Impact for Children's Health

LUMINESCE
Alliance
Innovation for Children's Health

Contents

Message from the Chair

A few years ago, patients presenting every year to our children's hospitals in Australia with serious inherited conditions often resulted in no diagnosis or cure.

The international explosion in genomic medicine has offered new hope of identifying the genetic cause of these diseases and finding targeted therapies to treat them – an advance called **precision medicine**. But there needs to be an organised, systematic way of introducing this model of care into the health system.

Luminesce Alliance was funded in 2018 by the NSW Government to create a paediatric translational research hub delivering twenty-first century precision medicine for the families of NSW.

We brought together NSW's leading paediatric medical research institutes with our children's hospitals network and universities to combine strengths and capabilities, creating a competitive advantage in paediatric research that was previously lacking in NSW.

With a strong translational focus, we have been able to fast-track discoveries in the laboratory into treatments for patients with rare diseases and cancer, sometimes in a matter of months.

Medicine that uses the power of genomics can be astonishingly successful. Rather than the incremental benefits we would normally expect from medicine, these new therapies have the potential to completely cure children of their condition.

While numbers are still small, it has been incredible to hear stories of babies with rare genetic diseases who have been given a chance of a normal life; of vision loss being restored; and of children with cancer achieving remission because their treatment is informed by genetic data.

The strength of Luminesce Alliance is in the collaborations it nurtures – collaborations between fiercely competitive research institutes and clinical campuses, between different research teams, between clinicians and scientists, and between people from a wide range of disciplines. The way these teams are now working together is, perhaps, our greatest achievement.

NSW is now at the international vanguard of paediatric precision medicine – but there is still so much more we could do.

We want to develop new treatments in NSW for our children and families, and export them to the world. Through nurturing paediatric research, our modelling shows we can attract even more investment to NSW, create jobs, and generate government cost-savings through the rapid diagnosis and treatment of childhood disease.

The discoveries being made will have impacts far beyond child health. Improving diagnosis and treatment of children will support families and communities, boost the economy through saving on health expenditure in later life, and lead to new understandings that will be applied to many common adult diseases in future.

Heartfelt thanks to everybody involved in the first few years of Luminesce Alliance for their wisdom, talent, energy and knowledge. I know we look forward to an exciting future ahead.

Ms Kathryn Greiner AO
Chair Luminesce Alliance

Message from the Executive Director

We know that the best research is done by groups of people who do not have the same backgrounds. Shared knowledge, skills and perspectives are a core driver of research excellence and better health outcomes.

While researchers often collaborate with each other, what we aimed to achieve through Luminesce Alliance was to broaden the collaboration to bring in clinicians and academics across multiple organisations to achieve a sum that was greater than the individual parts.

At first, this seemed like an impossible task. But by placing at the centre the importance of relationships, we mobilised multiple formal and informal opportunities for interaction to enable our people to connect, find each other, discover new networks, and share resources and capabilities.

The collaboration started at the top, but by the end of three years, it is permeating through all levels of our member organisations. We have created an environment where basic scientists can come to the same table as clinicians, data analysts, economists and psychologists to share not only new understanding of the science, but ways to bring it to life for patients in the hospitals.

This report demonstrates the ways we have increased the scale and enhanced the excellence of our translational and discovery research in paediatrics.

We have empowered the best and brightest people and provided them with an innovative hub of world class facilities, cutting edge equipment and technologies right here in NSW.

The foundation of our work has been our enabling platform strategy.

Enabling platforms are functional specialisations that cross disease areas and organisations. For example, we have developed capabilities in functional genomics, computational biology, clinical trials, psychosocial and health economic and implementation science – all areas of research that are more difficult to fund through traditional mechanisms.

Based on the successes of our first three years, we are now hoping to develop our enabling platform strategy further to provide the critical strengths and capabilities that enable truly world-leading research. We will focus future investment on five enabling platforms: Functional genomics; Data; Precision therapy; Psychosocial and Health systems implementation and economics research.

Our proposed model will apply these enabling platforms across the entire portfolio of child health research in NSW, underpinning the continued implementation of precision medicine for children in NSW. The enabling platforms will undoubtedly lead to learnings, insights and innovations that will also inform adult precision medicine.

I have been honoured to play a small part in the first years of Luminesce Alliance and would like to thank all those who have contributed to its success.

Ms Anastasia Ioannou
Executive Director Luminesce Alliance

Highlights

5x

five-fold return on NSW Government's initial $20 million investment; $101.5 million leveraged in additional research grants

85+

professionals employed – attracting and supporting leadership and training the next generation of STEM talent

217+

innovative and translational research projects

97

research publications

Our strengths

- Functional genomics
- Cell and gene therapy
- Translational vectorology
- Viral vector manufacturing
- Stem cell medicine
- Clinical trials
- Predisposition of cancer and rare genetic diseases
- Computational biology and bioinformatics
- Health economics and health implementation
- Psychosocial support for families, carers and healthcare professionals

100+

national and international collaborators

>10

clinical trials of novel therapies, including gene therapy, for children with high unmet clinical need

137

presentations made locally, nationally and internationally

7

facilitated R&D IPs with commercialisation opportunities

Our highlights

In collaboration with our partners, we have…

- facilitated multiple early phase clinical trials and fast-tracked translation to clinical practice, providing unprecedented access to novel therapies for children
- shown it is possible to deliver precision medicine in the health system through the Zero Childhood Cancer Program, Australia's most comprehensive national precision medicine and research translation program
- developed world-leading functional genomics expertise to understand the genetic cause of disease and rapidly translate that into new therapies for children
- developed world-leading expertise in gene therapy delivery using viral vectors, and built the first cGMP manufacturing facility in Australia
- developed an ecosystem of outstanding basic scientists, academics, clinician researchers, evaluation and implementation scientists to bring the bench to the bedside and back again
- built capability in precision therapies and shown how to deliver these in the health system
- developed the data algorithms and built a platform needed to interpret the vast quantities of data into clinically actionable actionable recommendations
- grown computational biology and bioinformatics workforce and capabilities
- boosted stem cell research in NSW by establishing the Stem Cell and Organoid Facility
- developed strength in new areas including health economics and health implementation across cancer and rare disease such as ocular gene therapies and Spinal Muscular Atrophy

"You cannot overstate the impact that genomic precision medicine is going to have on the whole of medicine. Its earliest major impacts are in inherited diseases of childhood and cancer, but it will spread quite rapidly throughout adult medicine. There is almost no aspect of medicine that will not ultimately be transformed by genomic precision medicine."

Prof Roger Reddel AO Lorimer Dods Professor
Executive Director
Children's Medical Research Institute

"Precision medicine offers a transformational approach to healthcare. It begins with a unique partnership between clinicians and researchers, working together to go beyond offering a diagnosis, to developing potential new treatments, and even cures, that can help children both now and in the future."

Ms Cathryn Cox PSM
Chief Executive
Sydney Children's Hospitals Network

"The impact of a genetic therapy for a child with a rare genetic disease is extraordinary. We are on the verge of a revolution that will change the way we approach medicine forever."

Prof Chris Cowell
Director of Research
Sydney Children's Hospitals Network

"We have provided evidence supporting this new model of care. In the future, I believe the use of genetic information will become standard for every disease in the same way patients currently get a blood test or an x-ray."

Prof Michelle Haber AM
Executive Director
Children's Cancer Institute

Rare diseases – individually rare, collectively common

There are thousands of rare and ultra-rare diseases, including cancers. Some are so rare that they do not even have a name.

While individually uncommon, these rare diseases 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.

Why invest in research into rare paediatric diseases?

Rare diseases and cancers typically have highly complex symptoms and children have significant ongoing health and psychosocial challenges.

The burden on their families, communities, the Australian health care system and broader society is vast.

Our economic modelling shows there is a clear cost benefit in rapid diagnosis and management of rare paediatric diseases, in terms of reduced healthcare expenses and future productivity of children and their families.

Most rare diseases are genetic and they usually present in childhood. Our research into rare paediatric diseases not only promises a better future for children, but holds immense potential for the treatment of adults with common conditions such as liver disorders, heart disease and macular degeneration.

Reference: Gene2Care, Sydney Children's Hospitals Network

< 5/10,000
a rare disease = less than 5/10,000

+ 7,000
rare diseases are identified

8%
of Australians live with a rare disease

50%
of rare diseases impact children

30%
of children will not survive beyond age 5

2,000
children referred to genetic departments annually across SCHN

30%
of NICU admissions relate to a genetic disorder

50%
of genetic conditions are diagnosed accurately

Precision medicine – a revolution in diagnosis and care

Precision medicine is a rapidly emerging model of care that provides new strategies for prevention, diagnosis and treatment based on an individual's genes, environment, and lifestyle.

Where diagnosis and treatment used to depend on the expertise of an individual doctor, care can now be informed by a mass of data.

We can now quickly analyse the human genome – the 6 billion letter code that makes us human – to discover the mutation or mutations that cause disease.

Identifying the genetic cause of a child's disease enables management tailored to their unique circumstances and that of their family. In many cases, it will be possible in future to correct the error in the DNA and completely cure the patient.

Precision medicine already benefits children and families in NSW

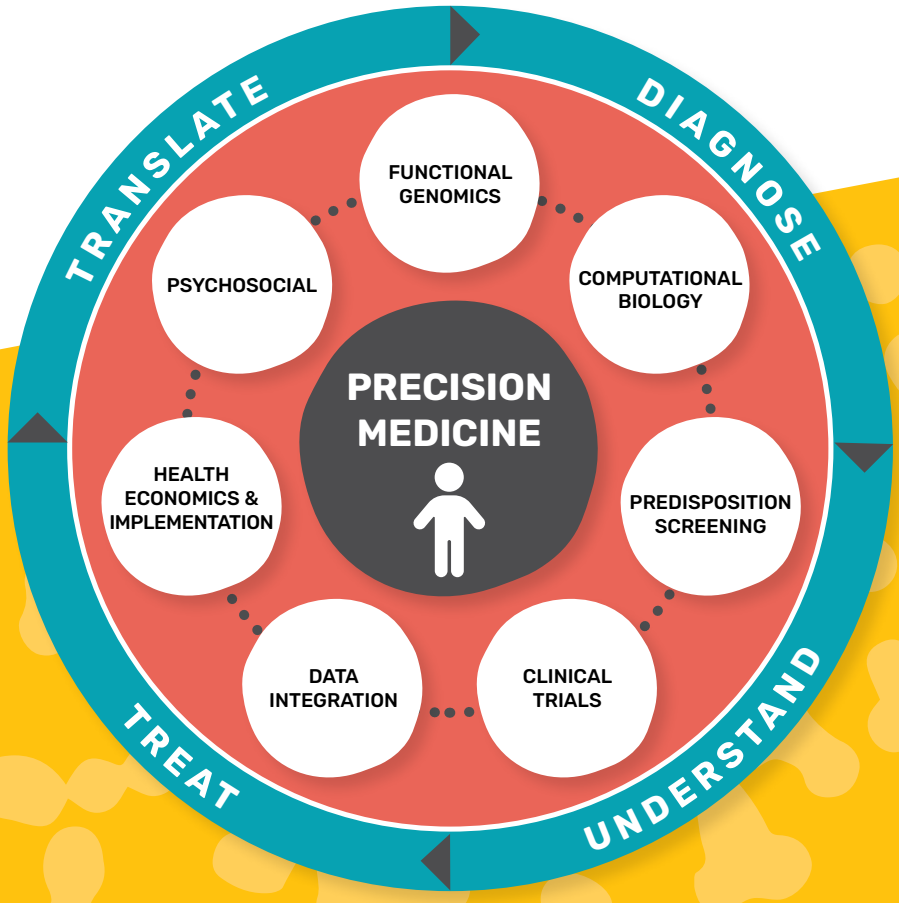
- Families at last have a diagnosis, ending a journey that usually takes 5 to 7 years
- There may be existing therapies that can benefit the child, or the child may be eligible for a clinical trial
- Advanced therapeutics such as gene therapy (correcting the genetic error) or stem cell therapy may be available
- Measures can be taken to prevent associated health problems in future
- Other family members may be identified who also need care
- Families can make informed choices about having future children

The work of Luminesce Alliance and its partners over the last three years has shown that precision medicine is effective and feasible, and can be implemented in the health system.

Luminesce Alliance Paediatric Precision Medicine Program

The Paediatric Precision Medicine Program (PPM) is a Luminesce Alliance initiative that commenced in 2019. It consists of 10 projects, focusing on a range of conditions across cancer and rare diseases.

The PPM program includes projects that are foundational to the adoption of precision medicine, including functional genomics, disease modelling, clinical trials, psychosocial impacts, health economics and health implementation, all of which guide the establishment of new models of care.



See page 65 for a full list of our Precision Medicine projects

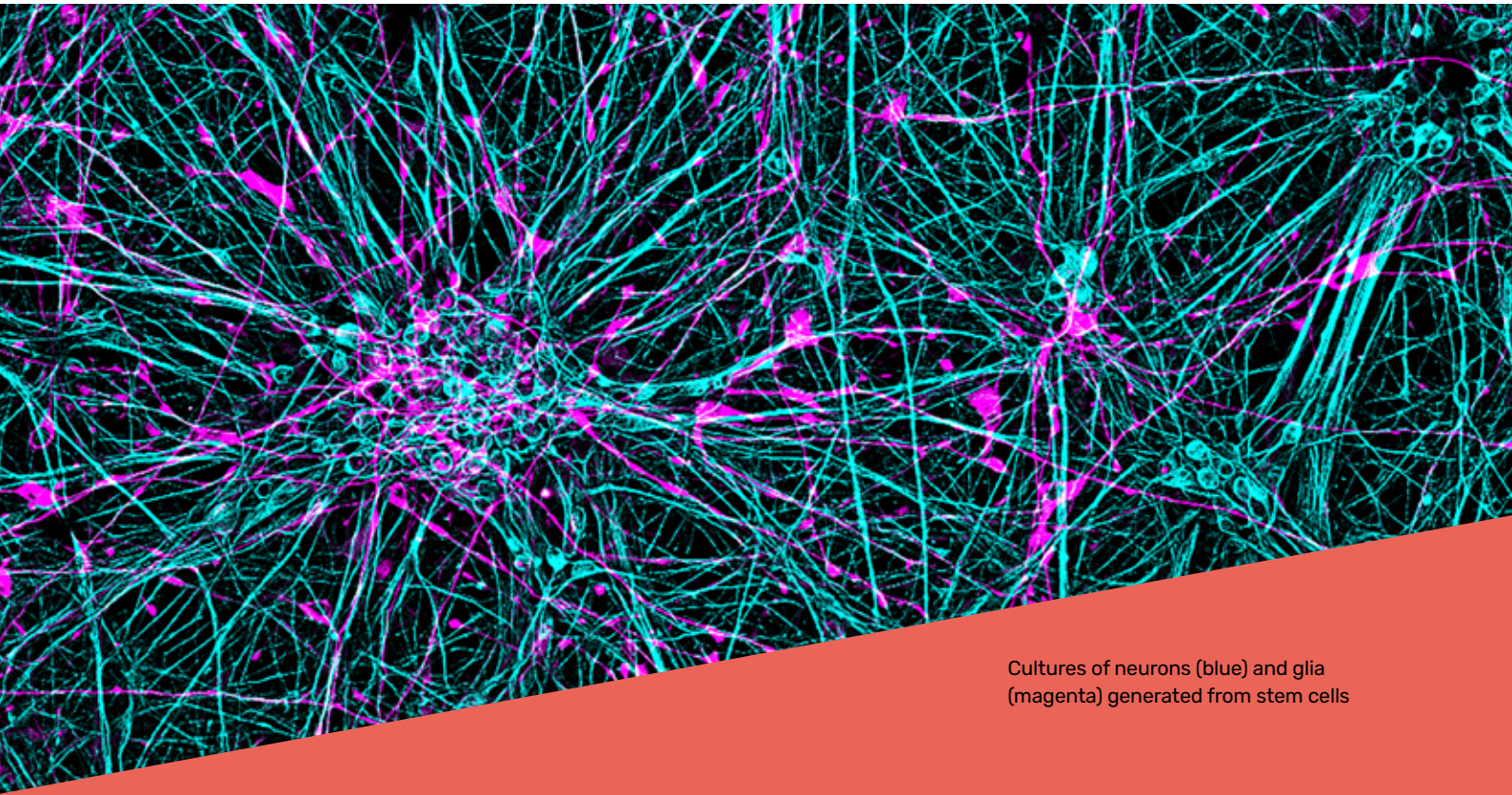
RESEARCH EXCELLENCE

CLINICAL EXPERTISE IN PAEDIATRICS

CHILDREN AND FAMILIES

NSW functional genomics initiative develops precision medicines for children

Rare genetic diseases



Cultures of neurons (blue) and glia (magenta) generated from stem cells

The issue:

There are thousands of rare genetic diseases and some cancers in children that are difficult to diagnose and treat because we do not fully understand them. Although most of these diseases are extremely rare, together they affect 5 to 10 per cent of the population.

What we did:

We established a translational research team and built on existing infrastructure to support a functional genomics capability.

The outcome:

We have created a new research resource and workforce capability in diagnostic genomics and applied genomics. This has led to the discovery of disease-causing genes and targets for treatment, and paves the way for advanced therapeutics.

With Luminesce Alliance funding, four research facilities have been established with the potential to transform the diagnosis and treatment of paediatric genetic diseases and cancers.

Functional genomics is the study of the intricate connection between genes and disease. When a gene defect is found to be implicated in a childhood genetic disease, functional genomics answers questions about how genes work and the disruption of the genetic pathway that leads to disease.

Luminesce Alliance funding of a functional genomics program for NSW has brought together a collaborative team with a wide range of skills to develop precision medicines for children. There is unlimited potential to use this knowledge to revolutionise the treatment of many paediatric and adult diseases.

The scientific discoveries will enrich the understanding of genetic diseases, identify targets for treatment, and develop precision therapeutics. These will include gene and cell therapies that can potentially cure some rare and devastating diseases, says program lead Prof Patrick Tam, Head of the Embryology Research Unit at the Children's Medical Research Institute (CMRI).

"Our vision is to provide efficacious health care for genetic diseases and childhood cancers. This initiative creates empowering research capacity and workforce capability and supports genomic medicine and stem cell therapies in NSW and more broadly in Australia," he says.

The research facilities provide advanced functional genomics support to biomedical and clinical researchers of the Luminesce Alliance, addressing diseases identified by clinicians in the Sydney Children's Hospitals Network.

The team's work has already helped some families by identifying the genetic cause of debilitating genetic diseases, including liver metabolic disorders, blinding eye diseases, cystic fibrosis, mitochondrial disorders, telomere and cancer disorders, neuromuscular diseases and neurodevelopmental disorders.

More importantly, the functional genomics knowledge gained is driving action to apply available therapies and develop new therapies for children with these diseases.

The Rare Disease Functional Genomics Laboratory

The Rare Disease Functional Genomics Laboratory studies how genetic mutations contribute to disease. Clinical cases that do not have a defined diagnosis are investigated to find out how the genes work, whether the mutated versions of the gene (called variants) are causing disease and, if so, what molecular and biochemical processes are affected.

"Finding a genetic variant is like finding a needle in a haystack," says Dr Lisa Riley, Head of the laboratory.

"If we can identify a disease-related gene and work out how it causes disease, it ends a diagnostic odyssey for a family and opens up diagnosis for other patients in the community."

The genetic cause and functional information are shared among practitioners in the clinical genetics discipline worldwide, so that other patients with the same variants can obtain a rapid definitive diagnosis. This means children can be treated quickly, if treatments are available, before their condition appears or further deteriorates.

The information also enables the genetic disease to be detected through screening of parents before they have a baby, minimising the chance of the disease recurring.

Stem Cell and Organoid Facility

A leading stem cell and organoid facility has been established to study genetic diseases. It tests new treatments on stem cells and different types of cells generated from them. In future, stem cells can be used for therapy by generating healthy cells to replace diseased cells.

Stem cells are the body's raw materials. Rather than harvesting them from embryos, the team is creating them by reprogramming cells taken from children's own blood or skin into induced pluripotent stem cells (iPSCs). The iPSCs can then be changed into any type of cell in the body.

Because they are derived from the children's own cells, iPSCs offer an unprecedent opportunity to study the child's disease and test whether new treatments are effective when targeted precisely to the child's individual genetic problems.

The team is also experimenting with 'organoids' produced using the iPSCs. Organoids are three-dimensional mini-organs created when stem cells organise themselves in the dish, such as into parts of the brain, eyes, inner ear and liver. The organoids are used to study the disease-causing process, and to test new gene therapies and stem cell therapies in a system that mimics a real organ.

Alternatively, healthy cells contained in the organoids could potentially be transplanted in children to carry out functions that their own organs cannot. The team is now close to trialling organoids to treat degeneration and loss of photoreceptor cells in the eye, and the loss of function of liver cells.

The facility is one of the few in Australia working on both stem cells and organoids and has the vision of generating stem cell products at the requisite standard for clinical use, says the facility's Manager, Dr Anai Gonzalez-Cordero.

Vector and Genome Engineering Facility

Gene therapy fixes or replaces disease-causing genes with a functional version of the gene, delivered to the patient using a virus preparation called a vector.

The Vector and Genome Engineering Facility is perfecting techniques for editing faulty genes, and is the only facility in Australia capable of producing research-grade vector for use in pre-clinical studies of gene therapy.

Single Cell Analytics Facility

This facility is working to identify the cells in the body that are directly affected by the diseased genes, so that the therapy can be targeted precisely to these cells for treatment of genetic diseases and childhood cancers. For example, by understanding the behaviour of cancer cells, it will be possible to develop better anti-cancer treatments with fewer side effects.

The team separates the whole tissue and organs into individual cells and performs genomic analysis and live-cell imaging on them, known as single-cell analytics.

The team has launched more than 20 projects in the past two years in the quest to identify the cell types affected in blinding eye disease, liver metabolic diseases, adrenal disorders, neuroinflammatory diseases and inflammatory myofibroblastic tumours, liver cancer and gliomas.

"The critical next step is to enhance the capacity of the program. Going forward, we want to dig deeper, to expand our knowledge in the functional genomics of disease-causing genes to many more disease types – and to accomplish this we need to expand across all the capabilities."

Prof Patrick Tam

Future potential

Prof Tam says the scientific information already generated by the functional genomics program should translate into treatments for children in the coming decade.

"The functional genomics program aspires to broaden its coverage of the types of genetic diseases, childhood cancers and neurodevelopmental disorders studied," he says.

"The critical next step is to enhance the capacity of the program. Going forward, we want to dig deeper, to expand our knowledge in the functional genomics of disease-causing genes to many more disease types – and to accomplish this we need to expand across all the capabilities."

"We have created an environment in which researchers can work with each other. In some of our workshops, people are meeting each other for the first time even though their offices are only in the premises next door to each other. They suddenly realise – 'I think I could have done something very special and productively with that person."

Prof Patrick Tam, Head,
Embryology Research Unit,
Children's Medical Research Institute

"These sorts of genetic conditions affect children their whole life. Our functional genomics program means we have a chance of identifying the genetic cause and informing families, and potentially finding an effective treatment or clinical trial. There are huge benefits over the lifetime of the child."

Prof Robyn Jamieson
Head of the Eye Genetics Research Unit
Children's Medical Research Institute
University of Sydney

"Our partnerships with the two children's hospitals have allowed us to identify the unmet need for genetic therapy. Our clinical partners help us to understand what's needed, and we the scientists let the clinicians know what is feasible with the currently available gene therapy toolset."

A/Prof Leszek Lisowski
Head, Translational Vectorology Unit
Children's Medical Research Institute

"We are at a critical stage. We have shown that advanced therapeutics can transform the lives of our patients – but there is still far to go to embed this platform into the health system."

Prof Adam Jaffé
Head of Paediatrics
University of New South Wales

"We all have different capabilities and complement each other well. Our collaborations have spanned several years, which means we can bring more capacity to demonstrate gene therapy is a possibility."

Dr Anai Gonzalez-Cordero
Group Leader Stem Cell Medicine and
Head of the Stem Cell & Organoid Facility
Children's Medical Research Institute

Patient story: Will

Will, 9, has a beautiful charm and a cheeky smile. He enjoys outdoor adventure and is loved by all who meet him.

However, Will has a genetic condition that causes global developmental delay. He has the cognitive age of a 2 to 3 year-old. His condition has deteriorated so he has vocal and motor tics, anxiety, severe obsessive compulsive disorder, and self-harm including head banging, slapping, scratching and hitting himself. He has also developed aggression toward others.

Will is now on a considerable amount of medication to help ease these episodes and keep him calm. He has very limited independence and requires a lot of extra attention and support.

After years of treating his symptoms and countless visits to the hospital, including long inpatient stays, genetic testing of Will's DNA led to diagnosis of a neurodevelopmental disorder caused by a variant in the VAMP2 gene.

The Rare Diseases Functional Genomics lab, led by Dr Lisa Riley, investigated the effect of the VAMP2 variant in skin cells collected from Will and found that it reduced the levels of the VAMP2 protein, leading to Will's condition.

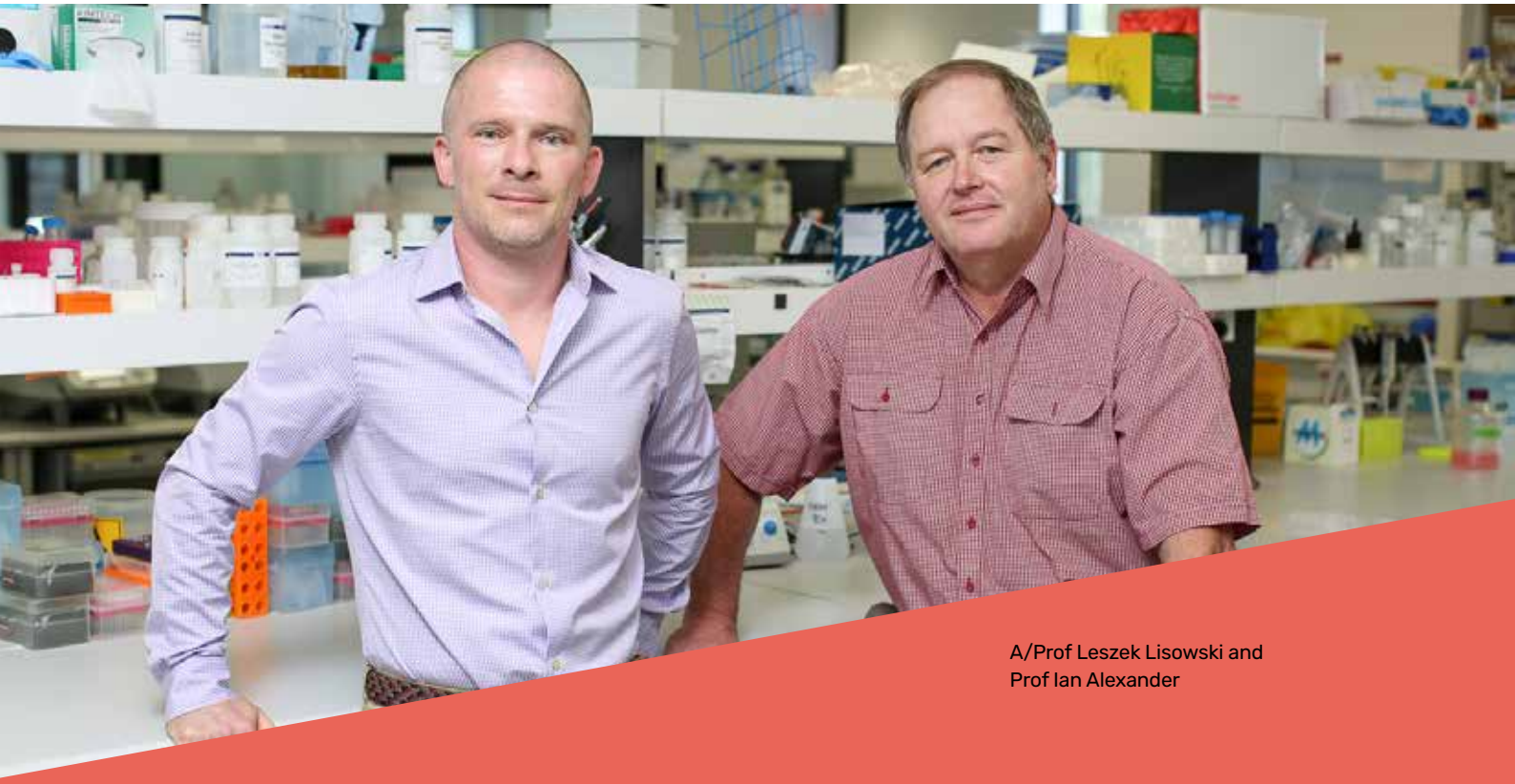
Once the diagnosis was made, researchers investigated the feasibility and safety of a potential gene therapy for people with VAMP2 deficiency. Will donated his blood to this research, which was reprogrammed into stem cells and used to grow neurons and mini brains (organoids) that mimic his own brain cells.

This research highlights the translational journey from detection to correction that Luminesce Alliance funding made possible. It accelerates a world-leading treatment for patients with VAMP2 deficiency who have previously been living with an incurable disease.

This research highlights the translational journey from detection to correction that Luminesce Alliance funding made possible.

Gene therapy manufacturing facility turns dreams into reality

Rare genetic diseases



A/Prof Leszek Lisowski and Prof Ian Alexander

The issue:

We are world leaders in using gene therapy to cure devastating genetic diseases, but we cannot make enough clinical-grade vectors (the product used to deliver the therapy into patients' cells) in Australia. Trials are being delayed and Australian patients are seriously disadvantaged because we currently need to outsource the production of vector overseas.

What we did:

We used seed funding from the Luminesce Alliance and NSW Health to establish a facility to manufacture clinical-grade vectors.

The outcome:

With additional leveraged funding, the facility is on track to start supplying clinical-grade vectors to Australia and the world.

Luminesce Alliance funding has put NSW in the race to meet soaring demand for clinical-grade gene therapy vectors.

Thirty years ago, using genes as medicine to treat disease was the stuff of dreams. But massive advances in technology have seen gene therapy explode as a field of medicine, and now it has the potential to revolutionise the treatment of devastating genetic diseases.

NSW is recognised globally for its expertise in gene therapy for children, and has already seen some stunning successes, such as in the treatment of spinal muscular atrophy, cancer, and blinding eye diseases. Some diseases can be cured with just one treatment, meaning children and their families do not need to cope with lifelong illness and disability.

However, clinicians in Australia face a major barrier in using the technology to treat sick children in our hospitals because we do not have the necessary manufacturing infrastructure to produce clinical-grade product.

For example, when world-leading gene therapy researcher Prof Ian Alexander wanted to launch a clinical trial of gene therapy to treat OTC deficiency, he discovered there was a two-year wait to have the necessary material developed overseas. OTC deficiency is a rare disorder that involves a lack of the enzyme ornithine transcarbamylase, which is needed to remove nitrogen from the body.

"In children with severe OTC, their only hope is to have a liver transplant. We can potentially fix their liver for them, but we cannot get hold of the clinical grade vector we need for our patients," says Prof Alexander, Head of the Gene Therapy Research Unit at Sydney Children's Hospitals Network (SCHN) and Children's Medical Research Institute (CMRI).

Surging global demand for gene therapy vectors

Gene therapy is when a genetic mutation that causes disease is 'edited', or corrected, in the patient's cells, or when a healthy copy of the gene is added to the affected cells.

A vector is needed to deliver the healthy genetic material to cells that need it. The most frequently used vectors are based on bio-engineered viruses.

Viruses are exquisitely effective at injecting their genetic material into cells. To produce vectors for gene therapy, the genetic material of a virus is removed and replaced with the therapeutic gene. The resulting vector seeks out and enters cells, inserting a healthy gene as a replacement for the faulty one that is causing a child's ill-health.

CMRI researcher A/Prof Leszek Lisowski and his team are experts in developing vectors that precisely seek out the cells that are causing disease. The vectors are like writing the correct address on hundreds of billions of packages and sending them into the body to deliver life-saving medicine to each cell that needs it.

A/Prof Lisowski created the world's first synthetic gene therapy vector based on adeno-associated virus (AAV), a virus that does not cause disease. This is now being trialled to cure haemophilia.

While Australia is already producing vectors that can be used in the laboratory, none of our facilities are accredited to manufacture vectors for use in humans. Stringent procedures and processes must be used to produce clinical-grade vectors, known as cGMP vectors.

With hundreds of gene therapy clinical trials underway around the world, global demand for cGMP vectors far exceeds supply. The problem is about to get much worse as therapies move from trials into routine clinical use, says A/Prof Lisowski, who leads the Translational Vectorology Unit at CMRI.

"These kids can't wait two years to get the clinical vectors manufactured – we need to shorten the timeline so we can put new therapies into the clinic much faster and the patients can benefit from this contemporary technology," he says.

"When overseas manufacturing companies are taking years to supply the vector we need, why can't we make our own here in Australia?"

Australia's first cGMP vector manufacturing facility

SCHN recognised the potential of gene therapeutics. In 2000, it began establishing the capacity and expertise to participate in gene therapy clinical trials with a view to also enable manufacturing of clinical-grade viral vectors. Ongoing investment by many funders, including Luminesce Alliance, has brought the venture to the point of realising this vision.

The Luminesce Alliance provided seed funding to establish the Vector and Genome Engineering Facility at CMRI. This is Australia's first preclinical grade gene therapy vector facility, and takes up a whole floor at CMRI. Since it was established in 2016, the facility has produced on average 350 preparations of vector a year for use in research.

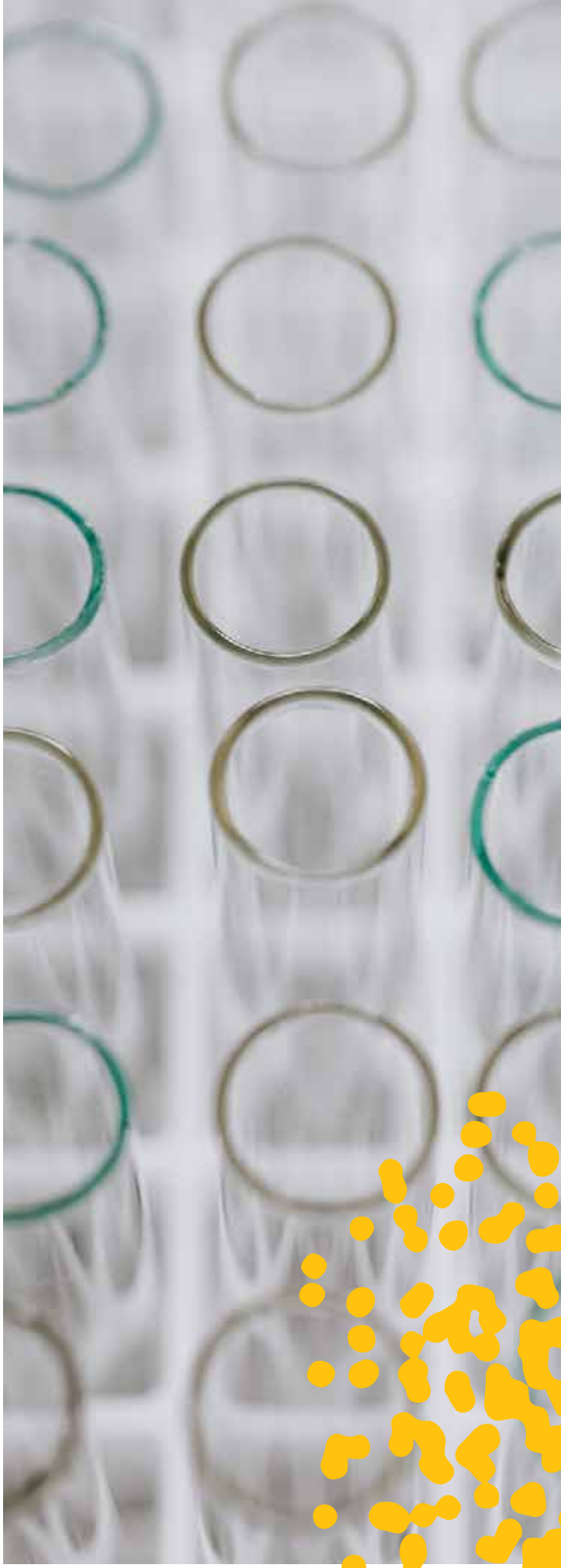
"This is a great indicator of the volume of research being undertaken in the gene therapy field and a prelude to the likely high demand for clinical-grade cGMP viral vectors by both academic and commercial researchers," says A/Prof Lisowski.

With recent further support from NSW Health, the SCHN/CMRI team has established a small-scale clinical-grade vector manufacturing facility in Westmead. When accredited, it will be the first cGMP vector manufacturing facility in Australia. NSW Health has provided further funding for the next stage, which will take the facility from its pilot, small-scale stage through to manufacturing larger amounts of vector sufficient to treat disorders of large organs like the liver or brain. Ultimately, it will be able to supply clinical-grade vector to Australia and the world.

Prof Alexander says supporting the facility to move toward large-scale vector manufacturing could be a game changer for NSW.

"There is demand waiting from around the world – everyone needs clinical-grade supplies. We have the capability right here in NSW, we're just waiting for the pathway to open to unlock this potential," he says.

"Not only will this facility lead to innovation, new technology and new jobs, we now have the capability to treat devastating paediatric illnesses and funding of the larger-scale facility will enable us to do it in Australia."



"This field is 30 years old now. It's been a long, hard road, but since 2011 there have been massive advances and we are now seeing a global explosion in biotechnology, a rise in clinical trials activity, and stunning impacts in the clinic."

Prof Ian Alexander,
Head, Gene Therapy Research Unit,
Sydney Children's Hospitals Network

Patient story: Jerry

Bess and Dave were devastated when they received the news that their 3 year-old second son, Jerry, had an extremely rare genetic disorder called SPG50, or associated hereditary spastic paraplegia.

Caused by a mutation of the AP4M1 gene, this disorder means Jerry's limbs will gradually be overtaken by spasticity until he is confined to a wheelchair. He may never talk, or he may develop seizures and go blind.

SPG50 has only recently been identified, and there is no treatment. The only option for Jerry's parents is to manage his symptoms at home and watch their little boy deteriorate.

Australia, however, is well placed to offer treatment to children who have rare conditions like Jerry. In NSW, globally recognised gene therapy and viral vector experts are working on personalised treatments that can transform the future of these children.

Gene therapy research supported by Luminesce Alliance aims to correct the mutation-causing genetic conditions like Jerry's. The development of viral vectors to deliver the gene therapy into cells is crucial to this work.

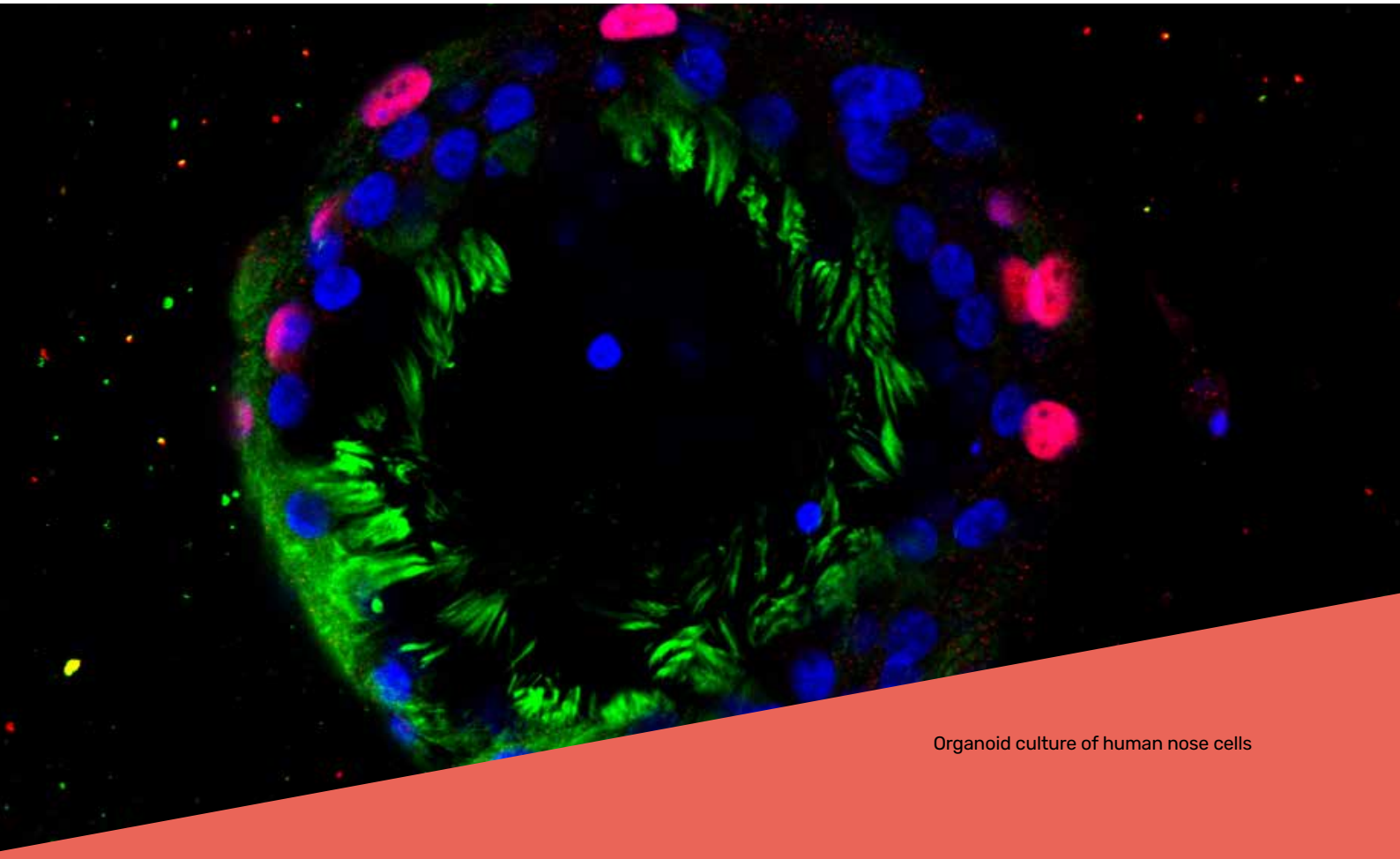
While the knowledge and diagnostic power around genetic disease has grown exponentially, the progress in disease prevention and treatment has been slower. Gene therapy has the power to fill the gap, and to bring real benefits to patients.

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.

> **Gene therapy has the power to fill the gap, and to bring real benefits to patients.**

Transforming the treatment of cystic fibrosis using precision medicine

Cystic fibrosis



Organoid culture of human nose cells

The issue:

There are exciting new therapies for children with cystic fibrosis, but there is currently no way of knowing which children will benefit, or how to treat children with rare or ultra-rare genetic mutations.

What we did:

We contributed to a new laboratory that is using organoids (mini-organs) grown from stem cells to test the effects of cystic fibrosis drugs.

The outcome:

This precision medicine platform aims to identify new therapies for cystic fibrosis, repurpose existing therapies for patients with very rare mutations, and ensure the right patients get the right drugs.

Luminesce Alliance is contributing to the only laboratory in the Southern Hemisphere that offers a precision medicine platform using stem cell biology for children with cystic fibrosis.

Initially developed with philanthropic funding, the laboratory is using mini-organs, called organoids, to study the response of individual children's cells to different medications now becoming available to treat the root cause of cystic fibrosis.

The project aims to find new therapies for children whose rare genes causing cystic fibrosis mean they are not eligible for current medications. It will also help to predict whether children will respond well to a certain medication, so doctors can make more informed treatment decisions, says Prof Adam Jaffé, Head of the School of Women's and Children's Health at UNSW Sydney.

"These new medications have completely changed the outlook for my patients with cystic fibrosis, but there are still 10 per cent who won't have access to the newest drug. Another challenge is knowing whether newer drugs are better than the ones they are already on. Patients ask me whether they should change from one medicine to the other and there is no way of knowing the answer," he says.

"Also, these medications cost around $300,000 a year for each patient. We want to be sure we are giving them to the right children who respond well, and we are not giving them to patients who do not respond, thus preventing them from potential harmful side effects with no benefit."

Studying mini-lungs and guts

The laboratory is solving these problems by testing drugs on patients' own cells.

Cells are collected from children with cystic fibrosis and stem cells are isolated in the laboratory. These are then grown into lung or gut cells that form themselves into microscopic primitive organs, called organoids, or CF Avatars. These act in the same way as cells would in the individual child.

In children with cystic fibrosis, the cells have a genetic defect that causes a dysfunction of salt and water balance. This is what makes their mucus thick and affects the function of their organs.

When exposed to effective drugs in the laboratory, the cells in the organoids 'dance' and swell as the water starts to flow in and balance is restored.

If the drug does not work, they remain inactive. The team has developed algorithms to determine how well an organoid is responding to a drug.

There is potential for this research to be translated into clinical care, giving clinicians confidence that certain medications will work and also reducing the risk of unnecessary side effects, says Dr Shafagh Waters of the Cystic Fibrosis Research Centre at UNSW Sydney.

"Ultimately, we would hope this can be embedded in health care as a companion diagnostic to demonstrate the suitability of drugs to individual patients," she says.

More work to be done

Prof Jaffé says precision medicine has already changed the outlook for children with cystic fibrosis. "While survival used to be no more than five years, new drugs that target the protein made by faulty cystic fibrosis genes have given real hope that children born with this condition will live to old age and be inconvenienced only by taking a couple of tablets a day."

But there is much more to do. As well as continued research funding to search for better treatments or find a cure for cystic fibrosis, there is an immediate need to develop better health technology assessment regulatory processes in Australia to get the right patients onto the right drugs.

This will require advocacy to adapt Australian protocols for children with rare diseases, says Prof Jaffé.

"We are at a critical stage of trying to make this sustainable until it is properly embedded in the health system," he says.

"While we have seen some remarkable health improvements such as curing cancer, unfortunately it is a harsh reality that the people we look after with cystic fibrosis all still die from their disease.

"The new drugs herald a new dawn in the outlook for people with cystic fibrosis, but we need more investment into precision medicine research to turn this into a reality for all children with cystic fibrosis in NSW."

Patient story: Robbie

Robbie has never had a normal life. He was born with cystic fibrosis, meaning he always had a continual cough, could not maintain his weight, needed constant physiotherapy to clear mucus from his lungs and was in and out of hospital every few months. His education suffered and his whole family has been affected.

When he was born, his parents were told the condition would limit his life expectancy. But thanks to a brand-new therapy called Trikafta, there is hope that he may live to a healthy, happy old age.

Trikafta helps the body to correct a protein made by the CFTR gene – the gene that has the mutations that cause cystic fibrosis.

The therapy has completely changed Robbie's life. Now 17, he has more energy, he has stopped coughing and he is enjoying a variety of foods. He has not been in hospital for months and, for the first time they can remember, his parents are making plans for the future.

> **As more medications become available for children like Robbie, precision medicine will become increasingly important to ensure every patient gets the drugs they need to make them well.**

Are some children predisposed to cancer?

Cancer

The issue:

We do not know why some children get cancer, how many of them have an underlying genetic abnormality that predisposes them to cancer, or what this means for the future management of these children and their families.

What we did:

We established a pilot program for family-based testing of the germline (normal DNA) for all children diagnosed with cancer in NSW (the PREDICT trial).

The outcome:

Our findings will show whether routine family-based germline testing of children with cancer is feasible and beneficial, what percentage of children with cancer have a genetic predisposition, and what the implications are for them and their families and how they are managed.

When children and adolescents present to our hospitals with cancer, we often suspect it may be caused by changes in their DNA that damage the genes they were born with.

Sometimes mutations, or variants, are passed from parents to their offspring via the sperm or egg, known as germline variants. We do not fully understand the potential germline genetic causes of childhood cancer, and until recently the only way to predict genetic risk was to look at children's family history.

According to the literature, about 8 per cent of childhood cancers may have a genetic cause. But when we conducted whole genome sequencing of children with high-risk, aggressive cancers who were enrolled in the Zero Childhood Cancer Program (ZERO) over the past five years, we found that double that number as many as 16 per cent had reportable genetic variants thought to be responsible for their cancer.

The PREDICT trial

To understand the full spectrum of these genes and variants and the contribution of heritable germline variants in the development of all paediatric cancer, it is necessary to broaden genomic germline sequencing to all children with cancer.

Luminesce Alliance funding has been used to develop and launch the PREDICT trial, which involves whole genome sequencing of the germline of every child diagnosed with cancer in NSW.

A/Prof Vanessa Tyrrell, Co-Head of Theme, Personalised Medicine at Children's Cancer Institute, and Program Leader of ZERO, says the project also expects to identify many new variants in known cancer risk genes, which have not yet been linked to predisposing a person to cancer – known as 'variants of unknown significance'.

"We want to understand the spectrum of cancer genetic risk variants in children, how prevalent they are, and how often they are contributing to the risk of cancer developing in children," A/Prof Tyrrell says.

The trial is unique as it takes a family-based testing approach, collecting and looking at the whole genome sequence of the germline DNA of both parents as well as the child – called trio-based sequencing – to understand whether the genetic variants found have been inherited or have developed spontaneously in the child's germline DNA.

Understanding the genetic predisposition to cancer will have several benefits for the child and their extended family, says Dr Luciano Dalla-Pozza, Director of the Cancer Centre for Children at The Children's Hospital at Westmead.

For example, it will influence treatment recommendations and play a role in determining outcome, such as whether a child may respond well to radiotherapy or certain medications. It provides the opportunity of personalising surveillance programs and implementing early intervention and lifestyle changes to prevent or treat cancer at an earlier stage.

"It also provides valuable information to patients and their families to help them make choices about future pregnancies, to understand how to minimise their own cancer risk and that of any future children they may have," says Dr Dalla-Pozza.

A complex, multidisciplinary model of translation research

The ultimate aim of the PREDICT trial is to assess the utility of routine germline sequencing at diagnosis for all children with cancer.

The premise underlying this research program is that germline sequencing is important and valuable and will contribute positively to the general health of the population.

Ultimately, if the PREDICT trial indicates that this work is feasible and useful, it will inform the roll-out of a national cancer predisposition pilot screening program through the Zero Childhood Cancer Program's clinical network. In the long term, that program will provide the opportunity to personalise surveillance and treatment plans for children and their families who are found to be at risk of cancer due to heritable germline variants.

"It will significantly change the way we manage childhood cancer and their at-risk family members, inching us closer to control and ultimately prevention of cancer in the long term," says A/Prof Tyrrell.

Using large datasets to optimise disease diagnosis, treatment and prevention specific to each patient

Cancer

The issue:
As precision medicine evolves, we need better ways of integrating and interpreting vast volumes of data to guide treatment.

What we did:
We funded a multidisciplinary computational biology team to accelerate the development of analytical and statistical approaches using computers.

The outcome:
We launched a platform that underpins precision medicine in our hospitals through computational analysis and interpretation of data from our patients and around the world.

Our investment in computational biology is contributing to better treatments for children with high-risk cancers.

Precision medicine targets treatments based on interpreting large datasets that include 'omic information (such as the genomic sequence, protein, metabolite and microbiome information) with biological and clinical data.

However, we have limited capacity to interpret this vast quantity of data and translate it into information that is useful for clinicians on the wards. The data are highly complex, come from many different sources, may not be complete, and take time to process.

To support the precision medicine program, Luminesce Alliance has established a digital infrastructure that will one day help clinicians make molecularly informed treatment decisions in real-time, using super computers to sift through the data.

The program brings together the largest computational biology team focused on children's cancer in Australia. Experts in biology, computing and informatics are working together to build computational tools that can analyse different datasets and extract clinical meaning from them.

"The dream is that every patient gets optimal treatment informed by every patient that's been before them," says team lead A/Prof Mark Cowley, of Children's Cancer Institute.

How does computational biology underpin precision medicine?

No two tumours are the same. By sequencing the entire genome of a tumour, it is possible to identify what is unique in its genetic code that might be driving the cancer.

The human genome comprises 6 billion pieces of information, and variations in any 5 million of these may or may not be responsible for a child's disease. The challenge is to work out which of them are clinically relevant, and to match these to treatments.

The computational biology program is developing new approaches to solve this problem by using massive super computers to make sense of the data.

Over several days, the computers compare the normal genome of a patient, derived from analysing a blood sample, with that of the tumour from the patient, derived from a biopsy.

Using a database of patients who have had this type of cancer previously, the software then identifies the genetic changes most likely to be implicated in the cancer, and what the best treatment approach is likely to be.

The result has global implications for the management of children's cancers. As an integral part of the Zero Childhood Cancer Program (ZERO), a trial that combines medicine, technology and research to provide personalised medicine for children and young people with cancer, the team is analysing the genomic data of all children with high-risk cancer across Australia.

This work has underpinned ZERO's success in identifying the genetic basis of disease in more than 90 per cent of cases.

Graphene – our new platform

The program is about to launch Australia's first open-source platform that brings together a range of analytical and statistical tools to enhance treatment of children with high-risk cancers.

The platform, called Graphene, uses different algorithms and software to sort the data into what is most useful for clinicians. It incorporates a database of clinical information on about 500 patients. Subject matter experts curate and interpret this information before a distilled version is provided to clinicians. The team is developing new artificial intelligence algorithms to support this labour-intensive process and enable the platform to make increasingly more accurate predictions.

The platform is being extended to support a NSW-wide childhood cancer predisposition program using genomics. This work will be shared internationally to improve patient outcomes around the world.

"Parents confronted with a devastating disease such as cancer in their child have an intense desire to understand not only the origins of the disease but also the risks faced by siblings and any future children. Cancer in children is a family affair and it rattles, disorients and terrorises. Providing families with accurate information is a powerful antidote."

Dr Luciano Dalla-Pozza
Head, Cancer Centre for Children
Sydney Children's Hospitals Network

"We may never prevent cancer as there are a myriad ways that tumours can form but by getting better at diagnosing, treating and identifying at-risk individuals, and proactively monitoring disease in unprecedented detail, we will one day cure most cancers."

A/Prof Mark Cowley
Head, Computational Biology Group
Children's Cancer Institute
Head
Luminesce Alliance Paediatric Precision Medicine
Computational Biology Program

"We are using the best that science has to offer to better understand how often childhood cancers are inherited within families. Once we know this, we may be able to screen and one day prevent childhood cancers."

Prof Tracey O'Brien
Director of the Kids Cancer Centre
Sydney Children's Hospital, Randwick

"This is real team science at work. We have a truly multidisciplinary model of translational research, bringing together numerous experts, clinicians, genetic counsellors, computational biologists, research scientists and more. It's about an enormous team of people working together to achieve more, learning faster together."

A/Prof Vanessa Tyrrell
Program Leader, Zero Childhood Cancer,
Co-Head of Theme, Personalised Medicine,
Children's Cancer Institute

Patient story: Jack

Jack was an all-action kid. Bubbly and energetic, he was always doing something and willing to try anything; he would never sit still.

When Jack turned nine, he lost his energy and began to get absent and dazed. An MRI showed a large brain tumour, classified as a low-grade glioma. After a successful operation, Jack was given a positive prognosis and returned to school within three months.

Just over a year later, Jack woke up with a terrible headache and started vomiting. The tumour was back. This time it had a devastating effect on his young body. This bright, energetic young boy was bedbound, going blind and in constant pain. The tumour was aggressive, inoperable and would not respond to any conventional treatment. His parents were forced to face the reality that they may lose their precious boy.

Jack was enrolled on the Zero Childhood Cancer Program (ZERO), where his tumour was analysed to determine its specific genetic make-up. A genetic mutation called BRAF V600E was identified as driving the cancer's growth, and there was a drug that would target it. Jack quickly improved and is now back at school – as active as ever.

ZERO is underpinned by the ability to interpret vast quantities of data. Luminesce Alliance's computational biology platform will mean that more precisely targeted treatments can help children like Jack.

Jack quickly improved and is now back at school – as active as ever.

International clinical trials offer hope for high-risk cancers

Cancer

NSW's growing reputation as a leader in paediatric precision medicine has attracted a collaboration with Europe that will see a raft of early-phase clinical trials open in Australia and offer hope to children with cancer who have no other treatment options.

"Investment in the Zero Childhood Cancer Program (ZERO) has provided some of the most in-depth genetic profiling of children's tumours anywhere in the world," says A/Prof David Ziegler, Group Leader of the Brain Tumours Group at Children's Cancer Institute and clinical lead of the Zero Childhood Cancer Program (ZERO).

"We have been really focused on understanding the biology of each child's tumour. Now, we are starting to build companion clinical trials that will allow these children to get new treatments that target the genetic changes in their tumour."

The first trial has been launched with the support of Luminesce Alliance funding to test whether two drugs work in combination to treat cancers for which there is currently no other treatment.

"Through this sort of funding, we are seen as national leaders in our field and we are attracting clinical trials to NSW. This is changing the paradigm for the children – making sure state-of-the-art treatment is available to children in Australia."

A/Prof David Ziegler

The INFORM2 (INdividualized Therapy FOr Relapsed Malignancies in Childhood) trial is testing the safety and efficacy of combining an immunotherapy drug called nivolumab with a drug called entinostat that targets the epigenome.

Immunotherapy has changed the paradigm for adult cancer treatment but has not been so effective in children because their cancers have fewer genetic changes for the drug to target.

A/Prof Ziegler says the aim of the trial is to 'unmask' the tumour cells by using a drug that targets the epigenome, thus making the immunotherapy drug more effective.

This phase two trial is recruiting patients with a high number of mutations in their tumour, or one of two genes that are targeted by each of the two drugs. About 24 per cent of children with the most aggressive and hard to treat cancer will have at least one of the targets that the drugs attack, says A/Prof Ziegler.

The trial is being conducted in collaboration with University Hospital Heidelberg in Germany, and could be the first of many more.

"We are seen as national leaders in this field because of this sort of funding. It means we will be able to bring more trials to Australia and make sure state-of-the-art treatment is available to children here."

A/Prof David Ziegler

"Luminesce Alliance funding means we are the first country in the world to open the trial and treat the first patient," A/Prof Ziegler says.

"We are seen as national leaders in this field because of this sort of funding. It means we will be able to bring more trials to Australia and make sure state-of-the-art treatment is available to children here."

A/Prof David Ziegler
Head, Clinical Trials Program
Kids Cancer Centre, Sydney Children's Hospital Randwick
Group Leader
Targeted Therapy Group, Children's Cancer Institute

Can we implement a comprehensive program to improve early recognition and treatment of rare genetic diseases?

Rare genetic diseases

The issue:

Children with rare genetic diseases may not get a diagnosis for many years, if at all. There is a desperate need to offer diagnosis and treatment equitably to those who need it.

What we did:

We are researching implementation of a holistic program of care, Gene2Care, to provide access to the best diagnostic approaches and expert support and management in a systematic way to families with rare genetic diseases.

The outcome:

We have worked with clinicians and families to develop a new program of clinical and research genetics, Gene2Care. We are gathering data on the clinical utility and cost-effectiveness of this program, to help us make the case for further support for its roll-out across NSW genetic services.

Families whose children have rare genetic diseases often embark on a diagnostic odyssey. They visit many different specialists and often wait years before they receive a diagnosis. An accurate diagnosis is essential for children because it guides their future treatment and management.

Even after diagnosis, care may be fragmented. Children may need to see a wide range of specialists who may not communicate well with each other.

"There is no 'home' specialty for genetic diseases in the healthcare system, so families can bounce from one doctor to another, they are in and out of hospital and they never know what's around the corner," says Dr Elizabeth Palmer, consultant clinical geneticist from the Centre for Clinical Genetics, Sydney Children's Hospital.

"Now, with advances in genetic testing, we are increasingly able to provide a diagnosis so that the child's GP, paediatrician and other specialists all have a clear plan, and the family can receive the support they need."

A/Prof Meredith Wilson, consultant clinical geneticist based in the Department of Clinical Genetics at The Children's Hospital at Westmead, says genetic testing has revolutionised the outlook for some children and families but is not offered equitably in Australia.

Timely access to genetic services is the first barrier. Even then, at least 50 per cent of children do not currently receive a diagnosis after Medicare-funded genetic testing.

"Children can usually only be offered further cutting-edge genetic testing when there are individual disease-specific projects that have achieved research funding. This may be too late for families who may need urgent access to treatment, or information to inform future pregnancies," A/Prof Wilson says.

Implementation of a new program of care

Dr Palmer and A/Prof Wilson are leading the development and trialling of a new concept of care for families whose children have genetic diseases.

They are studying how to build scalable approaches to access diagnosis and multidisciplinary care and identify patient cohorts for clinical trials within the Luminesce Alliance network and beyond.

They have launched Gene2Care, an integrated, collaborative, clinical research program to optimise care for, and in partnership with, children and families with rare genetic disorders. The program has three parts.

GeneSTART is a rare genetic disorder registry – a comprehensive database of families who have given consent for their records to be shared across both children's hospitals. Families on the registry will have access to improved clinical care, be connected rapidly with relevant clinical trials, and receive support and information.

Selected high priority patients from the 50 to 60 per cent of families for whom there is still no diagnosis are connected with a research pathway called **GeneAdd** (Genomics Testing and Functional Studies for Additional Yield in Undiagnosed Genetic Disorders), which aims to improve the diagnosis rate through further testing not available or funded in clinical laboratories, including whole genome sequencing and functional genomics studies.

"We are supporting Luminesce Alliance's innovative research by identifying patients who might have rare genetic diseases, but they are not just cells on a petri dish – they are children and families," says Dr Palmer.

The last element, **Gene Compass**, is designed to help families navigate the health system by providing information to clinicians and a central point of contact for families.

"We are bringing all the elements of their journey together in a way that provides support and integrated care."

Research to understand what works for families

The program links across the Sydney Children's Hospitals Network, with shared ethics and governance. After a pilot phase, the aim is to offer it to every child in NSW who presents with a rare genetic disorder.

Ultimately, it is hoped this will be a way to offer all families the best chance for timely diagnosis; new hope provided by research opportunities; better communication in both the specialist centre and with their local hospital and GP to improve coordinated care; family psychosocial support; and access to rare disorder support networks.

The researchers are studying implementation and systems to understand the best way of introducing the program to the health system, as well as analysis of clinical utility to understand what is and is not working, and to improve equity and accessibility.

The project is co-designed with families, and is constantly measured, evaluated and iteratively improved to ensure their needs are met.

The data on diagnoses achieved through the program will help make a case to government about the cost-effectiveness of funded genetic testing for children, and the need for an enhanced clinical workforce to meet the requirements of implementation and sustainable service delivery.

Dr Palmer says this work comes at a critical time, following the Federal Government's launch last year of the National Strategic Action Plan for Rare Diseases.

"We are responding to every aspect of the Action Plan and see ourselves as part of a global movement to understand and improve the care for children with rare diseases," Dr Palmer says.

Patient story: Eleanor

Until the age of five, Eleanor lived with an undiagnosed rare disorder. At four months old, she was not meeting her developmental milestones, and by eight months it seemed she was going backwards. But doctors were unable to make a diagnosis for her condition.

In 2019, Eleanor took part in a world-first global study headed up by geneticist Dr Elizabeth Palmer. Through collaboration with international colleagues, Dr Palmer was able to describe for the first time the disorder CHEDDA – congenital hypotonia, epilepsy, developmental delay and digit abnormalities, a very rare genetic disorder caused by changes to the ATN1 gene on the 12th chromosome.

Eleanor was the first patient in the world to be given this diagnosis. Since then, almost 20 people worldwide have been diagnosed, and there will be more.

For Eleanor's family, the most important part of having a diagnosis was finally knowing that Eleanor's condition was not degenerative or terminal.

It has also opened the door to the best possible medical care for Eleanor. For example, her doctors now know that she may develop heart, brain and spinal complications, and can monitor her closely. The diagnosis with CHEDDA also means Eleanor will receive speech therapy to prevent feeding issues that can happen with this condition.

For Eleanor's family, the most important part of having a diagnosis was finally knowing that Eleanor's condition was not degenerative or terminal.

A success story of translation: screening babies nationally for spinal muscular atrophy

Spinal muscular atrophy

The issue:

Spinal muscular atrophy (SMA) is a previously untreatable disease that paralyses babies. Now treatment has become available, there is an urgent need to identify and treat babies before they develop symptoms.

What we did:

In a multidisciplinary collaboration across Luminesce Alliance, we supported a successful pilot that added the first genetic test to the Newborn Screening Program in NSW and the ACT. All babies are now screened for SMA and inherited immune disorders.

The outcome:

Our extensive data are supporting the national roll-out of newborn screening for SMA.

Until 2017, paediatric neurologist A/Prof Michelle Farrar could only offer supportive multidisciplinary care to families whose babies were diagnosed with spinal muscular atrophy (SMA). Without a treatment for the disease, she watched babies quickly deteriorate after diagnosis.

This devastating genetic motor neurone disease quickly paralyses babies, who survive on average 9 to 10 months. While their brains remain unaffected, they lose the ability to move, feed and ultimately breathe. SMA affects one in 10,000 births and was once the leading genetic cause of infant death.

New treatments have revolutionised the outlook for babies with SMA. "Families now have two birthday parties – one to mark the day the child was born, and the other the day they got their treatment. Before it was uncommon to celebrate first birthdays," A/Prof Farrar says.

However, the treatment is most effective when given before a baby develops symptoms – by this time they may have already lost 90 per cent of their nerves. The best way to identify babies who need the treatment is to screen at birth.

"Every day counts. Any delay could be the difference between a child living in a wheelchair or not," A/Prof Farrar says.

The power of working together

In a collaborative effort supported by Luminesce Alliance, specialists from across both children's hospitals and the associated universities have worked together to have a molecular test for SMA included in the newborn screening test offered to all 100,000 babies born in NSW and the ACT each year.

Newborn screening involves taking three drops of blood from a newborn baby's heel. This is then analysed using biochemical tests for more than 25 medical conditions.

To include a new test in the newborn screening program, a number of criteria must be met, says A/Prof Veronica Wiley, principal scientist at NSW Newborn Screening.

"The main criterion is whether or not there is an intervention that is relevant, and whether it will be accepted by the population.

The impetus to test newborns for SMA was boosted by an international gene therapy trial, including NSW children, which indicated a single dose of gene therapy could potentially reverse the disease.

With world-leading expertise in SMA, newborn screening and gene therapy, the members of Luminesce Alliance realised there was an opportunity to show international leadership in this space.

In 2018, they launched a pilot of the first genetic test to be included in the newborn screening program.

The new test involves extracting the baby's DNA from the heel prick test and looking for genetic variants that indicate SMA as well as some primary immunodeficiencies. The test is highly specific and sensitive and can be conducted on site at Westmead.

If a baby's genes suggest they may have a form of SMA, further tests can be conducted to confirm the diagnosis and start life-saving treatment.

Making the test available to babies throughout Australia

The two-year pilot was completed in 2020 and was then continued with NSW Health funding. The data were analysed by the Federal Government, which recently recommended that newborn screening for SMA should be implemented nationally.

The pilot boosted the case with implementation and health economic data that showed newborn screening for SMA was value for money, led by Prof Georgina Chambers from the National Perinatology Epidemiology and Statistics Unit.

A/Prof Farrar says this work would not have been possible without the connections, reputation and organisational support offered by Luminesce Alliance.

"The strength of Luminesce Alliance is that there is an integrated, comprehensive team to address all the elements of how to introduce our research into the health system – for example implementation science and health economics – with a focus on better health outcomes for kids."

"As scientists, we do our research, advance knowledge and publish papers, but the holy grail is to improve health outcomes and practices for children. We have shown what can be achieved from working together; it was the strength of us all believing in the vision, with our focus on children and families with SMA."

A/Prof Michelle Farrar,
Specialist Child Neurologist,
Sydney Children's Hospital and UNSW Sydney

Patient story: Baby M

A few days after Baby M's newborn heal prick test, his parents received some devastating news: their perfect little boy had inherited the most severe form of the genetic condition Spinal Muscular Atrophy (SMA).

While he had not yet developed symptoms, they were told he would progressively lose the ability to roll, sit up, crawl, walk and, eventually, breathe. In 9 to 10 months, his condition would be fatal.

One of the options available to them in NSW was to take part in an international clinical trial of a gene therapy for SMA, with the aim of assessing its safety and efficacy. This investigational medicine was given as a single injection with the gene delivered inside a viral vector.

Baby M's parents and research team hoped that the science would offer him the chance of a healthy life. The family made the difficult choice to enrol their baby in the gene therapy trial, trusting that the science and medicine would be positive.

One year later, Baby M is reaching his milestones and defying his prognosis; he is sitting independently, breathing, feeding and swallowing normally, and is learning to walk.

Since the introduction of SMA into the newborn screening program in 2018, more than 200,000 babies have been screened, which has helped significantly with early identification of the condition.

In future, it is likely that gene therapy will rewrite the outlook for other babies in Australia who are born with SMA. Baby M's parents have generously supported the research program to produce evidence looking at the acceptability, health economics and implementation of this new model of care for SMA, so that this can change health practices and inform sustainable health policy.

One year later, Baby M is reaching his milestones and defying his prognosis; he is sitting independently, breathing, feeding and swallowing normally, and is learning to walk.

Translating our leading-edge science into standard care: a new infrastructure for precision medicine clinical trials

Clinical trials

The issue:
Clinical trials are necessary for new treatments to become standard care, but Australia does not yet have a clinical trials infrastructure to test new advanced therapies in children.

What we did:
We built capacity across our children's hospitals to deliver clinical trials of precision medicine to patients.

The outcome:
We have delivered gene therapy trials in children with rare neuromuscular disorders and are prepared to test the large volume of new therapies that are about to emerge from our research in coming years.

Luminesce Alliance funding has been used to establish a paediatric clinical trials program for advanced therapeutics.

Clinical trials are fundamental to test new treatments for safety and efficacy before they can then be approved by governments as standard care. But only about one-third of clinical trials involve children, delaying the translation of our scientific discoveries into clinical practice.

Special expertise is required to run an early-phase paediatric clinical trial – one that tests a new therapy for the first time in humans or after only limited information on the effect of the therapy is available. These trials are complex due to need to ensure patient safety, the strict regulatory standards governing treatment of children, complex ethics and consent arrangements, and a high level of administration required.

The lack of capacity in NSW to offer novel drugs and gene therapies to children with genetic rare diseases and cancer means our patients are potentially missing out on treatments that are being developed locally and internationally.

The NSW Government has recently invested heavily in developing capacity for NSW to conduct world-class clinical trials. Luminesce Alliance is extending that capacity to include paediatric clinical trials for advanced therapeutics such as gene therapy, stem cell medicine and new molecules, or repurposed medications.

Prof Craig Munns, who leads the clinical trials program at The Children's Hospital at Westmead, says the initiative is the first in the southern hemisphere to run early-phase clinical trials in cohorts that are exclusively children.

"We are setting a new paradigm for paediatric clinical trials globally," he says.

"Our aim is to drive and increase the amount of early-phase studies of advanced therapeutics, which will increase opportunities for patients with very rare diseases to access medications that can be life-changing or life-saving."

Supporting scientists and clinicians to run early-phase clinical trials

With Luminesce Alliance funding, we have appointed two senior doctors, one at The Children's Hospital at Westmead and the other at the Sydney Children's Hospital, Randwick, to act as a bridge between scientists and clinicians and provide support to test new discoveries in clinical trials.

The team provides a central knowledge base to ensure children and their families know about and can access new therapies, and that clinicians and the health system are able to run the trials.

The team includes support personnel to help develop new trial methodologies and design protocols for very small patient cohorts, which are often needed in a clinical trial of a therapy for a rare genetic disease or cancer. Even if only one child is enrolled in a clinical trial, the team puts the necessary complex procedures in place to ensure the therapy is given safely.

The team is also educating and training both the research and clinical communities to ensure they are working towards a common goal and understand the possibilities of advanced therapeutics. As these are new therapies that require new ways of working, we have to ensure that the health system is ready to translate our discoveries into clinical care.

Boosting the capacity to run clinical trials in NSW will provide necessary evidence to achieve regulatory approval in Australia and internationally, says clinical trials lead Dr Laura Fawcett.

"We have amazing scientists inventing the cures – our job is to advance the therapeutic pipeline by taking the new therapies developed in our laboratories and bridging them into action in a clinical trial, so they can become standard care," she says.

The team engages with biotech and pharmaceutical companies to attract early-phase clinical trials at the Sydney Children's Hospitals Network. Their work is already garnering interest from overseas, positioning NSW to attract even more trials in future.

"This work is demonstrating global leadership and capability, and will help Australia to attract as many clinical trials as possible," says Prof Munns.

"There is a tsunami coming of new advanced therapies that need to be tested in clinical trials – and if we are ready, there is a whole bunch of kids who will benefit."

Finding clues in big data to improve understanding and treatment of rare diseases and cancer

Rare genetic diseases and cancer

The issue:
Combining various administrative health and clinical data collected throughout children's lives provides a powerful tool to understand long-term treatment outcomes and provide better care.

What we did:
We established a number of exciting new projects for children with rare conditions to combine genomic and clinical data with administrative health data.

The outcome:
We hope our findings will improve our understanding of the causes of rare childhood conditions and inform decision-making for the management and treatment of children to improve their long-term health and wellbeing.

Rare childhood conditions can affect a child's health and wellbeing throughout their lives. The direct and indirect effects of their condition may show up later in their physical or mental health, school performance and quality of life.

Data are collected each time a child interacts with the health, education or other sectors. By analysing this routinely collected data, we can track the effects of a child's condition as they grow up. Our findings directly inform patient management and long-term follow-up.

For the first time in a paediatric population, we are combining administrative data with clinical treatment data and genomic information for children with rare diseases and cancer.

Project lead, epidemiologist Prof Natasha Nassar, says linking these data will provide a better understanding of the risk factors associated with both the underlying condition and management of rare diseases and cancer. This will enable personalised treatment and prevention pathways to be developed.

"This way, we can start to understand how the underlying condition or treatment of rare diseases and cancer in childhood can affect outcomes in adolescence and adulthood, identify what kind of conditions they experience, how frequently they are presenting to hospital, and how their life is affected," Prof Nassar says.

Informing clinical decision-making

The insights from this project will inform treatment and management by improving understanding of long-term impacts of treatment on children's health, and identifying factors that can potentially be modified.

The project involves integrating and linking clinical treatment and genomic data with population-based administrative health data, such as inpatient hospital admissions, emergency department presentations, NAPLAN scores and data about the socio-demographic environment.

The project is establishing data governance and consent protocols with scientists and researchers across computational biology, predisposition screening and clinical trial programs, and developing data linkage protocols and resources to integrate the data in the future.

The data will be de-identified and merged to track each child individually, as well as aggregated across the population of NSW.

The researchers will then conduct advanced biostatistical and bioinformatic analyses to provide new insights in understanding childhood cancer and rare childhood diseases in a way that is meaningful for clinicians.

Prof Nassar says conducting this work through the Luminesce Alliance has enabled her to form new connections with a wide range of clinicians, scientists and decision makers.

"Different datasets are like foreign languages, and we are trying to bring these together into a common language – and for that we need to work with many people with different expertise and backgrounds.

"Involvement with Luminesce Alliance has opened up my world. I have had the opportunity to meet and work with oncologists, geneticists and clinicians from across both Sydney Children's Hospitals Network campuses and different universities," she says.

Prof Natasha Nassar
Chair in Translational Childhood Medicine
Financial Markets Foundation for Children
University of Sydney

"Involvement with Luminesce Alliance has opened up my world. I have had the opportunity to meet and work with oncologists, geneticists and clinicians from across both Sydney Children's Hospitals Network campuses and different universities"

Prof Natasha Nassar

Informing resource allocation and supporting the sustainable delivery of precision medicine

Health system

The issue:
To turn the dream of precision medicine into reality, it is necessary to understand whether it is cost-effective, and what are the barriers and enablers to implementation. These data are largely missing for paediatric precision medicine in Australia.

What we did:
We supported implementation science and health economics projects to study the roll-out of the Zero Childhood Cancer Program.

The outcome:
We have provided implementation recommendations, and are developing an economic evaluation model to understand the costs and cost-effectiveness of this complex program.

Luminesce Alliance has provided funding to support implementation and health economics evaluations of the Zero Childhood Cancer Program (ZERO), obtaining insights that will be invaluable to other precision medicine programs in future.

ZERO is Australia's first personalised medicine program for children and young people with high-risk cancer.

To support successful scaling of the comprehensive genetic testing component of ZERO, Luminesce Alliance is supporting an analysis to measure the benefits of precision medicine for families and the healthcare system.

This includes implementation science and health economics analysis to reveal the barriers and enablers to delivery of a precision medicine program of this scale, and whether or not it is cost-effective.

Delivering precision medicine in a complex health system

ZERO is at the frontier of medical science. However, its successful delivery depends on people working in the healthcare system – all of whom have different ways of behaving, interacting and communicating.

Adding to this complexity is the fact the program spans different organisations and cultures, says Prof Jeffrey Braithwaite, Director of the Australian Institute for Health Innovation (AIHI) at Macquarie University.

The AIHI team studied the complex interactions involved in ZERO's implementation, and how it affected the system. The work involved mixed research methods such as social network analysis, ethnography, and interviews with the many clinicians involved in ZERO.

The ZERO team validated the results throughout the project and iteratively adapted their practice to ensure smooth running of the program.

"As far as we know, this is the first time anyone else in precision medicine has put implementation science lens of this kind alongside an intervention they are trying to do to change practice on the ground," Prof Braithwaite says.

Dr Janet Long, a Senior Research Fellow at AIHI, says the research showed successful implementation needed a flexible, adaptive approach, frequent multidisciplinary meetings, and to build on existing culture within organisations.

"Our findings will apply to many projects of this kind," Dr Long says.

Studying the cost-effectiveness of precision medicine

Previous research into the effectiveness and cost-effectiveness of genomic sequencing for rare diseases has shown significant cost savings. However, there has been no analysis of this kind for genomic medicine in the paediatric cancer setting.

"Analysing this large and complex program requires specialist expertise because economic analysis of precision medicine in the field of paediatric oncology is in its infancy," says Prof Deborah Schofield, Director of the Centre for Economic Impacts of Genomic Medicine at Macquarie University.

For example, the number of genetic conditions for which a molecular diagnosis is possible is constantly changing. There are continual improvements in the ability to provide effective therapy or management to those who are diagnosed.

Another challenge is how to model cost savings over a child's lifetime for conditions that have had a very high mortality in early life but now have effective therapies, as we do not yet know what the long-term outcomes will be.

Using a methodology developed across numerous genetic conditions and refined for ZERO, Prof Schofield's team is initially collecting data about the costs incurred through ZERO, such as sequencing, data storage and staff costs.

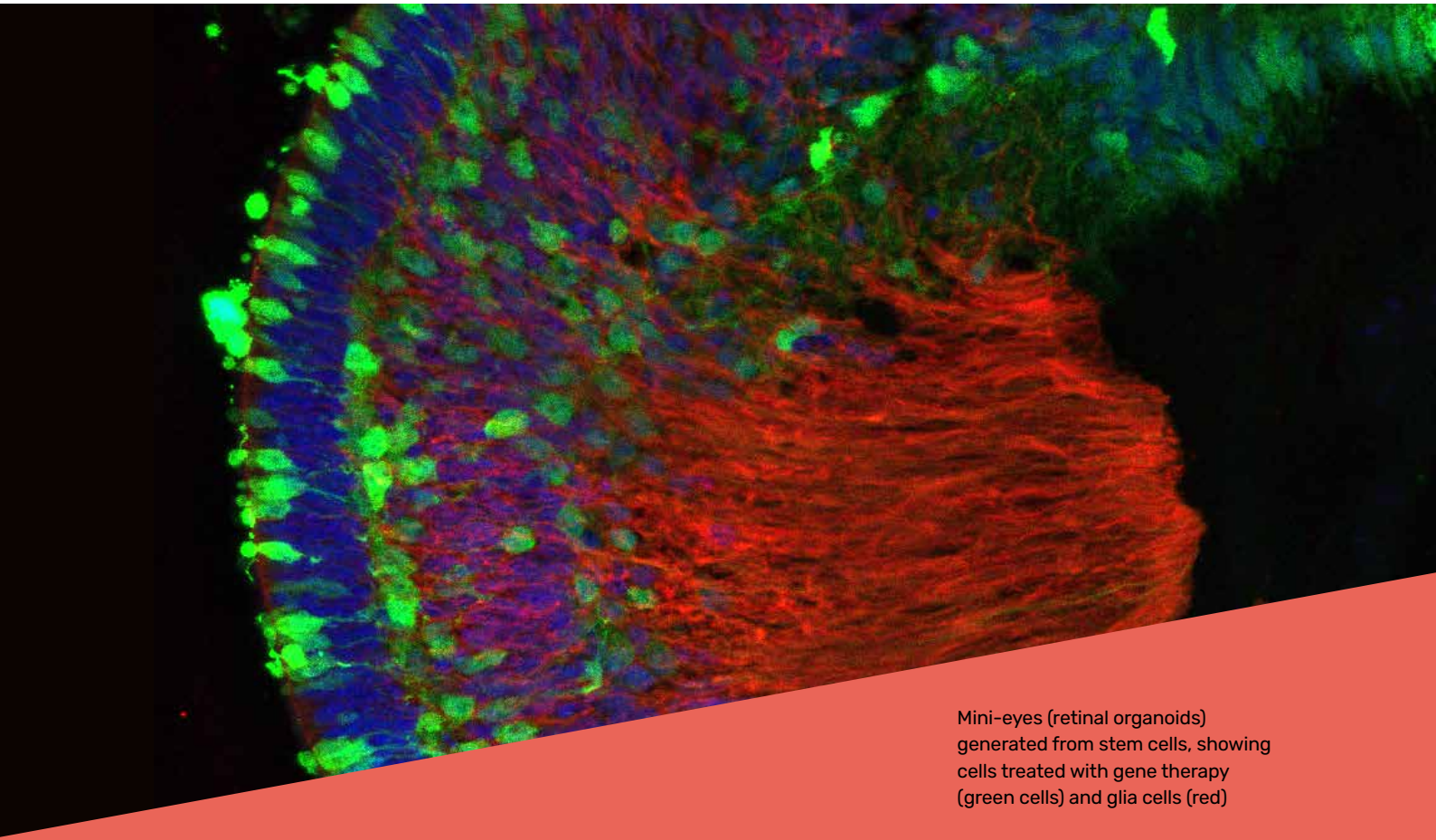
In cases where an informative result is obtained from genetic sequencing that leads to a change in management, they will model future costs and savings incurred as a result.

"An advantage of this project is that it has provided opportunities for early career researchers to work in this field," Prof Schofield says.

"This project will contribute to the development of early career researchers," she says.

A compelling economic argument for precision medicine

Genetic retinal diseases



Mini-eyes (retinal organoids) generated from stem cells, showing cells treated with gene therapy (green cells) and glia cells (red)

The issue:

Genetic retinal diseases gradually turn people blind. We now have the potential to diagnose and cure them, but for further support for this work we need to show that it has benefits beyond individual patients and families.

What we did:

We are conducting the first project of its type into the costs of genetic retinal eye diseases in children across the lifespan and the cost-effectiveness of routine genomic testing.

The outcome:

We will produce one of the first health economic models showing the benefits that precision medicine can bring to society and the economy.

When we tell families that their child's vision will deteriorate into blindness, we often hear parents say something like: "If they didn't have this disease, my child could become a pilot, a surgeon, a builder…"

Families know only too well the significant costs of having a blinding genetic eye condition. Parents must often give up their job and must find many thousands of dollars in medical bills and equipment.

The impacts of genetic eye diseases ripple throughout the entire community, in terms of lost education and employment opportunities for the child, lower productivity and absenteeism from parents, and the costs of mental health conditions such as anxiety and depression that can impact families who experience incurable genetic conditions.

However, these costs have never been quantified. And without understanding the true burden of blinding genetic eye diseases, it is hard to argue for the cost-effectiveness of treating them with precision medicine, says Prof Robyn Jamieson, head of the Eye Genetics Research Unit at the Children's Medical Research Institute (CMRI).

Now that a potential therapy for blinding genetic eye conditions is in the pipeline, there is an urgent need to show the return on investment for governments to fund treatment, she says.

"These genetic conditions affect children their whole life. If we can treat them and improve their vision, then they have a better opportunity to take advantage of education and they are better able to participate in the workforce of the future," she says.

Tangible and intangible costs of genetic eye diseases

This project is the first of its kind to collect data from families and patients in different age groups, from babies to middle age, on the costs of genetic retinal diseases across the lifespan.

In interviews with the research assistant working on this project, families are describing how these diseases can affect quality of life as well as finances. Personal costs include struggles navigating the National Disability Insurance Scheme, social isolation, and lifelong impacts on relationships, work, study and mental health.

The researchers ask a set of validated questions that enable these intangible costs to be quantified. This has never been possible with genetic eye diseases before.

Patient Care Coordinator, Lorraine Villaret, also working with the team, says the research has highlighted the importance of early intervention to link families to services and support them through the disability system.

"Whenever a patient is identified through this project who has fallen through the gaps, I am able to link them with appropriate resources so they can access support they need to alleviate the impact of the condition," she says.

The second part of the project is developing a health economic model based on quality of life and health cost data to estimate the cost-effectiveness of the use of genomic testing and precision treatments for genetic eye conditions.

This model will enable funders to quantify, for the first time, the health economic impact of genetic blindness and the benefits that could be achieved with precision medicine.

Prof Jamieson says the research will ultimately result in data on the financial, social and psychosocial costs of different retinal dystrophies, providing economic evidence to support future applications for genomic testing and new therapies.

Making the economic argument for precision medicine

Providing the first economic model of genetic blindness has potential benefits for other genetic diseases, by enabling researchers to clearly show the cost savings that could be achieved through precision medicine.

"This work is critical," Prof Jamieson says.

"Currently, access to genomic testing and therapy is not equitable across Australia due to different funding mechanisms across jurisdictions."

"If we can make a compelling economic argument showing the huge benefits of genomic investigations and precision therapies, then there is more chance that genomic medicine will be more equitably funded across Australia."

World-first psychosocial research translates into better experiences of care

Value-based healthcare

The issue:
Attending to the psychosocial needs of patients and their families is critical to improve experiences of care and enhance treatment outcomes. But we do not yet understand the potential psychosocial benefits and harms of genetic testing and precision medicine.

What we did:
We conducted psychosocial assessments over time of children, parents and healthcare professionals in the precision medicine programs across all children's hospitals in Australia.

The outcome:
We collected world-first data that will be directly translated into targeted resources on precision medicine for families and supports to improve the experiences of those who provide care.

We are conducting one of the first studies in the world into the psychosocial implications of precision medicine for children, their families and health care to develop targeted resources and support to improve experiences of care.

While precision medicine improves treatment options for patients and potentially improves clinical outcomes, parents' understanding may be limited and they may have unrealistic expectations of the potential benefits. The psychosocial implications of precision medicine have rarely been studied before.

International research shows that psychosocial factors may influence up to 30 per cent of the long-term morbidity of children with physical illnesses. That is because patients' and families' experiences, understanding and communication around treatment are key to health outcomes as well as their level of satisfaction.

Luminesce Alliance funding supported a pilot trial of the Zero Childhood Cancer Program (ZERO) called TARGET to gain an in-depth understanding of the experiences of all stakeholders involved in precision medicine, including parents, their child's healthcare providers, and the scientists who conducted the laboratory research.

Uniquely, our new study of the psychosocial implications of the ZERO national clinical trial, called PRISM-Impact, is gathering longitudinal data over five years, so it is possible to identify how experiences change and when new issues emerge.

This world-first data on the participants' psychological function, wellbeing and quality of life will inform targeted resources and support to enable patient-centred, holistic care, says Prof Claire Wakefield, of the School of Women's and Children's Health at the University of New South Wales and Sydney Children's Hospital.

"If parents aren't coping, that flows onto the child. Ultimately, we would like every family to feel well informed and confident that they know what's happening and also to feel well supported, no matter what language they speak or where they live," she says.

"It's not about taking away their sadness and grief, but making sure they have the support they need from the moment of diagnosis to the long term, when they go home."

Meeting the psychosocial needs of children and families

The research found that, as would be expected, parents experience high levels distress around the time of their child's diagnosis. However, for some this does not resolve long term, and parents are often unable to attend to their own emotional needs when their child is so sick.

Some parents had a lack of understanding and awareness of precision medicine, and unrealistic expectations of what it could achieve.

If these problems are not addressed, families enrolled in precision medicine trials are at increased risk of long-term distress, and may experience regret, mental health conditions, relationship and family problems, and poorer health outcomes.

The data collected will be translated into a range of resources such as brochures, videos and telehealth support that are accessible to families whenever they need them during this difficult time in their lives.

The study also gathered the world's first data from children themselves, whose distress levels are hard to capture while they are so unwell. An initial survey of children aged 12 and over is providing unique insights into the needs of children having these revolutionary new treatments.

Meeting the needs of healthcare professionals and scientists

The research is also asking healthcare professionals and scientists about their experiences of providing precision medicine. Participants have identified a recurring problem when caring for families in how to communicate realistic expectations of treatment while maintaining hope.

The research has found that healthcare professionals feel they would benefit from peer-to-peer support, so they are able to share the emotional burden of their work with others when they encounter a difficult case.

The research also includes nurses, clinical research associates who run clinical trials, genetic

counsellors, surgeons and pathologists, all of whom may have different experiences of providing precision medicine.

“Having difficult conversations can be a real burden for health professionals, and not all of them may be aware of the trials the patients are enrolled in,” says Dr Kate Hetherington, of the School of Women’s and Children’s Health.

“Many of them were amazed to be asked about the new developments in their work and how they feel about them; it’s unique for them to have this opportunity to feel heard, and it will be important for implementation of precision medicine.”

The PRISM-Impact trial is now being expanded, and more research is underway into the experiences of non-English speaking and Aboriginal families.

“This work is a way of translating the intention of the health system into families’ experiences of it – of ensuring families get the best experiences possible, even when their child is unwell,” says Prof Wakefield.

“The interventions we will design are low cost but have a big gain. They will lead to better outcomes for decades, rather than ongoing problems for the rest of patients’ lives.”

"Our dream is that every family feels well informed and confident they know what's happening and that they feel psychologically supported. It's not about taking away their sadness or grief, but making sure they have the support they need no matter what language they speak or where they live."

Prof Claire Wakefield,
School of Women's and Children's Health,
University of New South Wales

Innovations projects

In 2020-21, Luminesce Alliance offered researchers within the Luminesce Alliance partnership seed funding for innovative paediatric precision medicine research projects. The intentions of these seed funding grants were to:

- Initiate innovative and new paediatric precision medicine-based research projects
- Assist these projects to gather evidence and data to seek further funding and/or
- Use this evidence or data as a means to translate precision medicine into the clinical setting

Curing genetic liver disease

Until recently, the only option for children born with many rare genetic liver diseases was to follow highly restrictive diets and, ultimately, to have a liver transplant.

In recent years, however, gene therapy has offered the hope of a cure for these conditions by adding functional copies of a gene to the liver, thereby fixing the genetic problem.

Luminesce Alliance seed funding is now being used to push the boundaries further – to research revolutionary new methods that allow children's own genes to be fixed.

"We are trying to make permanent changes to the genomes of these children, in a safe way, to effectively cure them of their genetic liver disease," says Senior Research Officer Dr Samantha Ginn, of the Children's Medical Research Institute (CMRI).

The project has two parts, both of which use CRISPR-Cas9 gene editing machinery, a relatively new technology that enables a cell's genome to be targeted at a certain location to remove or add desired DNA sequences into the patient.

The first part of the project is finding more efficient, safer ways of delivering the gene editing machinery to liver cells, using a combination of new gene transfer technologies developed at CMRI.

The researchers are exploring the use of adeno-associated virus (AAV) vector technology, which uses artificial viruses to act like taxis to deliver gene sequences specifically to the liver cells that need them, along with lipid nanoparticles, tiny spheres that deliver genetic code into the liver cells and then disappear.

That means that once the gene editing machinery is delivered to the cells that need it, it will make the necessary changes to precise locations in the genome to cure ornithine transcarbamylase (OTC) deficiency, and then clear from the body to reduce any potential side effects.

Dr Samantha Ginn
Senior Research Officer
Gene Therapy Research Unit
Children's Medical Research Unit

Dr Sharon Cunningham
Senior Research Scientist
Gene Therapy Research Unit
Children's Medical Research Institute

The second part of the project is using similar techniques to make epigenetic edits to the patient's cells. This does not change the genetic code, but instead switches genes on or off.

It is being investigated to treat girls with OTC deficiency, who have a mutant gene and a functional gene. In every cell, only one gene is switched on. It is hoped the technique will be used to switch on the functional gene in all the liver cells.

With Luminesce Alliance funding, the researchers hope to generate the preliminary data necessary to progress to the next stage of research, and ultimately to a clinical trial that may see an eventual cure for children with this devastating condition. If successful, the research will also have applications for other genetic diseases.

Senior Research Officer Dr Sharon Cunningham says the research would not have been possible without access to a world-leading gene transfer technique developed by Luminesce Alliance partners at CMRI and to liver models from The Children's Hospital at Westmead.

"We are privileged to have this relationship with the liver transplant team at The Children's Hospital at Westmead, and we also have access to the work of A/Prof Leszek Lisowski and Prof Ian Alexander, who are world leaders in the field of AAV gene transfer technology," Dr Cunningham says.

Introducing RNA diagnostics into clinical practice in NSW

DNA testing has transformed the diagnosis and outlook for many children with genetic diseases, but it still does not find an answer for about 60 per cent of patients.

The new frontier of genetic medicine involves the study of RNA, a single-stranded molecule similar to DNA that sits in a different part of the cell.

RNA creates the recipe that transforms the genetic blueprint into proteins that make the body function. Disorders can happen when there is a problem in the way the recipe is cut and pasted together, known as splicing.

MRFF-funded research led by Prof Sandra Cooper of the Kids Neuroscience Centre has shown that an RNA splicing problem was responsible for disease in more than 90 per cent of patients whose DNA tests returned a negative finding.

"Once they get a diagnosis, children and families can receive counselling, early intervention, personalised medicine and access to clinical trials. Their families can take steps to prevent disease in future," Prof Cooper says.

RNA testing has already been done in oncology, for example in tumours and a small subset of causative genes found in most body tissues. However, RNA testing has not previously been done systematically for rare disorders, which involve several thousands of causative genes, some of which are only expressed at detectable levels in the organ involved.

This study has refined and optimised ultra-sensitive approaches to detect trace levels of RNA in clinically accessible specimens. The process has been refined in the laboratories of Kids Research at The Children's Hospital at Westmead.

Luminesce Alliance funding has been used to fund an interdisciplinary collaboration between scientists, clinicians and pathologists to bring RNA diagnostics into clinical practice. The project will establish an accredited RNA Diagnostic Service in NSW – among the first accredited pipelines for RNA diagnostic testing in Australia and the world.

Prof Sandra Cooper
Co-Head & Scientific Director of Kids Neuroscience Centre
Children's Hospital at Westmead
Head of Functional Neuromics
Children's Medical Research Institute
University of Sydney

Through consultative co-design, the team has developed and implemented this work into health services through consensus standardised practices for RNA diagnostics that can be applied for any gene and any disorder.

Implementing clinically validated, evidence-based RNA diagnostic testing within health services could increase diagnosis for families with rare genetic disorders or germline cancers from around 50 to 75 per cent, says Prof Cooper.

"Every child affected with a genetic disorder is estimated to cost the health system $8 million. So this work could ultimately save NSW hundreds of millions of dollars," Prof Cooper says.

"The whole world is now interested in RNA, and this work will set the international standards for RNA diagnostics."

A serendipitous discovery: towards a new neuroblastoma treatment

A chance discovery in a laboratory at the University of Sydney may lead to an effective new treatment for neuroblastoma, a deadly brain cancer for which there is no cure for many young patients.

Prof Philip Hogg, Chair of Translational Research at the University, was testing a new molecule that he had created to target a certain protein involved in cancer. But instead of attaching to the protein, the molecule entered only the dead and dying cells in the tumour.

"We realised this molecule is unbelievably selective – it just doesn't get retained by healthy cells," Prof Hogg says.

In further testing, the new molecule has proven to be exceptionally specific for dead and dying tumour cells both in the laboratory and in humans. It has been called a Cell Death Indicator (CDI).

With Luminesce Alliance seed funding, Prof Hogg and his team are investigating whether they can use the dead cell-seeking powers of CDI molecules to deliver a targeted treatment for neuroblastoma using radioisotopes.

Radioisotopes are radioactive atoms that destroy cancer cells, and have been used successfully to treat prostate and neuroendocrine tumours in a new form of targeted therapy called theranostics.

The problem with theranostics is how to deliver the radioisotopes to the correct cells. This research project will hitch a radioisotope called Lutetium-177 to the CDI molecules, which will then find and enter the dead and dying cells in the tumour. Once in place, the radioisotope will kill the nearby viable tumour cells. The new therapy is called Lu-CDI.

First the patient would receive chemotherapy or radiotherapy to kill as many tumour cells as possible. The first dose of Lu-CDI would then create even more dead and dying cells, creating a self-amplifying effect that sensitises the tumour to the therapy with each dose.

Prof Philip Hogg
Chair in Translational Cancer Research
NHMRC Clinical Trials Centre, University of Sydney

Previous research has shown that CDI is safe in other organs and is naturally excreted from the body by the kidneys. The radioisotope Lutetium-177 has been widely studied and has been shown to be a safe and effective treatment for prostate and neuroendocrine cancer.

It is hoped that the Luminesce Alliance funding will lead to publications in top cancer journals and provide the necessary results for a Phase One clinical trial in neuroblastoma patients. If successful, it could change the paradigm for treating cancers that are hard to reach and treat, says Prof Hogg.

"All solid tumours have dead and dying cells, so this could also work for liver, pancreatic and other brain tumours," he says.

"This was a serendipitous discovery that, if it works as expected, would not only lead to new therapies for cancers that are tough to treat in our kids and adults, but would also reap potential industry and commercial returns."

Preserving sight in the retinal dystrophies

Inherited retinal diseases cause progressive degeneration into blindness when photoreceptor cells in the retina gradually become stressed and die. Eventually, the retina ceases to function and the person is unable to see.

For reasons we do not fully understand, it is not just the cells containing the faulty genes that die, but also some other healthy cells around them.

Luminesce Alliance seed funding has enabled a research team at the Children's Medical Research Institute (CMRI) to generate preliminary data on a newly identified pathway that could hold the key to preventing this process.

Prof Robyn Jamieson, Head of the Eye Genetics Research Unit at CMRI, hopes that developing a therapy to modulate this pathway will help to prevent the 'bystander' effect that causes the other cells to die.

"One day, this research has the potential to delay vision loss in conditions for which we do not yet have gene therapy or gene editing options," Prof Jamieson says.

The team is testing the significance of the pathway in retinal organoids. These are "mini-eyes" made out of stem cells taken from patients' blood, which are being used to study the contribution of different gene variants in disease.

Initial work on the organoids and other models has indicated that modulation of this newly identified pathway can successfully rescue vision.

Prof Robyn Jamieson
Head of the Eye Genetics Research Unit
Children's Medical Research Institute
University of Sydney

The team hopes to develop the research further by testing what happens if they combine modulation of the pathway with gene therapy to correct the genetic defect causing the disease. It is hoped that this combination may be more effective and lead to long-lasting therapeutic benefit.

Prof Jamieson says the preliminary data generated in this study will be used to progress the research in larger studies.

"I could see this had the potential to be really important, and with Luminesce Alliance funding we have been able to boost our functional genomics work to test it out," she says.

Patient story: Sora

Four-year-old Sora loves rainbows and dolphins – but she will never see them. She was born with Leber Congenital Amaurosis, a genetic condition that means she is legally blind.

While Sora can see light and large shapes, her condition is progressive and she is likely to lose all vision before she is an adult. Like other children with blinding genetic eye diseases, time is critical in finding a treatment.

Luminesce Alliance funding for Prof Robyn Jamieson's team to study genes in mini-eyes in the laboratory is providing hope for children like Sora and her family.

There are thousands of genetic mutations that cause eye diseases; studying them in detail means that gene therapy or other strategies may one day be developed to fix the problem and restore sight.

> **Gene therapy trials overseas have already proved highly successful. The world-leading work of Prof Jamieson and her team means that these exciting new therapies will be available to children in NSW too.**

Fishing for biomarkers for Rett syndrome

Rett syndrome is a rare genetic neurological and developmental disorder that gradually causes children to lose the ability to crawl, walk and communicate from the age of about 6 to 18 months. It affects 350,000 children worldwide, mainly girls, including 430 in Australia.

Girls with Rett syndrome are commonly misdiagnosed as having autism or mitochondrial disease, and it often takes around four years to receive an accurate diagnosis. There is no effective treatment for the condition, despite numerous national and international clinical trials.

One of the reasons clinical trials have failed is that no clinically useful biomarkers have been identified for Rett syndrome. Although mutations in the MECP2 gene are the main cause of Rett syndrome, these mutations are not found in all girls and therefore diagnosis is made on clinical investigations.

Luminesce Alliance funding is being used to analyse blood and urine samples from girls with Rett syndrome to find biomarkers – molecular indicators of the disease's severity and progression.

The study is searching for biomarkers among more than 700 metabolites (chemicals) in the samples, using state-of-the-art technologies that can identify any disruptions in these chemicals in one test.

Dr Wendy Gold, Head of the Molecular Neurobiology Research Laboratory at Kids Research, says the ultimate aim is for clinicians to be able to test for these biomarkers to aid in the diagnosis, and for scientists and pharmaceutical companies to have a reliable measure of disease improvement in clinical trials.

The advantage of this study is that it is using easy-to-collect samples, rather than samples that require invasive procedures.

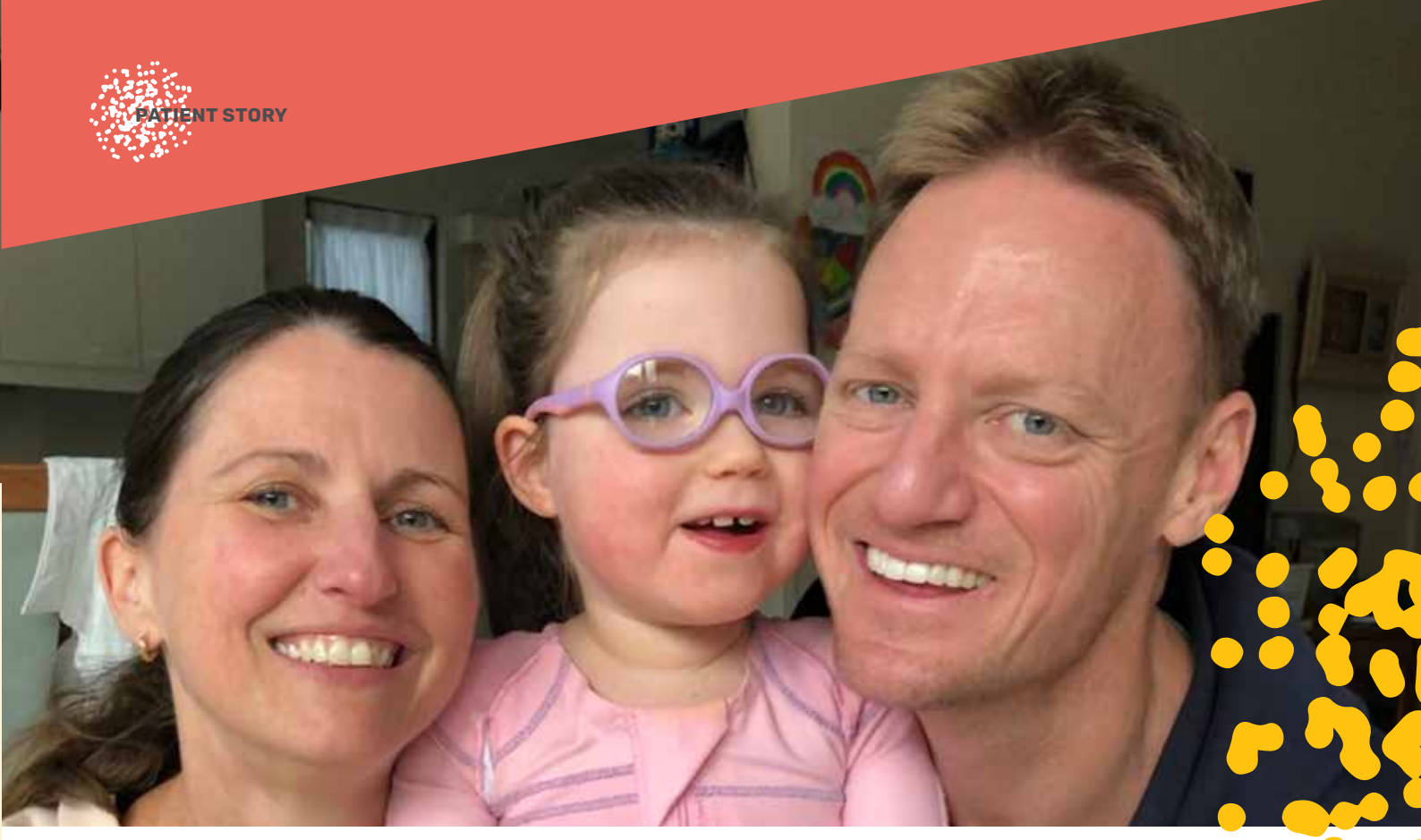
Dr Wendy Gold
Head, Molecular Neurobiology Research Group
Kids Neuroscience Centre, Sydney Children's Hospitals Network
Adjunct Research Scientist
Children's Medical Research Institute
Faculty of Medicine and Health, School of Medical Sciences
University of Sydney

"We would like to find a biomarker that is expressed at a different level between Rett patients and non-Rett patients. Then we can measure whether it changes with disease progression and treatment."

As well as this 'fishing expedition' to look for biomarkers among the metabolites, the seed funding is enabling Dr Gold and her team to study two specific biomarkers known to indicate mitochondrial stress, which they believe from laboratory tests could also indicate disease progression in Rett syndrome.

The project will determine whether these biomarkers can help diagnose the stage and severity of Rett's in girls, and whether they can predict the course of the disease.

"Traditionally, research funders don't like fishing expeditions – they want to see preliminary data first. Now we have shown there are fish out there, and hopefully this funding will enable us to catch them."



Patient story: Holly

Holly was born a healthy baby girl. But from the age of one her development stopped progressing; she could not crawl and her speech was delayed. She developed the symptoms of autism, cerebral palsy and Parkinson's disease, seizures and anxiety disorder.

After two years and numerous tests, Holly was diagnosed with Rett syndrome.

Holly's medical schedule is relentless; she has on average four to five appointments every week, three therapy sessions, plus additional medical or resource appointments. Her parents must do therapy at home and provide her with 24-hour supervision. The whole family is affected, including her siblings.

To understand more about Rett syndrome and to have a cure would improve Holly's life beyond measure.

Dr Wendy Gold's work to identify disease biomarkers to measure disease improvement, progression, stage and severity is an important step towards new, effective treatment options for girls with Rett syndrome.

> **Dr Wendy Gold's work to identify disease biomarkers to measure disease improvement, progression, stage and severity is an important step towards new, effective treatment options for girls with Rett syndrome.**

On the horizon

Luminesce Alliance researchers and clinicians are at the vanguard of paediatric genomic research. Working collaboratively, our member organisations have accomplished more than would have been achieved individually. In future, we will significantly scale up our research to improve the diagnosis and treatment of children with rare disorders.

Our upcoming endeavours will:

- Broaden our research focus to include neurodevelopmental disorders, eye and liver disease
- Increase and translate our knowledge and research capacity to the understanding of the functional impact of disease-causing genes
- Offer comprehensive molecular profiling of tumour and normal tissue for all children diagnosed with cancer in NSW
- Deliver a new platform to translate genomic and medical data into clinically actionable recommendations
- Build a pipeline to develop and test advanced therapeutics including cellular and gene therapy, newly discovered drugs and CAR-T therapy and apply these therapies in clinical trials and clinical care
- Position NSW as a leader in the development of novel technologies for vector-mediated gene delivery and gene-modified cellular therapeutics
- Attract international clinical trials to bring new treatments for children and families in NSW
- Offer psychosocial and equity-focused support and access to precision medicine to families across NSW, including families living in rural/remote regions, culturally and linguistically diverse families and Indigenous families
- Evaluate economically effective ways of implementing and delivering care for children, measured by changes in policy

Our enabling platform model

The early successes of Luminesce Alliance are underpinned by its enabling platform model.

We will invest in five enabling platforms that will support research across the entire portfolio of child health research in NSW.

Enabling platforms are functional specialisations that cross disease areas and organisations. The enabling platforms are more than shared equipment and resources. They are the people, expertise and collaborations that drive our ground-breaking research and its implementation in the health system.

Through our enabling platform strategy, this multidisciplinary, collaborative research can be used or expanded by the cancer, rare diseases and neurodevelopmental disorders teams to support their work.

We are proposing to build on our strengths across five enabling platforms:

Functional Genomics

Genomic research and translation to understand the functional impact of disease-causing genes and identify new targets for novel therapies

Data

New methods and infrastructure to rapidly translate massive amounts of complex data into clinically relevant advice

Precision Therapy

A genome-based therapeutics pipeline to develop novel technologies, build drug discovery capacity and run early phase clinical trials

Psychosocial

A world-first platform focused on ensuring the psychological, emotional, social and educational well-being of patients, their caregivers and health care professionals is not left behind with the rapid advances of precision medicine

Health systems implementation and economics research

Development and evaluation of the effectiveness, cost-effectiveness and implementation of precision medicine intervention pathways

Ms Kathryn Greiner AO

Chair

Kathryn Greiner has had the opportunity to contribute in a wide range of leadership positions in public and private companies, government bodies and non-profit organisations. She is currently Chair of the Pennington Institute, Australia's pre-eminent harm minimisation for drugs education program; Chair of the Ministerial Advisory Council on Ageing (MACA), providing advice on issues and concerns of older NSW citizens to the NSW Government; and Chair of Lifestart Co-op Ltd, a disability support service. Ms Greiner is a director of the Paul Ramsay Foundation and Relationships Australia (NSW). From 1995-2004, Ms Greiner was an elected Councillor to the Sydney City Council. She is the recipient of an Order of Australia (AO).

Ms Cathryn Cox PSM

Director

Cathryn Cox was appointed Chief Executive of Sydney Children's Hospitals Network in August 2020. She was also appointed to the Luminesce Alliance Board in August 2020. Ms Cox has many years' experience as an Executive within the NSW Ministry of Health, with responsibility for a range of health policy, planning, infrastructure and strategic reform programs. Her early role as a physiotherapist at Royal Prince Alfred Hospital paved the way for a long-term career in health which included leading Health Infrastructure as its interim Chief Executive.

Ms Elizabeth Crouch

Director

AM BEc MCyberSec

Elizabeth Crouch is Chair of the Sydney Children's Hospitals Network, the Customer Owned Banking Association and SGS Economics and Planning. She is also a non-Executive Director of ReadyTech Holdings, Bingo Industries and Angus Knight. Ms Crouch chairs Audit and Risk Committees for the City of Sydney and IPART and is on the Boards of the NSW Institute of Sport and Health Infrastructure. Ms Crouch spent 16 years with the Federal Government including with Federal Health, Industry and Innovation and more than a decade in the private sector including as Chief Executive of the Housing Industry Association.

Prof Sean Emery

Director

BSc, PhD Brunel

Prof Sean Emery is the Senior Vice Dean of Research and Operations at UNSW Medicine and Health. He is an internationally recognised clinical scientist whose contributions through research translated directly into international treatment guidelines for HIV infection. He created and led large international collaborative research networks for the design and conduct of clinical trials. He has taken on incremental levels of organisational responsibility, from Departmental to Institute and more recently Faculty leadership roles. He has played a significant role in the development and implementation of strategic planning in each setting.

Prof Michelle Haber

Director

AM, BSc (Psych) (Hons), PhD, Hon DSc (UNSW), FAHMS

Prof Haber joined Children's Cancer Institute as a staff scientist in 1984. She was appointed Director of the Institute in June 2000 and Executive Director in June 2003. She is known for her world-class research into the treatment of neuroblastoma and acute lymphoblastic leukaemia in children. Prof Haber holds a conjoint appointment as Professor in the Faculty of Medicine at the University of New South Wales. In 2007, she was appointed a Member of the Order of Australia for services to science in the field of research into childhood cancer, to scientific education and to the community. She leads the Zero Childhood Cancer national child cancer personalised medicine program, which tailors therapy to the specific genetic and biological characteristics of each child's individual tumour, and which has created a new model of care that will be rolled out by 2023 to all 1000 children and young people diagnosed annually with cancer in Australia.

Emeritus Prof Richard Henry

Director

AM, MB BS, Dip Clin Epi, MD, Hon DUniv (UNSW), FRACP, FRSN

Emeritus Prof Richard Henry works as a consultant in health and higher education. He had a long career in academic medicine and hospital paediatrics before his appointment as Vice-President and Deputy Vice-Chancellor (Academic) of the University of New South Wales from 2006-2012. He is Chairman of Trustees of Sydney Grammar School; former Chair of the Centre for Social Impact and a Board member of Legal Aid NSW. He has been a Director of Children's Cancer Institute since 1999 and is a member of the University Relations subcommittees. Prof Henry was appointed a Member of the Order of Australia in 2007 for service to paediatric medicine as a clinician, researcher, educator and mentor, and serving in a range of roles with professional medical organisations.

Prof Frank Martin

Director

MBBS FRANZCO FRACS AM

Frank Martin is a visiting ophthalmologist at the Sydney Children's Hospitals Network and at Sydney Eye Hospital. He is the President of the Asia Pacific Society of Paediatric Ophthalmology and Strabismus and a Past President of the International Paediatric Ophthalmology and Strabismus Council (IPOSC). He is President of the Children's Medical Research Institute and serves on the Boards of Luminesce Alliance and the Lowy Medical Research Institute.

Mr David Nott

Director

BEc FCA

David Nott served for almost 30 years as a partner with KPMG, a global professional services firm providing leadership in Australia and internationally. In addition to being an Independent Board member of the Sydney Children's Health Network, Mr Nott serves as the Board's representative on the Network's Audit and Risk Committee. He previously also held the role of Chair of the Audit Committee of the Southern NSW Local Health District. He is currently the Chair of the Luminesce Alliance Audit and Risk Management Committee.

Prof Roger Reddel

Director

BSc (Med) MBBS PhD FRACP FAHMS FAA AO

Roger Reddel is Executive Director of The Children's Medical Research Institute (CMRI), and the Sir Lorimer Dods Professor, Sydney Medical School, University of Sydney, since 2007. He is also Head of CMRI's Cancer Research Unit, Director of CellBank Australia and Co-Director of ProCan®. Prof Reddel was awarded the Ramaciotti Medal for Excellence in Biomedical Research in 2007, was elected as a Fellow of the Australian Academy of Science and of the Australian Academy of Health and Medical Sciences in 2010. In 2011, he received the NSW Premier's Award for Outstanding Cancer Researcher of the Year, and he was awarded the Neil Hamilton Fairley Medal of the Royal Australasian College of Physicians in 2017. In 2021, he was awarded an Order of Australia. He also serves on many medical research advisory panels.

Prof Laurent Rivory

Director

BVSc, PhD

Prof Laurent Rivory is the Pro Vice-Chancellor (Research) at the University of Sydney. His responsibilities include the large-scale collaborations such as the Charles Perkins Centre and the Brain and Mind Centre, the Core Research Facilities and the management of external partnerships, particularly in health. He has 20 years' experience in research and leadership, which has spanned the higher education, hospital and industry sectors. He is widely recognised for his research in cancer drug pharmacology and has extensive experience in the management of key research program in virology, immunology, cancer, RNA therapeutics and diagnostics.

CMRI: Children's Medical Research Institute
CCI: Children's Cancer Institute
SCHN: Sydney Children's Hospitals Network
CHW: The Children's Hospital at Westmead
SCHR: Sydney Children's Hospital Randwick
UNSW: The University of New South Wales
USyd: The University of Sydney
KCC: Kids Cancer Centre

Precision Medicine Projects

The Paediatric Precision Medicine Program consists of the following projects:

Project	Lead investigator/s
Centralised capacity to develop functional genomics for Paediatric Precision Medicine	**Prof Ian Alexander**, Head, Gene Therapy Research Unit, SCHN and CMRI **Prof Patrick Tam**, Head, Embryology Research Unit, CMRI
Cystic Fibrosis	**Prof Adam Jaffé**, Head of Paediatrics, UNSW **Dr Shafagh Waters**, Senior Lecturer, Head of Molecular Integrative Cystic Fibrosis Research Laboratory
Computational Biology	**A/Prof Mark Cowley**, Head, Computational Biology Group, CCI **A/Prof Vanessa Tyrrell**, Program Leader, Zero Childhood Cancer, Personalised Medicine, CCI
Paediatric Cancer Predisposition Screening	**Prof Tracey O'Brien**, Director, KCC, SCHR **A/Prof Vanessa Tyrrell**, Program Leader, Zero Childhood Cancer, Personalised Medicine, CCI **Dr Luciano Dalla-Pozza**, Director, Cancer Centre for Children, CHW **A/Prof Mark Cowley**, Head, Computational Biology Group, CCI **Prof Claire Wakefield**, School of Women's and Children's Health, UNSW, Head, Behavioural Sciences Unit, KCC **A/Prof Judy Kirk**, Director, Familial Cancer Service, Westmead Hospital **A/Prof Kathy Tucker AO**, Head, Hereditary Cancer Clinic, Prince of Wales Hospital Randwick and Chair, NSW Combined Family Cancer Clinic Group
Paediatric Rare Diseases Predisposition Screening	**Dr David Mowat**, Clinical Genetics, Head, Centre for Clinical Genetics, SCHR **A/Prof Meredith Wilson**, Medical Geneticist, Department of Clinical Genetics, CHW **A/Prof Kristine Barlow-Stewart**, Senior Research Genetics Counsellor, Department of Paediatrics **A/Prof Tony Roscioli**, Staff Specialist in Clinical Genetics and Genomics, NSW Health Pathology, Randwick Group Leader, Neurogenomics NeuRA
Translation of Paediatric Precision Medicine - Clinical Trial	**Prof Chris Cowell**, Director of Research, SCHN **Ms Lani Attwood**, Advanced Therapeutics Program Manager, Kids Research, SCHN
Paediatric Precision Medicine Integrated Data Linkage System	**Prof Natasha Nassar**, Financial Markets Foundation for Children, Chair in Translational Childhood Medicine, USyd

Economic Impact and Framework for Sustainable Implementation of Paediatric Precision Medicine in the Australian health system	**Prof Tracey O'Brien**, Director, KCC, SCHR **A/Prof Vanessa Tyrrell**, Program Leader, Zero Childhood Cancer, Personalised Medicine, CCI **Prof Jeffrey Braithwaite**, Australian Institute of Health and Innovation, Macquarie University **Prof Deborah Schofield**, Director GenIMPACT: Centre for Economic Impacts of Genomic Medicine, Macquarie University
Blinding Genetic Eye Conditions: Economics and Impacts of Genomics and Precision Medicine	**Prof Robyn Jamieson**, Head of the Eye Genetics Research Unit, CMRI and USyd
The psychosocial implications of genetic testing and precision medicine for children and their families and the healthcare professionals who care for them	**Prof Claire Wakefield**, School of Women's and Children's Health, UNSW, Head, Behavioural Sciences Unit, KCC **Dr Kate Hetherington**, Clinical Psychologist and Post-Doctoral Research Fellow in the Behavioural Sciences Unit in the School of Women and Children's Health, UNSW
Establishment of Vector and Genome Engineering Facility	**Prof Ian Alexander**, Head, Gene Therapy Research Unit, SCHN and CMRI
INFORM2: An exploratory multinational phase I/II combination study of Nivolumab and Entinostat in children and adolescents with high-risk Malignancies	**A/Prof David Ziegler**, Head, Clinical Trials Program, KCC, and Group Leader, Targeted Therapy Group, CCI **Prof Olaf Witt**, Director, Translational Pediatric Oncology Hopp Children's Cancer Center, Heidelberg
Newborn Screening Program Pilot for Spinal Muscular Atrophy and Primary Immunodeficiency in NSW & ACT	**A/Prof Michelle Farrar**, Paediatric Neurology, School of Women's and Children's Health, UNSW, and Lead, Neuromuscular Diseases Clinical and Research Program, SCHN **A/Prof Veronica Wiley**, Director/Principal Scientist, NSW Newborn Screening Program, SCHN **Prof Georgina M Chambers**, Director and Scientia Fellow, National Perinatal Epidemiology and Statistics Unit, Centre for Big Data Research in Health and School of Women's and Children's Health, UNSW
Luminesce Alliance Centre for RNA Diagnostics	**Prof Sandra Cooper**, NHMRC Senior Research fellow of USyd, Co-Head and Scientific Director of Kids Neuroscience Centre, CHW, Head of Functional Neuromics, CMRI, USyd
Genomic and epigenomic editing in the human liver	**Prof Ian Alexander**, Head, Gene Therapy Research Unit, SCHN and CMRI
Advancing biomarker discovery for Rett syndrome	**Dr Wendy Gold**, Head, Molecular Neurobiology Research Group, Kids Neuroscience Centre, SCHN and USyd
A new treatment modality for neuroblastoma	**Prof Philip Hogg**, Chair in Translational Cancer Research, NHMRC Clinical Trials Centre, USyd
Precision medicine addressing a novel disease pathway to preserve sight in the retinal dystrophies	**Prof Robyn Jamieson**, Head, Eye Genetics Research Unit, CMRI and USyd

Glossary

Term	Definition
AAV (Adeno-Associated Virus) vector	A type of virus engineered to deliver DNA to target cells. In gene therapy, the virus's own genes are removed, and replaced with therapeutic DNA.
Biomarker	A molecule, gene or other characteristic that indicates the presence of a certain body process or disease.
Chromosome	A structure found inside the nucleus of a cell. A chromosome is made up of proteins and DNA organised into genes. Each cell normally contains 23 pairs of chromosomes.
Clinical trial	A research investigation in which people volunteer to test new treatments, interventions or tests.
CRISPR	A genome editing tool.
De novo	A genetic alteration that is present for the first time in one family member as a result of a mutation in an egg or sperm of one of the parents, or a mutation that happens in the fertilised egg itself during early formation of the embryo. Also called de novo mutation, new mutation, and new variant.
DNA	Deoxyribonucleic acid, the molecule inside cells that contains the genetic information responsible for an organism's function. DNA molecules allow this information to be passed from one generation to the next.
Epigenetics	Inherited changes that do not affect the DNA sequence but influence gene expression (see below).
Functional genomics	The study of how the genome, genes, proteins and metabolites work together to produce an individual organism.
Germline DNA	DNA found in the reproductive cells (egg and sperms) that will be transmitted via these reproductive cells of the parents to the next generation. A germline mutation may be passed from parent to offspring. Also called constitutional DNA.
Gene	A basic inherited unit that occupies a specific location on a chromosome. Most genes code for a specific protein or segment of protein leading to a particular characteristic or function.
Gene editing	Manipulating genetic material by deleting, replacing or inserting a DNA sequence.
Gene expression	Converting the information in DNA into instructions to make other molecules or proteins.
Gene therapy	A therapy that treats human disease by using genes as medicine.

Glossary

Term	Definition
Genome	The complete set of genes present in an organism.
Lipid nanoparticle	A tiny particle made of lipids (a type of molecule) that can deliver drugs into cells.
Metabolite	A substance used or made when the body breaks down food, chemicals or its own tissue for energy, growth and repair (the metabolism).
Mutation	A genetic alteration that increases an individual's susceptibility or predisposition to a certain disease or disorder. When a mutation is inherited, development of symptoms is more likely, but not certain. Also called deleterious mutation, disease-causing mutation, predisposing mutation, and susceptibility gene mutation. See variant.
Organoid	A three-dimensional organ-like structure formed by cells.
Penetrance	The percentage risk an individual will develop a condition at a certain age.
Predisposition	The possibility of inheriting a condition, disease or disorder due to genes passed from parent to child.
Psychosocial	Involving psychological and social factors.
RNA	Ribonucleic acid, a molecule similar to DNA. It is responsible for translating information from the genes into proteins.
Somatic	An alteration in DNA that occurs after conception and is not present in the germline (see above). Somatic variants can occur in any of the cells of the body except the germ cells (sperm and egg) and therefore are not passed on to children. Somatic variants can (but do not always) cause cancers and other diseases.
Stem cell	A cell with the potential to develop into many different types of cells in the body.
Variant	An alteration in the genetic sequence that may be benign pathogenic, or of unknown significance. See mutation.
Variant of unknown significance	A variation in a genetic sequence for which the association with disease risk is unclear.
Vector	A genetically engineered carrier that delivers a gene into a cell. Certain viruses are often used as vectors because they can deliver the new gene by infecting the cell.
Whole genome sequencing	A laboratory process that is used to determine nearly all of the approximately 6 billion letters of an individual's complete DNA sequence.

www.luminesce.org.au

LUMINESCE Alliance

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

Children's Cancer Institute

CHILDREN'S MEDICAL RESEARCH INSTITUTE
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