benefit clinically from the treatment.

Cooper has now been taking the Ruxolitinib for 5 years and he still needs it. Without treatment, a child with the same genetic mutation sadly died at the age of 4, so stopping the medicine would be concerning.

In Australia and New Zealand, 7 children with AGS have been treated with Ruxolitinib, and the data shows that the drug reduces brain inflammation. However, at the moment, this drug is not on the Pharmaceutical Benefit Scheme for this indication, and this drug repurposing requires the hospitals to pay for the drug from their own budget ($25,000 a year); and, sadly some children are unable to access the drug at all.

It is important that clinicians, researchers, policy makers, Therapeutic Goods Administration, and consumers, work together with the pharmaceutical industry to develop and establish accelerated pathways ways into the repurposing, availability and funding of drugs like Ruxolitinib.

Recommendations

Recommendations Overview

The six Case Studies presented in this submission have identified the challenges for children with rare diseases and their families, particularly for their treatment; and, the ability to access to new drugs, clinical trials and novel medical technologies.

At the same time, the Case Studies have presented the immense opportunities that lay ahead to incentivise novel translational research, treatments, technologies and approaches; and, that this requires a strategic approach by relevant stakeholders to contribute to a platform of discussions and debates on the appropriate way forward. This also includes the importance in increasing investment in Australia's research and development sector.

Luminesce Alliance has consulted widely amongst its partners to put forward a series of recommendations, in order to encourage and promote a constructive dialogue and debate across a range of important and relevant issues. Centred right at the heart of this dialogue is the need to ensure the health, safety and wellbeing of children and adults alike, comes first and foremost.

Luminesce Alliance therefore recommends the following key guiding principles be considered when framing any proposed discussion platforms, which will undoubtedly arise from this important inquiry, they are:

1. The efficacy and safety of new treatments/approaches to care are paramount objectives of research.

   There are opportunities to explore how those objectives might be achieved more expediently, equally we must not allow proper scientific practice to be compromised.

2. New approaches to research methodology, the introduction of new technologies and increasingly sophisticated and influential end-user involvement need to be embraced in re-imagining how research is undertaken; and, how resultant data are subject to review for registration purposes.

   The world is different but the scientific approach is little changed over the last thirty years.

Finally, Luminesce Alliance would like to offer their support to a platform of discussions among relevant stakeholders (domestic and international) to discuss views and develop consensus statements to reflect state of the art practice; and, how to integrate, in an equitable manner, powerful new approaches to addressing access to new therapeutic and technological responses for rare diseases and conditions.

Luminesce Alliance hopes the Committee will consider our offer of assistance if it is required; and, we would welcome any opportunity to discuss how best to support this important inquiry.

Measures that will address and optimise access to new drugs, personalised drugs and off-patent drugs that could be repurposed and used to treat new conditions; without, comprising safety and through greater use of international approval processes, greater alignment of registration and reimbursement processes or post market assessment - Terms of Reference 2 and 4

To enable Australia to continue being well positioned to access the growing areas for demand for medicines, measures need to be taken to respond to global emerging trends and improve the barriers to approval processes. The time is ripe for a concerted effort to improve the therapies available for children.

Recommendations

A multi stakeholder engagement is key to an informed legislative and regulatory framework that will ensure children in Australia have timely access to much-needed new treatments. Areas of focus should include for example:

1. **Improving legislative and regulatory provisions/processes to boost the availability of medicines for children**

    a. **Molecular and genetic drivers of disease**

    Traditionally drugs have been licensed in Australia for diseases, not molecular indications – in an era of molecularly and genetically targeted drugs this creates artificial access restrictions.

    There is an opportunity to change regulatory provisions to facilitate the broadening of indications sharing the same molecular and genetic drivers of disease. A recent example from the US approval regime is Larotrectenib, the first drug approved for patients with a shared molecular driver of disease (NTRK fusion).

    b. **Early access, timely approval and appropriate reimbursement for new and novel drugs**

    Currently there is no legislative/regulatory provision to encourage early access to novel drugs for paediatric rare diseases. Unlike in the US and Europe, Australia does not yet align with international standards in this field.

    Significant lag times exist between approval (Therapeutic Goods Administration) and reimbursement (Pharmaceutical Benefits Scheme) for new drugs, hence even where drugs receive approval there remains an access question regarding who actually pays for the drugs. Given that targeted agents come at significant cost, reimbursement is a critical factor for making these novel agents available to all patients, regardless of their financial means.

    Consideration should be given to joining the International Horizon Scanning (BeNeLuxA) Initiative. This is currently a pilot project involving eight European countries, that aims to seek successful ways of collaborating on pharmaceutical policy, anticipating the impact of high cost medicines. By utilising a central database to continuously gather data, analyse research and literature and facilitate information sharing about new and developing medicines, the framework serves to enable policymakers to identify future challenges, set priorities, improve insight in expected costs, and facilitate timely decision and joint negotiations for lower drug prices.

    c. **Age restrictions**

    There are age restrictions on drugs coming to market. Changing of age restrictions would dramatically increase the availability of clinical trials of new experimental agents at least to a sub-population of childhood cancer patients. There is an opportunity to define a child <12y similar to EU and FDA legislation for paediatric medicines

d. Off label drugs

Currently, children are denied equitable access to subsidised medication. The Pharmaceutical Benefits Scheme does not include off-label prescribing.

Off-label use of medicines is the norm for paediatric cancer: in Sydney Children's Hospitals Network 68% of standard chemotherapies are used off-label and >80% of newer cancer agents (therefore pharma companies are not collecting safety and efficacy data). It is important to note that the appetite for risk of off-label use of drugs differs at different centres, resulting in equity/access issue for patients nationally.

Furthermore, there is also a heavy reliance on off-label use of drugs in paediatric rare diseases, which disadvantages children by removing the incentive for the pharmaceutical industry to properly evaluate drugs for paediatrics

2. Pharmaceutical Benefits Scheme criteria for paediatric rare diseases

Children are disadvantaged because there are no specific Pharmaceutical Benefits Scheme criteria for paediatric cancers and other rare diseases. The small patient population means we never get numbers sufficient to power clinical trials, hence drug approval reliant on Australian data only is not an efficient and feasible framework for a rare disease.

There are efforts underway to trial international collaboration within the adult cancer field to share the regulatory burden between different jurisdictions; and, efforts to anchor these collaborative ventures more broadly across rare diseases need to be encouraged. Similarly, there is an opportunity to change the onus of approval to include different levels of evidence required for approval, such as the inclusion of real world evidence outside the gold standard of randomised controlled trials, such as observation in clinical practice and the use of clinical quality registries for a staged approval of drugs for paediatric indications.

3. Implementing a compassionate access scheme with recognition of the value of real-world data and inclusion of the use of registries is a priority.

The use of compassionate access to drugs present significant health disparity and equity issues as they are deemed as a "lucky lottery". There is also no central collection of data on response to therapy representing a missed opportunity in terms of data that will allow a more accurate prediction as to drug efficacy and safety.

Pharma companies in Australasia, mostly subsidiaries of global enterprises, also have limited decision making authority in Australia to enable access through the various provisions, leading to further inequity.

Measures that could make Australia a more attractive location for clinical trials for new drugs and novel medical technologies - Terms of Reference 3

Clinical Trials

Historically, Australia's well-structured health sector, strong research competence, diverse demographics and competitive completion times have made it an attractive clinical trial destination. However, the country's clinical trial industry is now facing a series of challenges including, but not limited to: inflexible governance and regulation, significant infrastructure investment needed to support emerging capabilities; health readiness and capacity for rapid translation of novel therapeutic approaches, as well as, competition from more populous regions such as Asia.

Australia can differentiate itself as a highly skilled, cost effective and efficient clinical trial destination, targeting companies seeking certainty around cost and time, and as a location that provides scale and a vibrant environment for local innovators, and thus becoming a valuable source of revenue, growth and innovation for the sector.

Recommendations

4. **Sensible, efficient and effective governance and regulation is crucial to the success of clinical trials within Australia.**

   As global competition for clinical trials increases, regulatory bodies will need to ensure they create an attractive and workable environment for both local and international trials, e.g. harmonised ethics reviews across states and predictable approval timelines.

   Engagement between Therapeutic Goods Administration, Office of the Gene Technology Regulator, Industry and disease specific clinical research communities is therefore important in order to prepare for new clinical trials and development of regulatory strategies for advanced therapeutics.

5. **Enhanced support for information and health technology platform development to increase diagnostic capacity and improve triaging of patients to enable rapid access to emerging therapies via clinical trials or special access schemes.**

   Emerging capabilities for data linkage, 'omics and organoids present an opportunity to transform the way we identify, diagnose and select patients that are likely to benefit from novel or repurposed therapeutic approaches.

6. **Enhanced national and international collaborative relationships to more efficiently and effectively identify areas of unmet need, guide the development of policy and regulation, and facilitate timely decision making in collaboration with industry.**

   To optimise outcomes for patients, families and the community, it is important that policy and regulatory pathways support timely, equitable and sustainable access to life changing drugs and models of care, aligned with international practices. The SMA case study clearly illustrated that NBS and clinical trials have realised a significant paradigm shift and major change in health outcomes. The challenge for SMA is to now move from research to health practice and policy, to enable early and equitable access to diagnosis and treatment that is sustainable and cost effective across Australia. This can only be achieved if a strong multi-stakeholder collaborative approach is adopted to put in place appropriate levels of regulatory, legislative and funding support. The International Horizon Scanning (BeNeLuxA) Initiative is an example of a suggested framework approach that seeks to enhance engagement between industry, government clinicians, and researchers.

7. Develop an Australian wide rare disease clinical trials network and infrastructure to accelerate clinical trials in rare diseases and attract Industry.

8. Establishment and resourcing of clinical quality registers and a national portal to enable access to Australian patient cohorts and support the rapid start-up of clinical trials.

   Paediatric Trials Network Australia (PTNA) is an existing national alliance of Australia's leading tertiary and quaternary paediatric healthcare providers and clinical trial sites that could be resourced to provide a one-stop, centralised gateway for pharma and biotech. PTNA is a member of Australian Clinical Trials Alliance (ACTA) and its members are part of the Australian Health Research Alliance.

   PTNA comprises the Sydney Children's Hospitals Network, Murdoch Children's Research Institute/Royal Children's Hospital, Queensland Children's Hospital, Perth Children's Hospital, Telethon Kids Institute and Monash Children's Hospital. As such, PTNA would provide an Australian equivalent to highly successful overseas models.

   The UK has two key initiatives that are enabling clinical trials of innovative therapeutics for children with rare diseases, the Medicines for Children Network and the Advanced Therapeutics Centres. These initiatives along with public investment in cell and gene therapy manufacturing, Catapult UK has made the UK a lead country in trialling and delivering novel therapies for children and families with rare diseases.

9. Implementation of models for ensuring that, once baseline safety and efficacy have been established, novel therapies for rare disease and conditions of unmet clinical need can be quickly and equitably be made available to patients.

   This could include support for shared approval processes with international regulatory agencies to reduce duplication of approval processes in certain circumstances, and mechanisms for immediate provision of therapies through compassionate and special access schemes based on clinical need and therapeutic indication rather than jurisdiction or treating clinician.

10. Support for initiatives to increase health system readiness and capacity for the rapid translation of the novel therapeutic approaches into clinical care.

    Whereas conventional approaches to pharmaceutical development can involve many years of clinical trials before a drug is introduced into the healthcare system for clinical use, the rapid advances and transformative benefits of novel therapies has reduced that period to months in some cases. While beneficial for patients and families with no alternative treatment options, this rapid translation of new therapies into clinical settings places enormous strain on doctors, nurses, pharmacists, allied health professionals, clinical educators and other staff involved in these early deployments.

11. Development of Advanced Therapeutic Centres in Australia

    Sydney Children's Hospitals Network has experience in trialling several advanced therapies including CART treatments for cancer, Zolgensma for spinal muscular atrophy and are implementing several into the health system including Kymriah, a CART for haematological cancer, Zolgensma for SMA and Luxturna for a single gene blinding eye disorder. The therapies have had transformative outcomes for children and represent the future expansion in advanced therapeutic options for children and families with rare diseases in the next few years.

    The complexity of undertaking these therapies whether within a trial or as part of clinical care cannot be underestimated and requires resourcing with highly skilled staff, specialised facility requirements and

knowledge and access to regulators. SCHN has developed an Advanced Therapeutics Steering Committee to help inform and address the many complexities in a considered whole of organisation framework.

12. **Making Consumers the Centre of Research**

    Patients need to be at the centre of research and drug development. Traditionally approval of drugs relies on data from clinical trials utilising standard end points; there needs to be shift to understanding the importance of meaningful patient-centred outcome measures in assessing efficacy

Precision Medicine

Australia, is well placed to lead in paediatric precision medicine and in turn make Australia a more attractive location for clinical trials for new drugs and novel medical technologies.

The current rapid advances in precision medicine technologies is, however, outstripping regulatory responses. Regulatory agencies will need to understand precision medicine technologies and practices and be agile to ensure that the field can advance rapidly, but with community engagement and support to ensure public trust and confidence. Appropriate regulation that maximises the potential benefits while avoiding potential harms to society and excessive bureaucracy, will be key for the implementation of precision medicine.

Incorporating a Precision Medicine Advisory Committee into national strategy, that will work closely with regulatory agencies to develop expertise and knowledge of precision medicine and promote greater harmonisation of the regulatory approval processes across states and territories, is essential. Similarly, assessing the way in which precision medicine technologies will be financed and funded will also have a significant bearing on the efficiency, equity and sustainability of the health system.

Recommendations

13. **Incorporate a Precision Medicine Advisory Committee into national strategy to advise on implementation strategies in childhood disease and to bridge the current gaps in regulatory authorities.**

    The Committee will work with the regulatory authorities to understand precision medicine and agree on Health Technology Assessment principles for rare diseases, that include:

    a. Understanding the role of novel technologies in patient selection; such as organoids in CF and 'omics' to allow repurposing of drugs.

       Furthermore, this approach can be used for patient selection to ensure the right patient gets the right drug, thus saving those who do not respond from potential side effects and reducing waste. This is particularly important given that many more CF modifying drugs are in the developmental pipeline. This is the approach The Netherlands has taken.

    b. Understand novel clinical trial designs such as n=1, adaptive trials, basket trials.

    c. Understand the importance of patient-centred outcome measures.

    The Committee will also work with clinicians, researchers, policy makers, Therapeutic Goods Administration, pharmaceutical industry and consumers to identify innovative ways to:

    d. Incentivise academic-driven translational research to develop cost-effective gene and cell therapies.

    e. Improve pathways and reduce costs associated with academic inventor applications (new patent applications).

f. Improve the commercialisation process to facilitate transition of successful programs from academia to pharma.

g. Improve commercialisation infrastructure, including incentives to enhance formation of academic therapeutic spin-out companies, which will enhance retention of the Australian technologies, job and wealth creation and prioritise patient access to novel therapies developed domestically.

h. Revise regulatory and approval processes to increase efficiency and time to clinic.

Rare Diseases

Australia has a responsibility to support the needs of around 8% of Australians (2 million people) living with a rare disease. The recent *National Strategic Action Plan for Rare Diseases* has outlined the necessary next steps that will ensure patients diagnosed with a rare disease will have access to the therapies and standard of health care the majority of Australians take for granted. In order to realise this strategy, the Australian Government needs to have an office that is the Focal point for rare diseases.

Recommendations

14. **Establish an Australian Office for Rare Disease within the Department of Health commensurate with other countries such as USA and Europe.**

    This office will oversight and have accountability for developing a fit for purpose Health Technology Assessment process that takes into account the use of precision medicine in rare diseases including the repurposing of drugs and the use of innovative technologies and clinical trial designs.

    The office could also assist in coordinating national leadership and stakeholder engagement to implement the recent *2020 National Strategic Action Plan For Rare Diseases*[1] which lays out numerous priorities that if adopted, would align with global standards, ensuring Australia keeps pace with advanced therapeutic, diagnostic and technological capabilities and innovation; and, importantly there is a policy focus on access and equity.

15. **Invest in National rare disease critical research infrastructure to ensure Australia is best placed to attract Industry.**

    This would include, but not limited to:

    a. Increasing the epidemiological understanding and reporting of rare diseases by establishing a nationally consistent approach to rare disease coding and data collection which would include investment in rare disease quality registries.
    b. Establish an Australian Rare Disease Clinical Trials Network.

[1] The National Strategic Action Plan for Rare Diseases was led by Rare Voices Australia with funding from the Australian Government Department of Health.

Terms of Reference 1 and 2

The range of new and emerging novel medical technologies in development in Australia and globally, including areas of innovation where there is an interface between drugs and novel therapies; and commercialisation opportunities

Viral Vector Manufacturing in NSW

As was outlined in the case study of Baby K, the NSW Government is investing $25 million to establish scalable advanced viral vector manufacturing within the Westmead Health Precinct, building on the network of process development and clinical manufacturing facilities across the State.

This is a key example of a mechanism by which an early investment in local capacity will provide significant downstream benefit to patients, the health system and the economy. This facility will produce clinical grade viral vectors to meet current national and selected international clinical trial demand, establishing the Westmead Health Precinct as an Australian leader in the manufacture of vectors for gene and cell therapies; and, enabling faster access to ground breaking clinical trials and licenced therapies for NSW, Australian and international patients.

The initial disease pipeline will include single gene disorders causing blinding eye disease, metabolic liver disease and childhood dementia as well as CART innovative therapies. It will also act as a catalyst for investment, attracting national and international biotech and pharma with the potential to seize a local share of what is anticipated to be a global market of around $20 billion annually within the next five to eight years. Based on overseas experience, concomitant jobs growth would be in the order of 200% over the next five years to support the technical, manufacturing and regulatory requirements of these emerging technologies.

Global Viral Vector Market

Viral vectors are essential components for most gene and cell therapies. These therapies are expected to form a $120 billion market by 2035. The increasing demand for viral vectors is exceeding manufacturing capacity, resulting in a global shortage. Ordering delays of up to two years are impeding progress and market access.

There are few large-scale facilities globally that manufacture high quality, clinical grade vectors at the scale required for clinical and commercial delivery. These facilities have limited capacity to provide vectors to support new clinical academic or commercial programs. Additionally, some of these facilities manufacture a narrow range of vectors.

These limits on manufacturing, combined with suboptimal manufacturing technologies and high-doses of the current generation vectors required to achieve clinical benefit, lead to global shortages in clinical vector supply and are keeping costs high. There are no facilities in South East Asia that can manufacture GMP-grade clinical and commercial vectors. Therefore the vision at the Westmead Health Precinct, is to fill this gap and be a global leader in manufacturing high quality, clinical grade natural and bioengineered viral vectors, to then accelerate translation of viral vector-based technologies and therapies to market.

Glossary

Aicardi-Goutières syndrome is a rare genetic disorder that affects the brain, spinal cord and immune system. It is a type of leukodystrophy, a group of conditions that affect the white matter of the brain. These diseases damage the myelin sheath, which surrounds and protects the nerve cells in the brain and spinal cord and speeds transmission of messages between cells.

CAR T-cell therapy is a type of treatment in which a patient's T cells (a type of immune system cell) are changed in the laboratory so they will attack cancer cells. T cells are taken from a patient's blood. Then the gene for a special receptor that binds to a certain protein on the patient's cancer cells is added to the T cells in the laboratory. The special receptor is called a chimeric antigen receptor (CAR). Large numbers of the CAR T cells are grown in the laboratory and given to the patient by infusion. CAR T-cell therapy is used to treat certain blood cancers, and it is being studied in the treatment of other types of cancer.

Cystic fibrosis is a genetic condition that causes severe damage to the respiratory and digestive systems. This damage often results from a build-up of thick, sticky mucus in the organs. The most commonly affected organs include the: lungs, pancreas, liver, intestines.

Genetics is the study of heredity106. As defined by the Cambridge Dictionary, it is 'the study of how, in all living things, the characteristics and qualities of parents are given to their children by their genes'107.

Genomics is the study of genes and their functions, and related techniques, and 'addresses all genes and their inter relationships in order to identify their combined influence on the growth and development of the organism'

Health technology is according to the World Health Organization (WHO), 'the application of organized knowledge and skills in the form of devices, medicines, vaccines, procedures and systems developed to solve a health problem and improve quality of lives.'

Health Technology Assessment (HTA) is a multidisciplinary field of policy analysis studying the medical, economic, social and ethical implications of the development, diffusion and use of health service delivery, and associated technologies, in a systematic, transparent, unbiased and robust manner. HTA encapsulates a range of processes and mechanisms that use scientific evidence to assess the quality, safety, efficacy, effectiveness and cost effectiveness of health service.

Infantile fibrosarcoma is a type of cancer that forms in fibrous (connective) tissue. Infantile fibrosarcoma usually occurs in infants and young children but it may also be found before birth by ultrasound. It can occur anywhere in the body. It tends to be slow-growing and is less likely to spread to other organs.

Mutation is a change that occurs in our DNA sequence, either due to mistakes when the DNA is copied or as the result of environmental factors such as UV light and cigarette smoke.

NTRK fusion is a mutation (change) that occurs when a piece of the chromosome containing a gene called NTRK breaks off and joins with a gene on another chromosome. NTRK gene fusions lead to abnormal proteins called TRK fusion proteins, which may cause cancer cells to grow. NTRK gene fusions may be found in some types of cancer, including cancers of the brain, head and neck, thyroid, soft tissue, lung, and colon. Also called neurotrophic tyrosine receptor kinase gene fusion.

Organoids are tiny, self-organized three-dimensional tissue cultures that are derived from stem cells. Such cultures can be crafted to replicate much of the complexity of an organ, or to express selected aspects of it like producing only certain types of cells. Organoids are used in the laboratory to study for example how normal tissues or diseases form and to test new drugs and other types of treatment before they are given to people.

Orphan drugs 'are so called because they are intended to treat diseases so rare that sponsors are reluctant to develop them under usual marketing conditions…113 The indications of a drug may also be considered as 'orphan' since a substance may be used in the treatment of a frequent disease and not have been intended for another, more rare indication.

Phenotype is a term that refers to 'the observable physical properties of an organism including its appearance, development and behaviour. Examples of phenotypes include height, wing length, and hair color. Phenotypes also include observable characteristics that can be measured in the laboratory, such as levels of hormones or blood cells.

Precision medicine is an emerging approach for disease prevention and management that tailors care to account for an individual's variations in genes, environment, and lifestyle.

Rare diseases are diseases which affect a small number of people compared to the general population and specific issues are raised in relation to their rarity. In Europe, a disease is considered to be rare when it affects 1 person per 2000. While Australia does not have an explicit legislated definition of rare diseases, the Therapeutic Goods Regulations 1990 states that, in order for a medicine to be designated as an orphan drug, it must be intended to treat a condition that affects less than five in 10,000 Australians at the time of application, or to prevent or diagnose a condition that would not be likely to be supplied to more than five in 10,000 Australians each year.

Spinal Muscular Atrophy (SMA) is a genetic disease that affects motor nerve cells in the spinal cord, causing progressive muscle weakness through to adulthood. SMA is the leading genetic cause of infant death in Australia, with the disease occurring in one in every 10,000 births.

SPG50 (Spastic paraplegia 50) is a form of spastic paraplegia, a neurodegenerative disorder characterized by a slow, gradual, progressive weakness and spasticity of the lower limbs. Currently, no specific treatment exists.

Viral vectors are tools designed to deliver genetic material into cells. Viruses have evolved to develop specialised mechanisms which transport their genomes inside the cells they infect. Modified viruses are used as viral vectors (or 'carriers') in gene therapy, protecting the new gene from degradation while delivering it to the "gene cassette" in target cells. There are several types of viral vectors that can be used to deliver nucleic acids into the genetic makeup of cells including retrovirus, lentivirus, adenovirus, adeno-associated virus and herpes simplex virus–each with its own advantages and disadvantages for specific applications.

WOREE Syndrome (WWOX-related Epileptic Encephalopathy) - Children affected by WOREE syndrome display the following symptoms in varying severity: refractory epilepsy, profound global delay and severe cognitive impairment. Most children will not live through to adulthood with an average life expectancy of 4 years. At present there is no cure, but it is our aim to change that. WOX is an abbreviation of the name of an enzyme and associated gene called "WW domain containing oxidoreductase" located on Chromosome 16 at band 16q23.1-q23.2. An extremely rare recessive mutation of the WWOX gene causes a deficiency of this enzyme which has a severe impact on brain development.

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