Impact for Children's Health 2022 - 2023

LUMINESCE Alliance

Innovation for Children's Health

Our Vision

is to be Australia's most groundbreaking, innovative and translational paediatric research hub that will change children's health around the world.

Our Mission

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

Our Purpose

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

Partners

The Sydney children's Hospitals Network

Children's Medical Research Institute

Jeans for Genes

Children's Cancer Institute

The University of Sydney

UNSW Sydney

Acknowledgment of Country

Luminesce Alliance acknowledges the Traditional Custodians of Country throughout Australia and their connections to land, sea and community. We pay our respect to their elders past and present, and extend that respect to all Aboriginal and Torres Strait Islander peoples today.

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About Us

Luminesce Alliance was established with the support of the NSW Government to coordinate, integrate, galvanise, and accelerate paediatric research.

The Alliance is a unique world-class paediatric research cooperative, comprising five leading health delivery and medical research organisations in NSW — Sydney Children's Hospitals Network (SCHN), Children's Cancer Institute (CCI), Children's Medical Research Institute (CMRI), UNSW Sydney and The University of Sydney.

We fund researchers who are working collaboratively to deliver better health outcomes for children, particularly those impacted by cancer, early onset diseases and neurodevelopmental disorders.

Despite medical advances, cancer and inherited diseases are the leading causes of death in children worldwide.

At least one in 20 babies is born with an inherited disease or developmental disorder and around 1,000 young people are diagnosed with cancer annually in Australia. Many diseases of adulthood start in childhood, so advances in detection and treatment benefit the whole community.

First funded by a $24 million investment from the NSW Government in 2019, the Luminesce Alliance created its first enabling platform - the Centre for Paediatric Precision Medicine. From that initial funding, the Alliance leveraged more than $284.71 million in additional funding.

The Luminesce Alliance has supported several groundbreaking clinical trials. We have embedded newborn screening for spinal muscular atrophy, a genetic motor neurone disease and a leading cause of genetic infant death. We have pursued gene discovery and therapy approaches, and enhanced the Zero Childhood Cancer Program (ZERO).

By fostering greater collaboration between the partner organisations, we have promoted a true bench-to-bedside research model. Frontline clinicians and their patients work alongside research teams to enable a more rapid translation of medical breakthroughs — transforming the way children are cared for.

It is expected that our research will also generate long-term benefits to the broader NSW community and economy, including reduced disease burden, more employment opportunities — particularly in STEM jobs — and increased investment and commercialisation opportunities in medical research.

Message from the Chair

Our vision is to be Australia's most groundbreaking, innovative and translational paediatric research hub that will change children's health around the world.

Our first four years have been an exciting journey, during which we have developed the blueprint for paediatric precision medicine in NSW.

We have demonstrated the need and value of implementing a new way of caring for patients and families impacted by high-risk cancers, rare diseases and neurological disorders.

Combining the diverse experience and expertise of our five powerhouse partners, we focus on improving the prediction, detection and treatment of a variety of childhood diseases and conditions.

With the vital support of the NSW Government, the Luminesce Alliance has delivered major outcomes through its first enabling platform, the Centre for Paediatric Precision Medicine. The achievements and potential of our research is outlined in this Impact Report.

By championing novel research, first-in-human trials and personalised diagnosis and therapy, the Alliance is on the threshold of preventing some childhood conditions, and saving years of heartache and expense for families.

Bringing together and leveraging talent with diverse skillsets and expertise through multidisciplinary teams has enabled the Alliance to unlock synergies beyond the scope of what individual members could do on their own.

We are working at a scale that ensures considerable cost savings and resource sharing. This enables clinicians to drive the research agenda, and supports the rapid clinical adoption of researchers' work.

Our work is keeping children out of the hospital system, perhaps for ever, and providing a quality of life they have never known.

Not only will the outcomes of the Luminesce Alliance be amazing for sick children, we are also growing jobs and research capacity in NSW.

This means we will have more children's health specialists coming to us than we have leaving to work overseas. We are starting to become a world leader in paediatric research.

Ms Kathryn Greiner AO
Chair
Luminesce Alliance

Message from the Executive Director

The Luminesce Alliance journey to date has been characterised by extraordinary achievements, and there is huge potential for the future. These outcomes have been powered by the unique combination of talent, knowledge and experience that our organisation has accumulated and developed since its inception.

It is, without doubt, our Partners' commitment to true collaboration that has been pivotal to our impact and success. This has empowered the best and brightest people to connect and to take advantage of the innovative hub of world-class facilities, cutting-edge equipment and technologies available right here in NSW.

It has been a privilege to be part of a team that is unlocking treatments and cures in paediatric medicine and cementing NSW's reputation as a centre of research excellence.

This report highlights the impact of projects funded through our Centre for Paediatric Precision Medicine and demonstrates ways in which we have increased the scale and enhanced the excellence of our translational and discovery research in paediatrics.

The Luminesce Alliance journey now continues with the recent funding of our Enabling Platforms, which will drive groundbreaking research and its implementation in the health system; and offer better health outcomes for children and their families.

Ms Anastasia Ioannou
Executive Director
Luminesce Alliance

Highlights

12x

twelve-fold return on NSW Government's initial $24 million investment; $284.71 million leveraged in additional research grants

114

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

301+

innovative and translational research projects

136

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

370+

national and international collaborators

20

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

164

presentations made locally, nationally and internationally

7

facilitated R&D IPs with commercialisation opportunities

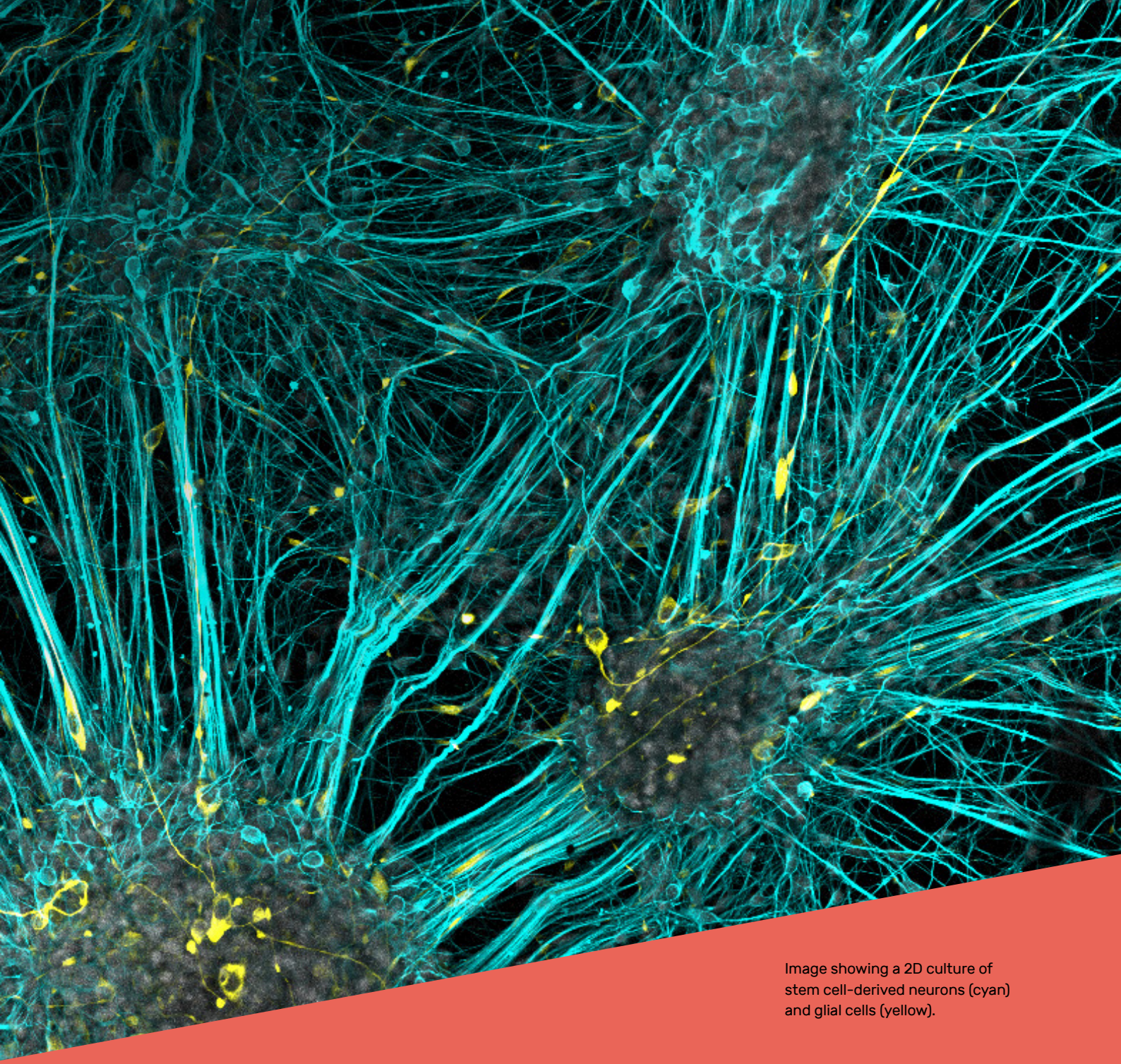


Image showing a 2D culture of stem cell-derived neurons (cyan) and glial cells (yellow).

Our Impact: Functional Genomics

Understanding and treating rare diseases one gene at a time

When a sick child presents to our children's hospitals and doctors cannot work out the cause, studying their genome and comparing it to that of healthy individuals sometimes highlights a problem in one or more of their genes. We look for a genetic mutation (also known as a variant) that causes a spelling error in their genetic script and is responsible for their disease.

Although the human genome sequence is known in detail, we are a long way from identifying the millions of genetic variants that potentially cause diseases. And, even when a disease-causing variant is found, we do not always understand why and how that mutation affects the wellbeing of the child.

Functional genomics is a rapidly advancing medical research field that aims to understand the relationship between genes and disease. We address questions about how genes work and interact with each other – and what happens when there's a problem with our genes.

Gaining knowledge about genes and their function is essential for developing new treatments. Identifying the disease process caused by a genetic mutation enables us to search for new therapies or to repurpose existing therapies to provide the best healthcare options for children and their families.

With support of the Luminesce Alliance, a leading NSW functional genomics program has been established that is pushing the boundaries of medicine by using cells and DNA to develop safe and effective treatments.

The discoveries made by our functional genomics teams mean children may receive a precise diagnosis for their condition and potential access to advanced treatments and clinical trials.

"We have established the core research support and facilities needed to take the first step towards better understanding of the functional impact of disease-causing genes," says program lead Prof Patrick Tam, Head of the Embryology Research Unit at CMRI.

"This research program has immense potential for improving diagnosis of childhood cancers, neurodevelopmental disorders and genetic diseases, and could lead to novel and effective therapies."

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.

The Luminesce Alliance has established, resourced and promoted facilities and services at CMRI, including the Stem Cell and Organoid Facility, Single Cell Analytics Facility, Vector and Genome Engineering Facility, and Rare Disease Functional Genomics Laboratory.

We contributed to the establishment of the Vector and Genome Engineering Facility – an innovative academic scientific core facility at CMRI supporting translational research in vector-based gene editing and therapy to target genetic diseases by developing

and distributing viral vector tools for use in preclinical studies.

The Rare Disease Functional Genomics Laboratory studies how genetic mutations contribute to disease. The information also enables the genetic disease to be detected by screening parents before they have a baby, minimising the chance of the disease recurring.

Researchers at the Single Cell Analytics Facility identify the cells in the body that are directly affected by diseased genes, so that the therapy can be targeted precisely to these cells for treatment of genetic diseases and childhood cancers. The team has launched more than 45 projects in the quest to identify the cell types affected in blinding eye disease, liver metabolic diseases, adrenal disorders, neuroinflammatory diseases and inflammatory myofibroblastic tumours, as well as liver cancer and gliomas.

The Luminesce Alliance also funded the first laboratory in the southern hemisphere to use precision medicine to test whether drugs do or don't work in children with cystic fibrosis – using patients' own cells. Ultimately, this will mean children will receive only medications we know will work, removing the risk of unnecessary side effects and costs.

This work is still in the experimental phase, but with continued support could one day become part of routine care in the health system, ensuring all children with cystic fibrosis have access to the medications they need.

"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. To accomplish this, we need to expand across all the capabilities," says Prof Tam.

Finding novel pathways to restore sight

Inherited retinal diseases (IRDs) cause progressive degeneration of eyesight into blindness.

Around one in 1,000 people is affected by IRDs. Vision loss is caused when retinal cells die and light messages can no longer be sent to the brain. Cell death is seen in cells with genetic faults and also in other surrounding cells.

Seed funding from the Luminesce Alliance has enabled a research team at CMRI and SCHN to investigate cell pathways that could hold the key to preventing or delaying 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.

The team worked with retinal organoids that are generated in the lab using stem cells from patients with eye diseases.

Using the organoids, the researchers tested hypotheses about the potential pathways causing progressive degeneration in retinal photoreceptor cells.

Preliminary data from the research using organoids and other models has indicated that modulation (interruption or alteration) of a newly identified pathway can successfully reduce the toxic factors contributing to vision loss.

"The preliminary data is exciting. We need to keep pushing forward," Prof Jamieson says. "This research has the potential to delay vision loss in conditions for which there are no genetic therapies, or may enhance available genetic therapies.

For inherited retinal eye diseases there are more than 250 disease genes, so the work we are doing has the potential to positively impact many of these."

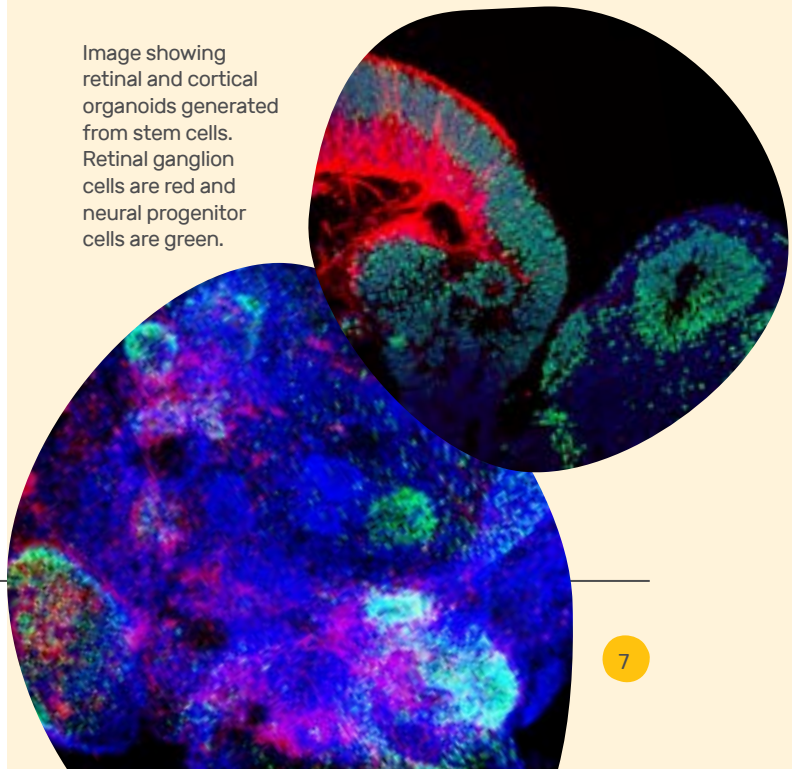


Image showing retinal and cortical organoids generated from stem cells. Retinal ganglion cells are red and neural progenitor cells are green.

Taking big steps with mini organs

A pioneering facility producing mini organs from stem cells is providing novel ways to understand and treat a range of devastating diseases.

The Stem Cell and Organoid Facility was established with Luminesce Alliance funding in 2019. Led by Dr Anai Gonzalez-Cordero and her team at CMRI, the facility is the only one of its kind in Australia working with both pluripotent stem cells and organoids.

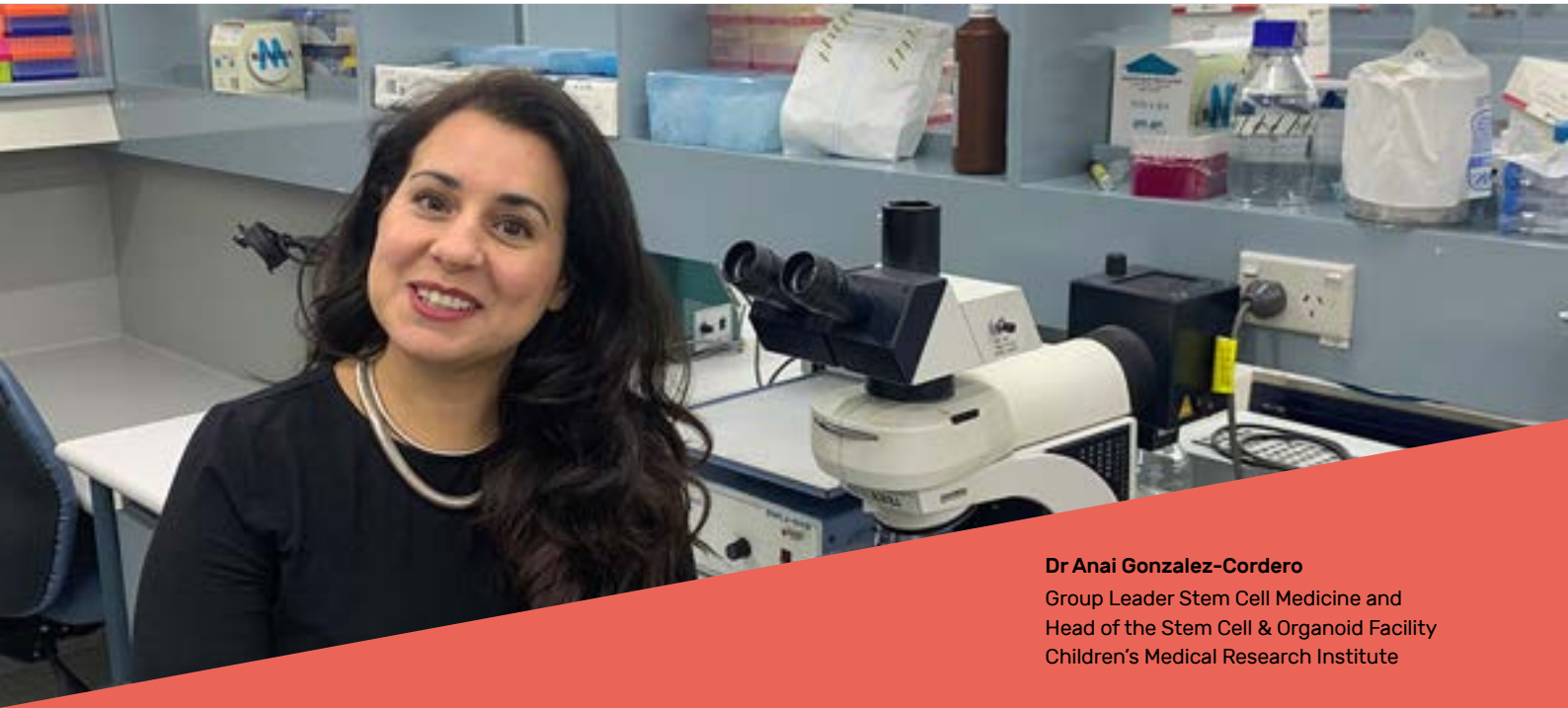
"With the support of the Luminesce Alliance, I was able to establish stem cell and organoid technology in NSW – at which point we were the only facility in Australia offering organoids generated from iPSCs (induced pluripotent stem cells)," says Dr Gonzalez-Cordero, Group Leader, Stem Cell Medicine, CMRI.

"That initial investment was critical. We set up a whole new area of medical research here in NSW and we have researchers from other states coming to work with us."

While her own research focuses on inherited retinal degeneration that causes blindness, Dr Gonzalez-Cordero is sharing her organoid expertise to support a variety of studies throughout NSW and across Australia.

"The beauty of stem cells is that they contain the same genetic condition as the patient, and we can use them to generate almost any organ we need to study," Dr Gonzalez-Cordero says.

"Organoids offer new human models to scientists. These were previously very scarce and difficult to get. Our hope is that it will speed up the development of safe and effective treatments for



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

Pluripotent Stem cells can give rise to all the different cells in the body. The team generates stem cells in the lab, known as **iPSCs** (induced pluripotent stem cells).

They are created by '**reprogramming**' cells taken from patients, such as skin or blood cells. iPSCs offer an unprecedented opportunity to study genetic diseases and new treatments.

Organoids are three-dimensional mini organs, created from stem cells in a dish. These **mini organs** mimic the real organ and can be used to study the disease-causing process, and to test new gene therapy and stem cell therapies.

millions of children affected by genetic and acquired disorders."

It takes a few months to generate iPSC lines and even longer to grow the organoids, but this depends on the organ.

Since becoming operational in 2020, the team has established the ability to generate thousands of organoids at a time.

The Stem Cell Facility provides human stem cell derived cells, tissues and organoids to all groups and researchers at CMRI and affiliated institutes. Ongoing projects include collaborations with scientists and clinicians who want to better understand diseases of the heart, liver and, most recently, the kidney.

The team is working with Prof Stephen Alexander and Dr Hugh McCarthy, nephrologists at SCHN, to generate organoids using cells from patients with kidney disease. These could be vital in developing new treatments.

"The Facility allows us to do this kind of translational research, to find solutions together," Dr Gonzalez-Cordero says.

"That's the power of the Luminesce Alliance. It has brought us into partnership to develop new therapies - combining the clinical side, human stem cell biology, omics, computational biology and medicinal chemistry."

Stem Cell Medicine Group - Attracting talent and funding

When she joined CMRI in 2019, Dr Gonzalez-Cordero also established her independent research program to continue her work on in vitro models of retinal and auditory organoids. Her group of talented scientists, including international PhD students, all work in novel and exciting translational projects that aim to develop therapies for blindness.

Dr Gonzalez-Cordero says the "leap of faith" taken by the Luminesce Alliance with its initial investment in the stem cell and organoid technology has led to success in applications for future funding by the Stem Cell Medicine Group, including two prestigious Medical Research Future Fund (MRFF) grants.

In September 2022, the Stem Cell Medicine Group was awarded $2.5 million from the MRFF to produce stem cells that can be used to create Australia's first cell therapies to treat vision loss in people with inherited diseases of the retina.

They are working with collaborators from Melbourne's Murdoch Children's Research Institute to produce Australia's first Good Manufacturing Practice (GMP) bank of iPSC lines. This means the cell lines would be of the high quality required for therapeutic use in humans.

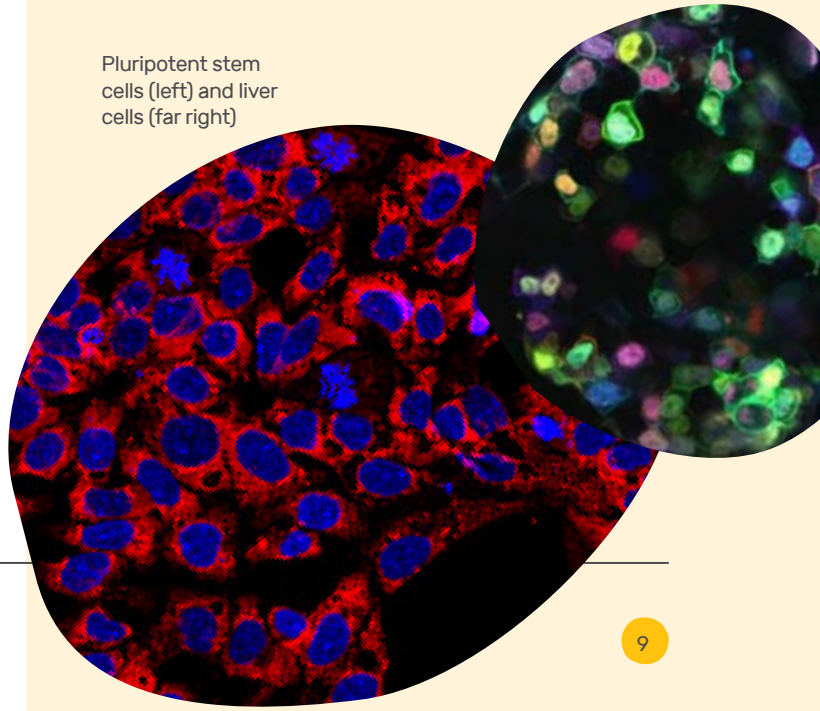
Millions of people worldwide live with severe degenerative diseases of the eye that lead to progressive vision impairment and, eventually, total blindness. The majority of these inherited and acquired degenerative diseases affect the light-sensing tissue at the back of the eye, the retina, that contains the rod and cone photoreceptors and are currently untreatable.

"Cell transplantation with healthy cells holds great promise because this therapy can be applied irrespective of the underlying cause – be it genetic or a disease that is acquired," Dr Gonzalez-Cordero says. "If we can produce GMP-quality retinal cells, these cells can be used to replenish those lost during disease and hopefully contribute to the restoration of vision.''

The stem cell transplantation research was also given a boost via a Luminesce Alliance Innovation fund project in 2022.

"We have demonstrated proof-of-concept for the transplantation of mouse and human stem cell derived photoreceptors to restore visual perception in mice," she says. "In this project, we will move this therapy closer to implementation."

The results of the study could be extended further and provide hope for patients with other (non-retinal) blinding eye conditions.



Pluripotent stem cells (left) and liver cells (far right)

Pioneering gene therapy for liver disease

Safer and more effective ways of using gene therapy are being tested in a Luminesce Alliance-funded study investigating treatments for children with an incurable genetic liver disease.

The only option for children born with Ornithine Transcarbamylase (OTC) deficiency is to follow highly restrictive diets and, ultimately, to have a liver transplant. But gene therapy offers the hope of a cure by adding functional copies of a gene to the liver, thereby fixing the genetic problem.

Luminesce Alliance seed funding was used 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 Dr Samantha Ginn, Senior Research Officer at CMRI.

OTC deficiency is a rare and potentially devastating genetic condition caused by a lack of the OTC enzyme. It is more common in boys than girls and tends to be most severe when symptoms emerge shortly after birth.

OTC deficiency causes ammonia to build up in the body, affecting the nervous system and leading to vomiting, inability to eat, lethargy, and coma. Current treatments aim to control ammonia levels with a highly restrictive diet and medication.

A liver transplant may be needed.

Part of the project looked at ways to deliver gene editing technology directly into the liver cells, where it corrects the genetic code and then disappears, reducing the chance of side effects.

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

The researchers explored the combination of Adeno-Associated Virus (AAV) vector technology with lipid nanoparticles. AAV technology uses artificial viruses to act like taxis to deliver gene sequences specifically to the liver cells that need them, and lipid nanoparticles are 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 OTC deficiency.

"We have built a strong collaboration with researchers at Monash University, who are one of Australia's leading groups in lipid nanoparticle technology," Dr Ginn says. "Their main interest is in mRNA vaccine development, but they appreciate that we have excellent skills in gene delivery and have relevant preclinical models to test the therapies."

Dr Ginn says the preliminary results have proved the concept, but further investigation is required.

"The liver does take up those lipid nanoparticles efficiently, so it is an excellent target for this technology," she adds.

The research will also have applications for other genetic diseases.

The preliminary Luminesce Alliance-funded study data has led to a successful grant application with the Monash University team, led by Prof Colin Pouton, to do further testing of the safety and efficacy of the technique. The $99,000 accelerator fund will see the CMRI and Monash teams collaborate and combine expertise in mRNA and gene editing to develop a technological platform for gene correction and treatment of children with OTC deficiency.

Made possible by partnerships

Co-investigator in the Luminesce Alliance study, Dr Sharon Cunningham, Senior Research Officer at CMRI, 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 patient liver samples 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, SCHN, 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.

The partnership with the liver transplant team has been crucial. The researchers can model the disease in the lab using cells taken from donated diseased livers of children who have had successful transplants.

"It means we have a very unique way to test our gene delivery tools," Dr Cunningham explains. "Because we are working with human cells, we can test the sequences and the reagents that we would be using in patients, which is very powerful."

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

Flicking genetic switches

Luminesce Alliance-funded research has investigated the potential of using epigenetics to edit a patient's cells to switch genes on or off.

OTC deficiency is an X-linked disorder, meaning that the OTC gene is on the X chromosome. As boys have only a single X chromosome, they will have severe disease if that one copy of the gene is abnormal.

Girls have two X chromosomes - so if one copy is abnormal, usually they are well if the other X chromosome is functional. However, this is complicated by the fact that, in girls, one X chromosome is "switched off" in every cell in early development. This process can be random, but sometimes it is skewed.

The team has been able to model and understand the process of skewing by studying the liver cells from a female patient with OTC deficiency who needed a transplant.

In the girl's liver, which was donated for the research, the X chromosome with the OTC mutant gene was switched on in the majority of liver cells, eventually causing her to suffer from OTC deficiency and require a transplant.

The research has focused on understanding the behaviour of the female cells in the skewing process, while in parallel developing and testing gene-editing tools designed to reactivate the functional gene.

"We want to switch on the normal gene," Dr Cunningham explains.

"We are not editing the gene but changing the structure of the chromosome such that it can freely express the functioning gene, making the cell function again. We are getting very promising results."

Patient story: Emmanuel

When Emmanuel's mum Teresa gave birth to her fifth child, she was prepared for the chaos of bringing a newborn baby home. But nothing could prepare her for the blur of ambulance sirens, seizures, needles, endless tests, and being told to prepare for a funeral.

It was 1.00 am, only one day after Emmanuel was born, and Teresa was trying to feed him when she noticed he was cold. She took his temperature, which was 33 degrees, rang the hospital, and was instructed to call 000 immediately.

Two hospitals and countless tests later, Teresa and her husband Elias were told Emmanuel had a metabolic disorder called Ornithine Transcarbamylase (OTC) deficiency. It meant that his liver wasn't functioning properly to convert ammonia to urea following the breakdown of proteins. Instead, the ammonia was staying in his body and causing toxicity to his brain.

It was soon established that Emmanuel had a brain injury from his seizures. He is now non-verbal and struggles with muscle control so he can't hold himself up or walk.

At seven months, Emmanuel had a liver transplant. His family donated his liver to the CMRI team working on the use of gene therapy to treat OTC deficiency.

"I just feel like, every single day that we wake up, and we have him, it's a blessing again, to see his face. He loves to see his siblings, and he's happy laughing at them, he's a happy little boy," Teresa says.

> **"I want this whole experience to be purposeful – that this happened for a reason. But it's also because the researchers can do their work and make a difference in future generations."**
>
> **– Teresa, Emmanuel's mum**

Cracking the mechanisms of a devastating disorder

Researchers around the world are desperately looking for a treatment for Rett syndrome, a severe genetic disease that causes babies to lose movement and communication.

A multidisciplinary team across SCHN and CMRI is making progress in breaking down the molecular mechanisms of the disease, following the discovery of biomarkers in an innovative study funded by the Luminesce Alliance.

The absence of a biomarker – a measurable indicator of a disease or condition detectable in blood or other body fluids – has resulted in difficulties and often delays in diagnosis of Rett syndrome. It also makes it challenging to develop treatments or establish clinical trials, because it's impossible to measure the efficacy of an intervention.

"There have been around 60 clinical trials for treatments for Rett syndrome, but none have made it to the clinic as it's not possible to demonstrate if they are effective. That's because there's not an easy biomarker that can measure the change in the disease," says A/Prof Wendy Gold, Head of the Molecular Neurobiology Research Laboratory at Kids Research, SCHN.

A/Prof Gold and her team set out on a "fishing expedition" to search for a biomarker for Rett syndrome. Using state-of-the-art technologies, they sifted through more than 700 chemicals in urine samples from patients with Rett syndrome and compared them to controls.

They were able to identify biomarkers in the first phase of the research, and the next phase will see the combined use of 'omics' to better understand the disease drivers and potential targets for treatments.

Multi-omic approach

The use of high-input approaches, known as omics, has developed rapidly and revolutionised both the diagnosis and the understanding of the pathophysiology of many neurological disorders.

The multidisciplinary team will analyse blood samples from Rett syndrome patients, compared to controls – this phase of the research will look at genes, proteins, metabolites and cellular pathways.

A/Prof Gold is also collaborating with the bioinformatics team at CMRI, where scientists specialise in using computational biology expertise to study biological systems, developing software and novel mathematical methods for the analysis of biological data.

"Nobody else is doing this kind of research in the Rett syndrome space – integrating all of these technologies with a common goal," says A/Prof Gold.

"The ultimate aim is for clinicians to be able to test for these biomarkers to aid in diagnosis, and for scientists and pharmaceutical companies to have a reliable measure of disease improvement in clinical trials."

Being part of CMRI and the Luminesce Alliance has opened doors for making connections with other researchers, A/Prof Gold says.

She has also established a Scientific Medical Advisory Committee with Rett Syndrome Association. The group will enable closer communication and collaboration between clinicians, scientists, and families impacted by Rett syndrome.

A/Prof Wendy Gold

A/Prof Wendy Gold Head, Molecular Neurobiology Research Group
Sydney Children's Hospitals Network
University of Sydney

Patient story: Abigail

When little Abigail celebrated her first birthday, she was a bubbly girl who had reached all her milestones. But, within months, her parents were worried. Her baby babbling had stopped, she wasn't making eye contact, was having trouble using her hands, and had begun repetitive movements, like pacing.

The family returned home to Australia from overseas to seek medical help and Abigail was initially diagnosed with autism. She began a rigorous routine of therapy.

But her progress was limited and, by her third birthday, Abigail's parents had been given the "devastating" diagnosis that she had Rett syndrome following genetic testing.

Abigail's mother, Mary, says they began a journey from disbelief to acceptance, along with a lot of grief.

Rett syndrome is a rare genetic neurological and developmental disorder that affects the way the brain develops. It causes a progressive loss of motor skills and language and can also cause seizures, severe scoliosis, breathing abnormalities and unusual hand movements.

It impacts every aspect of Abigail's daily life.

"She is dependent on us for everything," Mary explains. "She has no functional hand use. So even for something as simple as having a drink, she relies on someone to remember to offer her one. We are very lucky that Abigail can walk – so many people with Rett syndrome never do."

Abigail is learning to communicate using an eye gaze device. The family were able to purchase the $13,000 piece of technology following a donation from an anonymous benefactor. Abigail uses her eyes to 'point' to symbols on a screen.

"We now some have some ways of communicating," Mary says.

Abigail, now seven, is still a little girl with a big personality. Amid a busy routine of various therapies and going to school, the highlight of her week is her horse riding lessons.

Mary has been working to raise awareness of the condition and to raise funds towards medical research for a cure. This includes launching Speechless, an annual event during Rett syndrome awareness month in October where volunteers are sponsored to spend a day without talking.

She is optimistic about the potential of a breakthrough from medical research like the work of A/Prof Wendy Gold and her team.

> **"I am confident that we will find a cure within Abigail's lifetime. I don't know what that will mean for Abigail. But I am really focused on finding a cure."**
> **– Mary, Abigail's mum**

Our Impact:
Data

Making sense of big data to cure childhood cancers

The Computational Biology Program at CCI is using vast cloud computing resources to help make sense of big data and improve the lives of children with cancer.

The team has developed a purpose-built precision medicine data platform that brings together a range of analytical and statistical tools to enhance the treatment of children with high-risk cancers.

"The Luminesce Alliance has helped us establish the largest computational biology program for children with cancer in Australia, which has had a massive impact and is enabling precision medicine to move closer and closer to the clinic," says A/Prof Mark Cowley, Lead of the Computational Biology Group at CCI.

Using supercomputers and custom-made tools and algorithms, the new digital platform is being used to help clinicians to better understand their patient's disease and to individualise treatments. It also enables researchers to understand why some children develop cancer, why some don't respond to their treatments, and to be able to identify new drug targets.

Turning data into insights

Huge datasets, including known genetic variations, drug responses and clinical information from thousands of patients, can be analysed and interpreted to provide recommendations for individual patients. This has the potential to provide more accurate diagnosis and treatment options.

Over about 24 hours, dozens of 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.

A/Prof Cowley says the process might identify millions of genetic changes in a patient and hundreds of thousands of genetic changes in a tumour, but there may be only one or two that predispose the child to a disease or point to a treatment.

"Cancer is cunning, it mutates the DNA in unusual ways and differently in each patient. There are thousands of these genetic changes where we still don't understand what they do. Some of the clues to solving those puzzles are in developing better algorithms and tools to make predictions," he says.

"Then there are a lot of genetic changes where we know exactly what they will do – and they are the ones that clinicians really want to know about."

Life-saving patient care

The team was asked to help with the case of a child who had a large tumour in their chest. Pathology results had not been able to provide doctors with the answers they needed to inform treatment.

Within six days, the scientists had identified a rare genetic change and were able to recommend a precise treatment – a specific drug that had recently been developed.

"This is a tangible example of discovering something which is rare, but where we were still able to interpret the sample, help make the diagnosis and get the patient on a life-saving drug," A/Prof Cowley says.

Making connections

The biggest users of the platform so far are clinicians of patients in the ZERO, the most comprehensive precision medicine program for children and young people with cancer in the world, led in partnership by CCI and the Kids Cancer Centre, Sydney Children's Hospital.

A/Prof Cowley says the work of the Luminesce Alliance team has been essential to the success and future expansion of ZERO.

The team has established collaborations across Australia and beyond, including working with world leaders in childhood cancer research in Toronto and Philadelphia.

"What we've been able to show is that precision medicine genomics has a real impact on patient care," adds A/Prof Cowley.

"The new frontier is how to get better clinical data and better outcome data, so that we can assess the benefit of precision medicine."

"We find ourselves in the precision-medicine revolution, where the idea is simply that we take more and more measurements from patients and translate that data into improved care: whether that's getting the right diagnosis, predicting if they're a good or high-risk prognosis, or finding the right treatment option for them. Data underpins all of these activities."

- A/Prof Cowley

A/Prof Mark Cowley
Head, Computational Biology Group
Children's Cancer Institute

Shining a light on genetic cancer risk: The PREDICT study

Genetic sequencing of patients diagnosed with childhood cancers is providing vital insights into whether some children are predisposed to develop the disease.

We know that certain variations or abnormalities within specific genes contribute to cancer development. More than 15 per cent of children with aggressive or recurrent cancers have specific genetic variants that we know play a major role in causing the disease, according to data from ZERO.

However, there are many more additional gene variants whose significance is unclear or unknown. We do not yet understand whether these gene variants have a role in increasing the risk of developing cancers in childhood.

A Luminesce Alliance-funded study, called PREDICT, gives all children diagnosed with cancer in NSW access to family-based DNA (genetic) testing. Results will provide a clearer picture of how genetic variants contribute to the risk of developing childhood cancer, and will be used to develop ways of managing this susceptibility.

"We want to understand the full spectrum of cancer genetic risk variants and how prevalent they are in children with cancer, and when a child has a particular variant, how likely it is to contribute to the risk of cancer developing in that child," says A/Prof Vanessa Tyrrell, Program Leader of ZERO, and Co-Head of Theme, Personalised Medicine at CCI.

More than 165 families have been recruited to the PREDICT study and around half have had their genome sequenced, with results returned to families.

Understanding genetic predisposition to cancer can have 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 can influence therapy recommendations which play a role in determining outcome and how a child might respond to treatments such as radiotherapy and chemotherapy.

It will also provide the opportunity to develop patient personalised surveillance programs to diagnose

A gene variant is a permanent change in the DNA sequence that makes up a gene. It can be inherited (you are born with the variant, referred to as a germline variant) or non-inherited (acquired at any time in a person's life, often referred to as a somatic variant).

Germline testing refers to analysis of tissue such as blood or saliva. This can identify inherited gene variants (germline variants) that may be passed from parent to child.

Dr Luciano Dalla-Pozza
Director, Cancer Centre for Children
The Children's Hospital at Westmead

cancer earlier and to implement early intervention and lifestyle changes to prevent cancer.

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

"It will provide 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.

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

"One of the strengths of the study is that it has been an iterative process," says PREDICT Lead Investigator A/Prof Kathy Tucker, Cancer Clinical Geneticist at Prince of Wales Hospital and Kids Cancer Centre, Sydney Children's Hospital.

"We have listened to feedback from families and made changes to things like our ethics processes. We are learning important lessons about how to provide information in a way that families understand. We also have two of the team doing PhDs, which means we are learning even more about implementing germline testing and precision medicine in childhood cancer."

The study is due for completion in June 2023. The three NSW paediatric Cancer Centres - John Hunter Children's Hospital, The Children's Hospital at Westmead, Sydney Children's Hospital - and CCI are all participants in the PREDICT study, ensuring all children in NSW with cancer have access to this innovative research initiative.

This research will help inform future models of care for children with cancer in Australia, helping to restore quality of life and ultimately relegating childhood cancer history.

A/Prof Kathy Tucker
Cancer Clinical Geneticist, Prince of Wales Hospital and Kids Cancer Centre
Sydney Children's Hospital

Patient story: Thomas

As a baby, Thomas was often unsettled and clingy, never wanting to leave his mother, Abby. But despite needing regular comforting, he became a regular, bubbly and energetic toddler.

The first real sign that something was wrong came when Thomas was two and a half years old. He began to consistently feel unwell and vomited a lot.

After becoming sick during a family holiday, he was taken to hospital and transferred to Monash Children's Hospital, where an emergency MRI scan revealed Thomas had multiple tumours on his brain and spinal cord. Even though the tumours were slow growing, many were located in areas that are inoperable. This significantly limited treatment options.

Parents Abby and John were crushed. Breaking the news to family that their little boy had cancer was difficult, but John says the hardest thing of all was telling Thomas' sister Lucy, then aged four.

Thomas went into surgery, and John and Abby had an anxious six-hour wait.

"Basically, it's a situation where you're waiting for someone to tell you that your child could be dead," explains John.

The operation went well, but it was still unclear which type of cancer Thomas had.

Thomas developed complications, suffering hydrocephalus (fluid on the brain) which needed surgery to insert a shunt to drain the fluid.

As a result of the tumour and surgery, he lost a significant amount of eyesight.

Weeks turned into months, and months turned into years. Thomas was in and out of hospital, suffering bouts of vomiting and needing multiple surgeries to clear his blocked shunt.

Scans were done every three months, then six months, to monitor his progress. Frustratingly, a precise diagnosis still proved elusive, and Abby and John were in despair.

It was then that Abby and John found out about ZERO. "The oncologist said, 'Let's look at what genetic mutation is causing his cancer, and see it from a completely different angle'," says Abby.

With Thomas getting sicker and in agonising pain, they were overcome with relief to find out he'd been accepted into the trial.

"I don't know what we would have done without it," says Abby. "There was no other option for us."

> **"The work that these guys are doing, it actually changes people's lives."**
> **– Abby, Thomas's mum**

A sample from Thomas' tumour was sent for analysis by the ZERO team. Fortunately, the analysis showed a mutation believed to be driving Thomas' cancer, and the ZERO team was able to find a therapy capable of targeting the mutation.

Thomas accessed a paediatric clinical trial using a gene therapy drug called Afatinib. His acceptance into the trial was only possible due to the ZERO program which included personalised analysis of Thomas' tumour sample.

It was a rocky first couple of weeks. Thomas suffered severe gastrointestinal side effects and had to discontinue treatment. However, after regaining some strength, he was able to start again.

In January 2020, after two months of treatment, Thomas' brain scan showed a noticeable improvement.

Over the following days, John and Abby were delighted to see Thomas's energy levels pick up, his headaches go, and his appetite return to normal.

Thomas's treatment lasted two years. Now 10 years old, he has been off treatment for 12 months and remains happy and healthy. His scans are stable.

> **"It's made a huge difference to us. It makes you so thankful for the little things again. We've been reminded just how precious life is."**
> **– John, Thomas's dad**

Lifting the lid on genes to streamline discovery of new targeted treatments for childhood cancers

The power of big data and cutting-edge gene technology are being harnessed by a Luminesce Alliance-funded study looking at speeding up and streamlining the discovery of new drugs to treat childhood cancers.

Outcomes for children with the most difficult-to-treat cancers remains dismal due to the lack of effective standard treatment options. By combining big data, computational strategies and novel experimental approaches in the laboratory, the project aims to identify molecular drivers of childhoods cancers, potentially leading to new treatments targeting specific genes.

The study, led by A/Prof Paul Ekert, Co-Head of the Personalised Medicine Theme at CCI, will address a critical gap in this process by using computational biology to sift the vast amount of genetic information being generated about childhood cancers.

"Over the last four years, the Institute has collected and profiled the genetic make-up of over 500 high-risk paediatric tumours through ZERO," A/Prof Ekert says.

A/Prof Paul Ekert
Co-Head, Personalised Medicine Theme
Children's Cancer Institute

"This provides us with an unprecedented dataset, from which we can gain insight into the specific molecular features and potential drivers of some of the most intractable paediatric cancers."

A/Prof Ekert and his team will sift through the vast amount of genetic information gathered about childhood cancers, including the data from ZERO and from cancer cells lines developed in laboratories.

"We want to know which genes are expressed differently in paediatric cancer samples and which ones would be potentially good drug targets," he explains.

Big data modelling

Utilising a model developed by Dr Antoine de Weck, Group Leader of the Computational Drug Discovery Biology Group at CCI, the team has identified 100 genes from the human genome that show signs of playing an important role in childhood cancers.

They include genes that have not been explored previously as potential targets for drug therapies.

"It's really intriguing. It suggests the possibility that there are potentially good specific targets for childhood cancers," A/Prof Ekert says. "It could also lead to discoveries that have implications for the treatment of adult as well as paediatric cancers."

The benefit of working at scale with such large datasets is that the chances of finding real biological phenomena are vastly improved.

The study will also involve investigating targeted genes with gene-editing tools, to try to tease out the likelihood of treatments being developed that can switch off or silence the cancer-causing mechanisms.

Genomics – lifting the lid on cancer cells

A/Prof Ekert is excited at the potential of genomics to speed up drug discovery in paediatric cancer treatment.

"It's like opening the hood of the car and seeing there are some things that make the car drive and some less important things, like the water for the windscreen wipers," he says.

"We can now look at a granular level and ask ourselves what's really important here? What makes this car – or these cancer cells – go? What could I pull out of this engine that will stop this car, stop it being cancer?"

Just like car engines, cancer-causing genetic changes might share similar mechanics, but operate differently.

"If there's one thing that we've learned through ZERO, it's that there's more diversity than we had imagined in these molecular features of paediatric cancers," A/Prof Ekert says.

"There are much more granular and refined classes of tumours than we've appreciated before. And there's a whole lot going on with the genes and the genomes that we do not yet understand."

The long-term goal of the study is development of novel drugs targeting the specific molecular drivers identified and validated for sarcoma and other paediatric cancers. The first step is to identify a small set of genes that deserve further investigation.

Collaboration is the key

"Collaboration is the future of cancer research without question," says A/Prof Ekert. "We need to bring together not only those who can do cell biology, but also those who can think about large datasets – the mathematics solvers of cancer – and those who can think about immunological perspectives.

"One of the aims of this pilot is to start to assemble that pipeline that could take us from prioritisation of a target gene, through validation, and on to the chemistry of drug discovery."

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

Linking data to improve understanding and treatment of rare diseases and cancer

Combining various administrative health and clinical data collected throughout children's lives provides a powerful tool to understand the impact of various childhood conditions, including treatment outcomes, to provide more tailored and better care.

Data is collected about us all through our lives – including every time we see a doctor or go to hospital and when we go to school or work - alongside information about the environment in which we live.

Our data linkage research took these datasets and combined them with genomic and clinical treatment information to understand the immediate and long-term impacts of treatment of childhood diseases, including cancer, congenital heart disease and other rare diseases.

When managing various illnesses and diseases, the focus of clinical care is on treatment and cure.

When de-identified data is combined from across the population, it provides a powerful tool to follow up patients and also to investigate the long-term effects of treatments. This provides valuable information on how we might need to adjust treatments to ensure better outcomes for children, both in the short and long term.

This data linkage work was led by Natasha Nassar, Professor and Financial Markets Foundation for Children Chair in Translational Childhood Medicine from The University of Sydney Clinical School in the Faculty of Medicine and Health, located at The Children's Hospital at Westmead. Her team focused on three projects examining linked datasets to discover insights and outcomes related to patient cohorts with three conditions:

- congenital heart disease
- childhood cancers
- juvenile arthritis.

"There's so much more exciting work that we can now do with the kids-link data platform. We've been able to leverage our initial findings to get more funding to repeat our studies and explore the health of children for all of Australia."
– Prof Natasha Nassar

The studies are the first of their kind using anonymised information from NSW paediatric patients.

From a dataset of more than 3,000 congenital heart disease patients, the team has identified a subset where genetic analysis will also be carried out. The results will help clinicians to identify genetic markers for the condition and help explain children's outcomes. The team will also use data to provide information for clinical counselling to help families understand the risk of recurrence of the disease and the likelihood of subsequent children having heart defects.

Prof Nassar is also combining health and treatment data for children diagnosed with cancer in NSW between 1984 to 2020 with the aim of learning more about long-term health following treatment, such as heart, bone and fertility problems.

"As well as survival, we want to look at longer term impacts for these children," Prof Nassar explains.

The project will be expanded to datasets from patients across Australia, and could inform treatment modifications or the introduction of post-treatment screening for future patients.

Improving outcomes for children with juvenile arthritis

Juvenile arthritis is the most common chronic inflammatory musculoskeletal condition in children and can lead to lifelong disability. There is no known cause or cure, and it can be difficult to diagnose.

"Better monitoring and data on engagement with health services is needed to help us understand the extent of the problem and how we can get children the support and services they need early on, as well as throughout their lives," says Prof Nassar.

The data linkage team mapped the prevalence of the juvenile arthritis. Prof Nassar's preliminary analysis of NSW data identified around 1,400 children aged under 16 years old were hospitalised with juvenile arthritis over the last 20 years. They required over 11,000 hospital visits to manage their condition and other health issues or complications.

Based on these findings, Prof Nassar was able to partner with the Juvenile Arthritis Foundation Australia to win a prestigious $1.6 million MRFF grant to establish a national data linkage surveillance system, bringing together health service data with consumer engagement information. The goal is to measure impact, pathways of care and outcomes to help improve children's health and wellbeing.

"Linked healthcare data will help us quantify the number of children affected by juvenile arthritis, to identify the types of health conditions affecting them, including complications, and examine the types of healthcare services children and families are accessing to manage their condition," says Prof Nassar.

Luminesce Alliance funding has helped build these linked data platforms and demonstrated the feasibility and potential of data linkage research in paediatric medicine, Prof Nassar says.

Improving the patient journey for children with rare genetic diseases

Families whose children have rare genetic diseases see many health professionals, from doctors to genetic scientists, genetic counsellors, and a range of medical specialists.

Rare diseases have a huge impact on the health of the nation. An estimated two million Australians live with a rare disease, with the majority starting in early childhood. There are 7,000 rare diseases, but each condition may only affect a small number of individuals, often making them hard to diagnose.

Even after a diagnosis, a family's doctor may not have heard of the condition, creating a barrier to support and management.

Luminesce Alliance funding supported the development of a new pilot program to coordinate and standardise care for all families.

The Gene2Care program was designed to improve standards of care, including enhanced diagnoses and access to management and treatment. The family-centred program combines the efforts of clinical geneticists and genetic counsellors across SCHN, while collaborating with world-leading experts in genomics.

"Collectively rare diseases are more common than diabetes. Families spend years not knowing why their child is sick and, even after a diagnosis, they could be the only person in Australia with the condition," says Dr Emma Palmer, Clinical Geneticist at Sydney Children's Hospital, Randwick.

The first step of the process is a consented database of patients called GeneSTART, being piloted at Sydney Children's Hospital. It involves recording patient details, their test results, and whether they are interested in participating in research programs or being contacted about support resources. The collated information can then be shared to allow families with genetic conditions to connect. It can also be used as a springboard for international collaboration on research.

More than half of the children suspected of having a genetic condition don't get an answer from standard testing. On average, the wait to receive a diagnosis is six years and within this time there are often two or three misdiagnoses.

For these families, there is renewed hope through GeneAdd, a component of Gene2Care recruiting families across SCHN. GeneAdd is a way of putting children in the best possible position to get a diagnosis. It involves enabling research and allowing access to existing or future genomic technologies locally, across Australia and even leveraging international efforts.

Luminesce Alliance funding was used to establish and support the program, set up the necessary databases, and to research how to make this program as beneficial as possible for families, clinicians and researchers.

The future could see new areas of study and even new jobs, including the possibility of roles focused on facilitating patient access to genetic therapies. SCHN is leading the way in this field. By improving processes and standards of care for rare genetic conditions, the door opens for other hospitals in NSW and across Australia to follow suit.

Our Impact:
Health Systems & Economics

Quantifying the benefits and sustainability of paediatric precision medicine delivery

Precision medicine is at the frontier of modern medical science – but it is expensive and challenging to introduce into the health system. While we know it brings health benefits for many children, the long-term costs or effects on the health system are less clear.

Luminesce Alliance funding has supported research that will contribute to answering these questions.

In collaboration with the Australian Institute of Health Innovation (AIHI) at Macquarie University, implementation scientists and health economists studied ZERO to see how the research and healthcare staff who deliver the program interact and communicate.

The AIHI team studied the complex interactions involved in ZERO's implementation, using a mixture of research methods such as social network analysis (as shown above), rapid ethnography and interviews with clinicians and health staff.

By watching how their relationships change and develop over time, the researchers can advise on what needs to be improved to support the smooth rollout of the program and remove barriers.

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

"One of the biggest challenges with research is translating and transferring it into the health system to support better health outcomes," explains A/Prof Vanessa Tyrrell, Program Leader of ZERO, and Co-Head of Theme, Personalised Medicine, at CCI.

"If we want to embed the precision medicine model of care into the health system in the longer term, we need to understand what the barriers might be. We also need to understand the cost-effectiveness of precision medicine programs."

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

The research team investigated the requirements of integrating precision medicine at scale in the paediatric health system.

"We were trying to understand what would be needed in terms of workforce planning and to identify potential bottlenecks or barriers we can address as we continue to expand the program," A/Prof Tyrrell says.

Issues highlighted by the researchers included a reliance on informal or invisible work by health professionals over and above their recognised roles, and the need for health workforce education in precision medicine.

Key to the successful implementation of ZERO is a whole of systems approach, workforce education, and the creation of extensive but previously non-existent connections and networks. However, the analysis also found a heavy reliance on informal roles and key individuals, an invisible workforce challenge to overcome.

"Our study highlighted that the whole system should be considered in all of its complexity rather than reducing it into constituent parts," Prof Braithwaite says.

Cost analysis

Previous research into the effectiveness and cost-effectiveness of genomic sequencing for rare diseases has shown significant cost savings. However, there has been no similar work done in the paediatric cancer context.

A health economics project has aimed to address this, done as a collaboration between ZERO and the Centre for Economic Impacts of Genomic Medicine (GenIMPACT) at Macquarie University. The researchers performed an economic analysis of ZERO, the first analysis of its kind specifically microcosting the comprehensive approach ZERO takes to precision cancer medicine in a paediatric cancer setting.

The initial findings indicate that costs were lower than previous studies, that this is likely due to continued downward trend in consumables costs and improved automation of computational and analysis pipelines, and that costs will continue to trend down over the next three years.

The findings of this soon-to-be published research and future studies will guide funders and policy makers in making better informed decisions when considering how to implement precision medicine in the care of children with cancer in the future.

Re-writing medical history and transforming lives

A multidisciplinary collaboration has radically shifted the model of care for the detection and treatment of a devastating genetic motor neurone disease, transforming the lives of families.

Spinal muscular atrophy (SMA) affects one in 10,000 births and was once the leading genetic cause of infant death. In its most common and most severe form, it quickly paralyses babies, who survive on average nine to 10 months. While their brains remain unaffected, they lose the ability to move, feed and ultimately breathe.

It is now possible to screen newborn babies for the disease and access life-saving gene therapy for those likely to develop severe SMA.

The breakthrough is the result of groundbreaking medical research and clinical trials by specialists from across SCHN and the Universities of Sydney and NSW Sydney. These teams worked together to prove the efficacy of screening and health economic benefits of a novel gene therapy developed and manufactured by an international pharmaceutical company.

"The success was achieved through many people coming together and the Luminesce Alliance helped to enable that," says A/Prof Michelle Farrar, paediatric neurologist at Sydney Children's Hospital and UNSW Sydney.

"We know that early identification is vital in the treatment of SMA and that is what the newborn screening program has allowed us to do. It has radically shifted our model of care and we are now in a position where we can rewrite the history of SMA."

Early screening and intervention

A pilot study began in 2018 to evaluate the addition of a genetic test for SMA to the Newborn Bloodspot Screening program, a routine test for Australian babies that detects around 25 rare genetic conditions and metabolic disorders in NSW and the ACT. More than 200,000 babies were screened during the pilot, funded by the Luminesce Alliance. The two-year pilot was completed in 2020 and then continued with NSW Health funding.

Data from implementation and health economic studies, funded by the Luminesce Alliance, confirmed that screening and treating newborns with SMA was value for money.

The gene therapy technique involves a single injection to deliver the missing gene that causes SMA. The therapy, Zolgensma®, costs $2.5 million per treatment and the best outcomes are achieved when therapy is given before symptoms emerge and motor neurone degeneration occurs.

Treatment saves lives and money

The economic research team, led by Director Prof Georgina Chambers from the UNSW National Perinatology Epidemiology and Statistics Unit, assessed the costs of including SMA in the Newborn Bloodspot Screening program – and using gene therapy to treat the disease before symptoms begin.

They compared the costs and associated health outcomes of early testing and treatment to the practice of diagnosing and treating children after symptoms appear. In the long term, newborn screening for SMA coupled with gene therapy would save more than $3.7 million ($US2.4 million) per 100,000 babies screened, according to the analysis.

The data was analysed by the Federal Government, which recommended that newborn screening for SMA should be implemented nationally.

Life-changing treatment

Since April 2022, families have been able to access Zolgensma® free of charge, thanks to its listing on the Pharmaceutical Benefits Scheme.

"We've gone from children being given a death sentence that was completely devastating, to transforming lives and seeing children and families thrive. It sounds like a story, but it's science not fiction," says A/Prof Farrar.

"This is an innovative clinical and economic model, where a single administration of a gene therapy can potentially have a lifetime of benefits."

A/Prof Farrar says there are lessons to be learned about creating learning health systems that can work to optimise new therapies.

"It's exciting, but the challenge now will be how do we take this and do it at scale?" she says.

"We have to look at how we can safely translate this technology to develop treatments for other conditions and to a broader population."

A timeline of translational medical research

For over 25 years, exceptional viral vector research led by Prof Ian Alexander and his team at CMRI and The Children's Hospital at Westmead has made significant contributions to the field of gene therapy. This research is now leading major advances in treatments for life-threatening genetic diseases.

Establishment of multidisciplinary neuromuscular clinics provide best care alongside leading translational research.

2018 - 2020	Pilot Newborn Screening for SMA in NSW and ACT	Supported by Luminesce Alliance, more than 200,000 babies screened over two-year pilot
April 2018 - Dec 2021	Clinical trial of gene therapy drug, Zolgensma®, a novel viral vector-based gene replacement therapy	The global trial called SPR1NT enrolled 29 children in the US, Asia-Pacific and Europe. In Australia, the trial was conducted by the Clinical Research Centre at Sydney Children's Hospital, and was supported by the NSW/ACT Newborn Screening Service, the Luminesce Alliance and UNSW Sydney

Following the successful pilot and continuation of screening in NSW and ACT, a submission to include SMA in the Newborn Bloodspot Screening program was endorsed by the Commonwealth Government. WA has implemented a pilot program. VIC and QLD have committed to implementing the screening in 2023.

Feb 2021	Zolgensma® approved by TGA (Therapeutic Goods Administration)	The therapy works by treating SMA at the root cause by a single intravenous injection to deliver the missing gene that causes SMA
Mar 2021	Families and clinicians express overwhelming support for SMA screening	The research, led by Dr Didu (Sandi) Kariyawasam, was published in *The Lancet EClinical Medicine* and funded by the Luminesce Alliance, UNSW Sydney, The Freedman Family Foundation Scholarship and Sydney Children's Hospitals Foundation
June 2021	Results of SPR1NT trial show babies are meeting normal developmental milestones at 18 months	Results of the trial were presented at European Academy of Neurology Conference and later published in two papers in the prestigious journal *Nature Medicine*
Aug 2021	A health economics study funds screening and treating saves both lives and money in the long term	The study, by UNSW Sydney's Centre for Big Data Research, was funded by the Luminesce Alliance and published in the *Journal of Neurology, Neurosurgery, and Psychiatry*
April 2022	Zolgensma® listed on PBS (Pharmaceutical Benefits Scheme)	The listing followed a $2.4 billion spending commitment from the Federal Government

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

Seeing the bigger picture: health economics of precision medicine for genetic eye disease

When Prof Robyn Jamieson began her career treating patients with blinding eye diseases, she faced the heart-breaking prospect explaining to parents that there was often no definitive diagnosis and no treatment options.

"We couldn't get a genetic diagnosis and there was no therapy," she recalls.

Now genetic testing is standard and Prof Jamieson, Head of the Eye Genetics Research Unit at CMRI and SCHN, is at the forefront of introducing revolutionary gene therapies with the potential to restore sight.

"This isn't like cancer, where there have been therapies in various areas for years," she says. "These patients had nothing. Their vision deteriorated and there was nothing we could do. So, the first gene therapy was a real icebreaker. And there are more gene therapies in the pipeline."

While the benefits to patients are easy to articulate, there had been no attempt to quantify how advances in gene therapy also translate into broader economic and societal advantages.

"These genetic conditions affect children their whole lives. 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," Prof Jamieson says.

With a lack of specific evidence of the cost-effectiveness of the emerging ocular gene therapies, a Luminesce Alliance project was designed to gather and analyse the data.

The first study of its kind, it was a collaborative effort between CMRI, SCHN, The University of Sydney and Macquarie University.

The research team first established a new sophisticated model for quantifying the quality-of-life costs of genetic retinal eye diseases, before using it to work on assessing the benefits of genetic screening and gene therapy treatments.

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

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. There are plans to expand the initial Luminesce Alliance-funded study across Australia.

"This work is critical," Prof Jamieson says. "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 equitably funded and available across Australia.

"This initial project, and the ongoing work associated with it, will help us with all the therapies we are developing," she adds.

The study included detailed modelling on the health and economic impacts of impaired vision and blindness due to inherited retinal dystrophies. It will pave the way for further detailed studies investigating the benefits of the first gene therapy for genetic eye disease (Luxturna®) and other gene-specific ocular therapies.

Gene therapy breakthrough

Luxturna® is the world's first approved gene replacement therapy for an inherited blinding eye condition and one of the first gene replacements for any human disease.

It is used to treat children and adults with biallelic pathological mutations in RPE65, a rare mutation that leads to vision loss and blindness. People with a mutation in both copies of the RPE65 gene can suffer from a range of symptoms, including night blindness (nyctalopia), loss of light sensitivity, loss of peripheral vision, loss of sharpness or clarity of vision, and potentially total blindness.

Ocular gene therapy works by injecting Luxturna® under the retina and carrying a functioning RPE65 gene to replace the faulty one, thereby preventing some of these devastating symptoms.

The first patients to benefit were teenage siblings treated at the at The Children's Hospital at Westmead after the therapy was approved by the Therapeutic Goods Administration in 2020.

The therapy was delivered as part of Ocular Gene and Cell Therapies Australia (OGCTA), a collaboration involving SCHN, CMRI and Save Sight Institute, University of Sydney.

"Inherited retinal disease is a devastating diagnosis. Up until now, these patients suffered progressive vision loss that led to blindness and there was no therapy for them at all.

"But through new genomic diagnostics and the use of ocular gene therapy, we are finding that we have the ability to not only stop this ongoing progression but also help to improve vision for people who have RPE65-related retinal vision loss."

– Prof Robyn Jamieson

Patient story: Arato

As a naturally gifted and determined young tennis star, Arato dreamed of one day becoming a professional player – until he started missing shots he had once found easy.

When Arato was diagnosed with genetic blindness, his father, Tim, recognised the symptoms because he also lives with the same condition. Stargardt's Disease often starts in childhood with black spots in the centre of the child's vision and sensitivity to light.

"It was 25 years ago when I was in full training as a triathlete myself," Tim says. "My training partners could see that I was hitting objects on the road or tripping over things on the footpath, and so I had a similar problem.

"People often ask me, 'Tim, what can you see?' I explain to them that I'm not walking around with a white cane all the time, but if you're standing a metre away from me, I can't see your face."

Arato now plays in Tennis Australia's Low Vision Competition, where he is experiencing great success. School is a bit more challenging because he struggles to recognise the faces of his friends.

"When he first knew about his diagnosis, I don't think he understood the impact to his life," says his mother, Junko.

> **"We remain hopeful that there will be a treatment for Stargardt's Disease, and hopefully that treatment will enable Arato's vision to be restored."**
> **– Tim, Arato's dad**

Our Precision Therapy

Clinical trials – leading the way with novel therapies

When scientists develop a new treatment, it needs to be carefully tested to make sure it's safe and effective. 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 when only limited information on the effect of the therapy is available.

Clinical trials are vital for the development of life-saving treatments for rare diseases. They can also provide treatment options for patients who might otherwise have no access to therapies.

We have supported the Kids Advanced Therapeutics team at SCHN in the shared vision of establishing NSW as a world leader in paediatric clinical trials.

With support from the Luminesce Alliance, SCHN has been the only Australian paediatric site to secure access to selected gene therapy clinical trials with global competitive recruitment targets. Successful participation in these trials has led to SCHN being the first Australian site accredited to deliver approved gene therapies to children.

The program is establishing the pathway to access new and novel treatments such as gene and cell therapies, bacteriophage therapies and personalised medicines for paediatric patients of NSW and Australia.

Our work is developing capacity to run the trials, linking scientists with clinicians and patients, and attracting interest from overseas companies to conduct their studies in Australia.

In the future, this investment will mean children in Australia have access to the newest drugs and therapies, and that the knowledge they help us to generate can quickly be translated into better ways of treating children around the world.

Ms Lani Attwood
Advanced Therapeutics Program Manager
Kids Research
Sydney Children's Hospitals Network

Luminesce Alliance funding has contributed to progress in advanced therapeutics including:

- Gene therapy clinical trials to support NSW's Newborn Screening Program for SMA. With over 200,000 newborns screened, more than 30 babies have received transformative gene therapy treatment for SMA at SCHN
- More than 10 pharmaceutically sponsored clinical trials of novel therapies in a variety of rare diseases, including gene therapy.
- Around 30 patients participating in rare disease clinical trials at SCHN.

We have provided "start-up" specialists and medical leads, dedicated to getting clinical trials up and running.

"Being able to have that position funded through Luminesce has meant that we've been able to really hit the ground running and get these trials open really quickly," explains Lani Attwood, Kids Advanced Therapeutics Program Manager.

"We are in talks with many pharmaceutical companies about potential trials coming down the pipeline, after building relationships with our clinicians and identifying suitable patient cohorts."

Patient story: Rebecca

For Rebecca, growing up with cystic fibrosis meant years of struggling with lung infections, bronchitis, pseudomonas, and nasal polyps.

At the age of eight, she contracted a bacterium which left her unable to maintain her weight and caused her lung function to significantly decline.

This germ, Mycobacterium Abscessus, lingered for five years, resisting treatment after treatment.

Rebecca was on a "cocktail of antibiotics." She relied on a nebuliser five times a day and had a gastronomy button for overnight feeds.

"Rebecca was on a spiral of ill health with a lot of medication that was not helping. It was five years of interruption to her life, her schooling and her growth," says her mother, Trudi.

Dr Paul Robinson, Clinical Professor Respiratory Medicine at The Children's Hospital at Westmead, suggested a century-old treatment called phages, which has recently returned as a novel therapy for antibiotic-resistant bacteria.

Phages, formally known as bacteriophages, are viruses that selectively target bacteria and can kill them. Rebecca was one of the first in Australia to be successfully treated with phage therapy.

Now aged 14, she has recovered and continues to do well.

"Rebecca is doing so well now – you wouldn't recognise her. She has really come on in leaps and bounds," Trudi says.

"She doesn't need her gastronomy button anymore, she is back at swimming, and she played every game of soccer with her team this season, where they were runners up. She's just doing amazingly. We couldn't be more grateful."

- Bacteriophages, or "phages", are viruses that live naturally in substances such as soil and sewage.
- Phages selectively bind to bacteria and infect and kill them by injecting their DNA.
- As superbugs become resistant to antibiotics, phages are seen as a promising alternative for patients who have run out of options, including infections in patients with cystic fibrosis.
- In phage therapy, a preparation containing bacteriophages tailored to target certain bacteria is given to patients.

Leading towards medical moments of discovery

Dr Michelle Lorentzos is a paediatric neurologist, with a particular interest in finding treatments for Duchenne muscular dystrophy (DMD), a progressive and life-limiting neuromuscular disease.

She is also the Clinical Trials Lead at The Children's Hospital at Westmead, a role funded by the Luminesce Alliance that is helping to facilitate advocacy, strategic support and development in this crucial area of research.

"Gene therapies are a priority for the network," Dr Lorentzos says. "For a number of previously devastating diseases, we have gene therapy treatments that are either here already or in the pipeline.

Dr Michelle Lorentzos
Clinical Trials Lead
The Children's Hospital at Westmead

"We want to be at the forefront of this research, because it's in the best interests of our patients, as well as children around the world.

"When a patient is diagnosed with a serious medical illness or a devastating condition, we don't want the best and emerging therapies from around the world to feel out of reach," she adds.

The role sees Dr Lorentzos working to ensure there is a coordinated approach to attracting international clinical trials and that processes are in place to support multidisciplinary teams to delivery clinical trials.

"We need efficient, robust processes that can quickly become bespoke to a particular condition, rather than having to reinvent the wheel every time there's a new therapy on the horizon," she says.

"I feel like this is a once in a career opportunity to be part of these medical moments of discovery. To be part of this international community of scientists and clinicians, to have a seat at that table, is incredibly exciting," she adds.

"We can't cure everything today and we won't cure everything tomorrow. But if there are obstacles that are modifiable, there shouldn't be any reason that we don't try to address those."

Lessons in novel treatments

Dr Lorentzos was the recipient of a Pfizer Global Medical Grant in 2022 for her project, "Multidisciplinary Gene Therapy Education - Recombinant Adeno-Associated Virus (rAAV)". This is a multidisciplinary approach to education regarding AAV gene therapy in Australia.

Adeno-Associated Virus (AAV) vectors use a non-enveloped virus as a vehicle to safely deliver vaccines and gene therapies into the cells or tissue of a patient with an otherwise difficult-to-treat genetic condition.

Gene therapy using AAV as a vector is emerging as a potential game changer in the treatment of genetic diseases.

"SCHN is emerging as a leader in gene replacement therapy and we are increasing our capacity to undertake more work in this exciting area. However, the delivery of complex and novel treatments is only possible through effective workforce education," Dr Lorentzos says.

Unlocking the key to personalised medicine

A new diagnostic pipeline for improving testing for rare disorders has been created by an interdisciplinary collaboration between scientists, clinicians and pathologists, funded by the Luminesce Alliance.

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

The potential to revolutionise screening for rare genetic disorders using RNA testing has been established by the team led by The University of Sydney's Prof Sandra Cooper, Adjunct Research Scientist at CMRI, and Co-Head and Scientific Director of the Kids Neuroscience Centre at SCHN.

Genetic disorders affect around one in every 20 children. While DNA testing has transformed the diagnosis and outlook for many children with genetic diseases, around 50 per cent of families do not receive a diagnosis.

"The cold hard reality remains that many of the people tested using DNA will not get answers, with massive implications for families and for health services," says Prof Cooper.

Research led by Prof Cooper has shown that many patients undiagnosed by DNA testing can get a diagnostic answer from RNA testing – leading to opportunities for treatment or improved management of their condition.

What is DNA and RNA?

DNA (deoxyribonucleic acid) carries the information and templates for making and maintaining all living things, including people.

RNA (ribonucleic acid) is copied from the DNA and carries the information into the area of the cell where it can be read. It contains long chains of bases connected by a sugar 'backbone'.

Changes in DNA – known as variants – can cause genetic conditions.

Variants can also be seen by looking in the RNA.

Source: Centre for Genetics Education

RNA the new frontier in diagnostics

Unlike DNA, which stores the genetic information for the cell, RNA uses the information stored in DNA to make proteins and acts as a messenger between DNA molecules and the protein-building machinery of the ribosomes.

Through RNA sequencing, researchers may be able to offer families living with rare genetic diseases or inherited cancer predisposition a precise genetic diagnosis and revolutionise their personalised healthcare options.

"The catch is that RNA testing is vastly more complicated than DNA testing," Prof Cooper says.

There are also gaps in terms of quality standards, guidelines for interpreting results in a clinical context and education of the medical workforce. Prof Cooper's work, supported in part by a Luminesce Alliance Innovation fund, aimed to create a new RNA diagnostic in clinical practice and to fill these gaps.

Prof Cooper is the founder of SpliceACORD – the Australian Consortium for RNA diagnostics – which has grown to around 170 expert members across Australia and New Zealand, including a majority of Australia's clinical geneticists and genetic pathologists.

"The idea was to bring everyone to work together and devise the best, safest, and fastest way to bring RNA into practice. And that's what we've been doing," says Prof Cooper.

Finding answers

A team at the Centre for RNA Diagnostics, based at the Kids Neuroscience Centre, analysed about 140 cases from pathology laboratories in Australia and four centres in the United States.

Three-quarters of cases tested using RNA were children with conditions caused by genetic variation in a single gene.

In almost 80 per cent of cases in the study, RNA testing secured evidence enabling an identified genetic variant to be classified formally as the 'cause of disease' and clinically actioned. For some patients, the molecular diagnosis led to access to treatments or eligibility to participate in clinical trials of drugs specific to their genetic disorder.

"When one child or affected individual is diagnosed, answers are provided for the wider family unit," Prof Cooper says. "As many cases involve severe or fatal conditions, some of the most meaningful impact of our study lies in enabling access to prenatal counselling and genetic screening for newborn disease prevention."

The clinicians who referred cases into the RNA trial were surveyed, showing both medical teams and families saw benefits from being part of the study – even when RNA testing didn't provide an answer.

In 2022, the results of the RNA trial were published in the SpliceACORD Consortium's first paper – "Standardized practices for RNA diagnostics using clinically accessible specimens reclassifies 75% of putative splicing variants" in *Genetics in Medicine*, the official journal of The American College of Medical Genetics and Genomics – quickly becoming the journal's most read paper for 2022.

In September 2022, Prof Cooper was awarded a prestigious $2.9 million MRFF Genomic Health Futures Mission grant to integrate RNA testing into mainstream clinical practice, to continue the collaboration between research centres, pathology labs and clinical genetic departments to embed RNA diagnostics as a new option for clinical diagnostics.

> **"We want to provide genetic answers for families who previously had none, enabling early diagnosis, early intervention, reproductive counselling, disease prevention and potential eligibility for relevant clinical trials.**
>
> **"A precise genetic diagnosis is the key to personalised health care, disease prevention, treatment and sometimes a cure and that is what this grant is helping us do." – Prof Sandra Cooper.**

Our Impact: Psychosocial

Our impact so far

Precision medicine has the potential to transform the care of children with high-risk cancers, who have tended to have limited treatment options.

New techniques, such as whole genome sequencing, are rapidly changing our understanding and treatment of cancer, rare disease and neurodevelopmental disorders, but the potential impacts of paediatric precision medicine programs on the psychosocial wellbeing of families are poorly understood.

To ensure that all children and young people benefit from precision medicine, it is necessary to extend research beyond the laboratory to address the psychosocial risks of precision medicine and ensure its equitable rollout.

Psychosocial approaches to medicine look at the interrelation of individual thought and behaviour, the surrounding social environment, and how these combine to impact the physical and mental wellness of individuals.

Luminesce Alliance-funded researchers have been developing world-leading programs to improve the understanding of how patients, carers and health professionals deal with the challenges of the introduction of precision medicine, such as the risk of unrealistic expectations and understanding the implications of genetic screening for the extended family.

While it's vital to understand family perspectives on new treatments, improved support can also impact clinical outcomes. Psychosocial factors may influence up to 30 per cent of the long-term morbidity of children with physical illnesses, according to international research. That is because patients' and families' experiences, understanding and communication around treatment are key to health outcomes as well as their level of satisfaction.

World-first psychosocial research into precision medicine for childhood cancer patients

Luminesce Alliance researchers have carried out one of the first studies in the world into the psychosocial implications of precision medicine for children, their families and health care.

Uniquely, our study of the psychosocial implications of ZERO, 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 families' 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 UNSW Sydney 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 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."

Highlighting the psychological impacts for patients and families

Initial findings suggest parents experience high levels of 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 have a lack of understanding and awareness of precision medicine, and feel unclear about what it could achieve.

"If these issues 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," says Prof Wakefield.

The data collected is being 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 experiences are hard to capture while they are so unwell. The inclusion of children aged 12 and over in PRISM-Impact is providing unique insights into the needs of children having these revolutionary new treatments.

Listening to healthcare professionals and scientists

The experiences of healthcare professionals and scientists were also captured in the study, with participants identifying a recurring problem when caring for families in how to communicate realistic expectations of treatment while maintaining hope.

"Having difficult conversations can be a real challenge for health professionals, and not all of the people involved in a child's care may be aware of

Dr Kate Hetherington

Post-Doctoral Research Fellow
Faculty of Medicine & Health
UNSW
Kids Cancer Centre, Sydney
Children's Hospital

the trials the patients are enrolled in," says Dr Kate Hetherington, of the School of Clinical Medicine at the UNSW Sydney.

"Delivering precision medicine involves a team of professionals working across many different patient-facing and 'behind the scenes' roles," she adds. "Many of the professionals involved in delivering the ZERO program appreciated being asked about the new developments in their work and how they feel about them; it's unique for them to have this opportunity to share their perspectives and will be important for the successful implementation of precision medicine."

With the upcoming expansion of precision medicine through the extension of ZERO to be available to all children in Australia diagnosed with cancer by the end of 2023, the psychosocial team will build on the achievements of PRISM-Impact. This includes projects to better capture the experiences of culturally and linguistically diverse families enrolling in paediatric precision medicine, and piloting of flexible telehealth support for families experiencing high distress and barriers to accessing existing services.

"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.

"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."

- Prof Claire Wakefield

Supporting families

A series of animated videos have been developed by the team, aimed at supporting families participating in ZERO.

"One of the important pieces of feedback we got was families were sometimes unclear what was going to happen and what the possibilities for precision medicine were," explains Prof Wakefield.

"The other thing families often tell us is that the information provided can be overwhelming and not visually appealing."

The animated video series includes an explanation of precision medicine, examples of possible outcomes of genetic sequencing, and reflections from families who have already been through the process.

It is hoped the videos can be incorporated in the consent process for families being offered whole genome sequencing following a cancer diagnosis for a child.

"The video format will mean that families can refer back to reinforce what the doctors have explained during the consent process or share them with friends and extended family, so that they also understand," Prof Wakefield says.

Global connections

Our researchers have been in demand across the world to share their expertise and form collaborations.

ZERO has formed several international collaborations to build a data sharing framework.

"ZERO data is contributing to global genomic data sharing efforts from St Jude's and Children's Hospital of Philadelphia. Collectively sharing data of approximately 10,000 patients, with rich clinical annotations, will become a game changer for paediatric cancer over time," says Prof Michelle Haber AM, Executive Director of the CCI.

Researchers in our psychosocial program have also forged links across the globe.

"Our team is considered a world leader in the research assessing the psychological impact of emerging genetic technologies and precision medicine on children, their families, and the health professionals at the forefront of this novel field," says Prof Wakefield.

The team at the Behavioural Sciences Unit (BSU) at UNSW Sydney is the largest paediatric psycho-oncology research unit in Australia and has published more than 30 research papers

Prof Claire Wakefield
School of Women's and Children's Health UNSW Medicine
Head, Behavioural Sciences Unit, Kids Cancer Centre
Sydney Children's Hospital

evaluating ethical questions of genetic testing and its psychosocial impact on those involved.

"To be successful in our work - at the intersection of medicine, science, psychology and ethics – and for our work to reach families around the world, we have built a large national and international collaborative network," says Prof Wakefield, Director of the BSU.

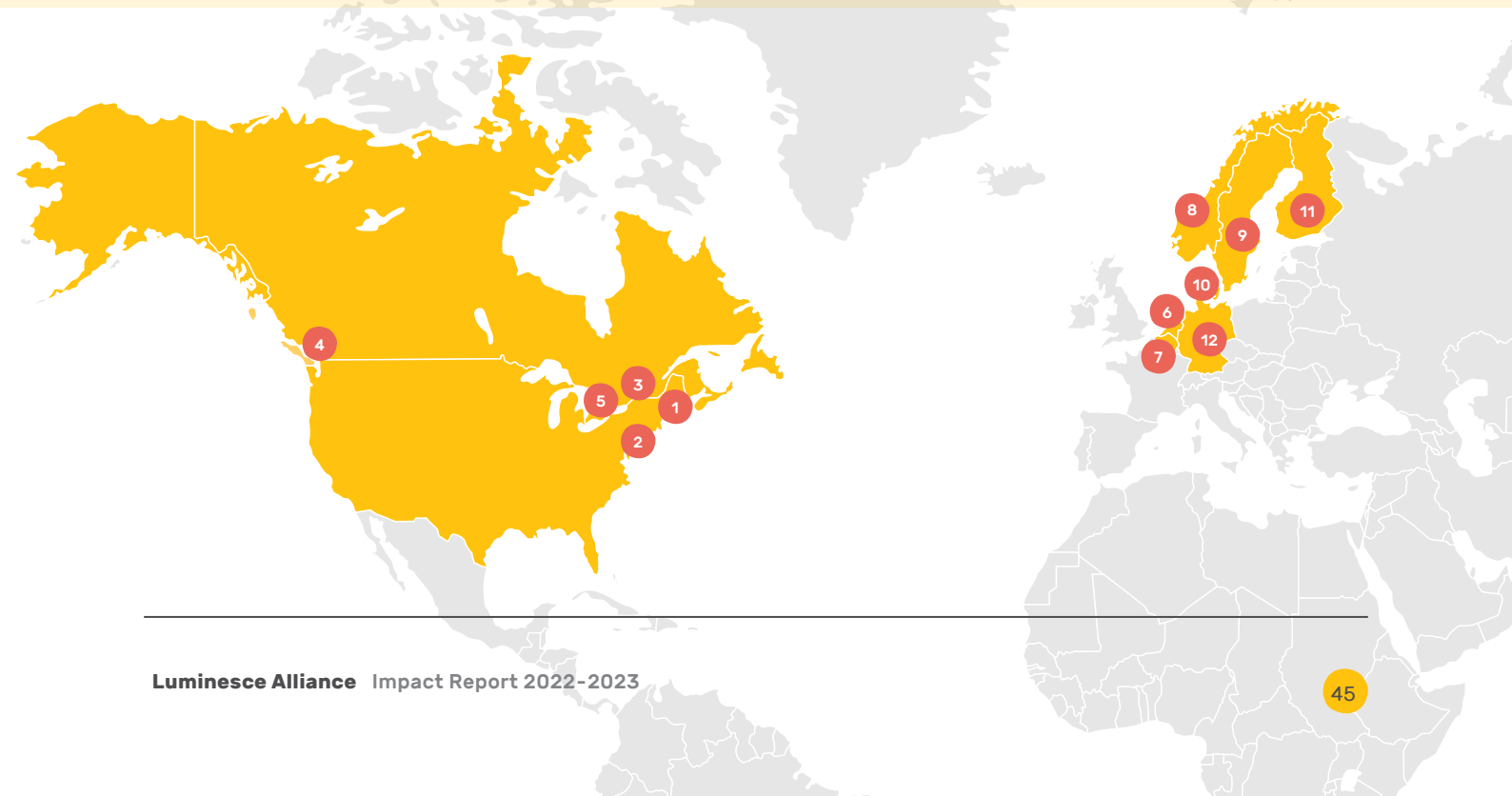
The research has led to collaborations across the globe, including in the United States, Canada, the Netherlands, Belgium, Norway, Sweden, Finland and Germany.

The interest in this work has allowed Prof Wakefield to run workshops on the ethics of precision medicine, including for the Pediatric Oncology Group of Ontario and at the annual congress of the International Society of Paediatric Oncology.

Prof Wakefield sits on the advisory board for the iCOPE study, a bi-national precision medicine study offered to eligible children in Denmark and Sweden. In collaboration with Dr Brittany McGill, she founded the Australia and New Zealand chapter of the Li Fraumeni Syndrome Association.

In 2022, Dr Kate Hetherington co-led the organisation of a Nordic-Australian collaborative meeting for researchers whose work focuses on the psychosocial impact of precision medicine and genetic testing for childhood cancer. Research groups from five countries, including Australia, Norway, Sweden, Denmark and Finland, each presented an overview of their relevant research projects and discussed avenues for future collaboration.

1. Dana-Farber Cancer Institute, Boston, **USA**
2. St Jude's & Children's Hospital of Philadelphia, **USA**
3. Montreal Children's Hospital, McGill University Health Centre, **Canada**
4. British Columbia Children's Hospital, Vancouver, **Canada**
5. Hospital for Sick Kids/University of Toronto, **Canada**
6. Princess Maxima Centre for Pediatric Oncology, **The Netherlands**
7. Ghent University, **Belgium**
8. University of Oslo & Oslo University Hospital, **Norway**
9. Karolinska Institute, **Sweden**
10. Rigshospitalet/University of Copenhagen, **Denmark**
11. University of Linkoping & The Finnish Institute of Bioethics, **Finland**
12. Medical University of Hannover, **Germany**



Nurturing the next generation of medical researchers

We are committed to empowering the best and brightest researchers and investing in the next generation of STEM expertise.

Across our multidisciplinary research teams, in the last four years we have sponsored 11 PhD students.

Research by women, for girls

Ashley Hertzog is undertaking her PhD as part of a multidisciplinary team of researchers including A/Prof Wendy Gold, A/Prof Ayper Tolun, Dr Gladys Ho and A/Prof Carolyn Ellaway, who are using novel approaches to better understand the rare genetic brain disorder Rett syndrome.

Ashley Hertzog
Senior Hospital Scientist, NSW Biochemical Genetics Service
The Children's Hospital at Westmead

Ashley will work across the multi-omic investigation into biomarkers for Rett syndrome, being funded by the Luminesce Alliance and led by A/Prof Wendy Gold, Head of the Molecular Neurobiology Research Laboratory at Kids Research, SCHN.

"I'm very grateful for this opportunity. If it wasn't for the funding from the Luminesce Alliance, I would not be able to do my PhD," Ashley says.

She will work on her PhD two days a week, while continuing her role as a Senior Hospital Scientist with the NSW Biochemical Genetics Service, at The Children's Hospital at Westmead led by A/Prof Tolun.

"We are very grateful for the ongoing support of the Luminesce Alliance by enabling research in rare disorders and creating research opportunities for scientists like Ashley in service laboratories," says A/Prof Tolun.

The study was an ideal next step for Ashley, following on from her Masters studying the biomarkers of mitochondrial dysfunction and drawing on her experience of working in the NSW Biochemical Genetics Service laboratory.

"I love learning new things, and I'm hoping that I can bring the skills that I learn through the multi-omics platform to my current professional lab work.

"It's a steep learning curve, but it's very exciting," she adds. "There aren't many places in Australia that are using this kind of technology and integrating the results in one meaningful way."

Ashley, 31, fell in love with Sydney when she came from the United States as an international exchange student. She was subsequently sponsored in a role researching diabetes at the CSIRO, before joining SCHN.

"I feel really lucky in the research environment I am in," she says. "All of my supervisors are women, and we are working on a disease that impacts girls. Research by women, for girls."

Paving new ground in the use of RNA for diagnostics in children with cancer

Chelsea Mayoh began her research career at the Genome Sciences Centre within the BC Cancer Agency in Canada, and joined CCI as the sole bioinformatician in 2015. She soon began to establish a Bioinformatics Group at CCI that she now leads.

Chelsea is passionate about RNA diagnostics. Her PhD project interrogates the use of RNA alongside DNA whole genome sequencing for children diagnosed with high-risk cancers who are participating in ZERO.

"What we get with DNA is like a blueprint," she says. "RNA is like overlaying a photo on that blueprint to really see what's happening. It gives us an extra layer of evidence or more clues as to what the gene mutation is doing. Using RNA with DNA, we might be able to put the puzzle back together and say, 'This is the piece that got damaged.'

Chelsea Mayoh
Senior Scientist Bioinformatics
Children's Cancer Institute

"That is really exciting and knowing that the work I do every day directly impacts children with cancer and their families gives me a great sense of pride, joy and contentment," she says. "That's what gets me out of bed every day."

Chelsea and her team also developed and maintain the drug discovery pipeline for the ZERO trial, enabling rapid screening of 125 drugs to identify which of these could potentially be effective in treating a particular child's cancer.

"Our team would not exist without Luminesce Alliance funding. I am really grateful for that and for the opportunity to finally do a PhD," she adds.

"To be able to support Chelsea to obtain her PhD is a real privilege, as she's really paving new ground in the use of RNA for diagnostics in children with cancer," says A/Prof Mark Cowley, Chelsea's primary PhD supervisor.

Improving organoid development and retinal therapies

Michelle O'Hara Wright graduated with First-Class Honours in Biochemistry and Genetics from the University of Nottingham in the UK before completing a Masters of Research in Biomedicine at University College London (UCL).

Michelle was fortunate to train with world leaders in gene and cell therapy and paediatric research at the UCL-Great Ormond Street, Institute for Child Health. She learned cutting-edge techniques in 3D stem cell culture working as a research assistant with esteemed Prof Robin Ali's group at the UCL Institute of Ophthalmology.

Michelle O'Hara Wrightt
PhD Student, Stem Cell Medicine Group
Children's Medical Research Institute

Michelle was fascinated by the capabilities of pluripotent stem cells to form organoids and decided to pursue a career in research in stem cell and regenerative medicine. She joined Dr Anai Gonzalez-Cordero in the Stem Cell Medicine Group as a PhD student in March 2020

Michelle's project investigates novel methods and technologies to improve organoid development and retinal therapies.

"Luminesce Alliance funding has allowed us to attract international students who want to stay in the lab and complete their PhDs," says Dr Gonzalez-Cordero.

Introducing Enabling Platforms

Luminesce Alliance is a paediatric research powerhouse committed to revolutionising paediatric healthcare and research by funding cutting-edge infrastructure, research and treatments for rare conditions, and clinical trials to deliver the best possible care for patients and their families.

Our next generation of research funded by the NSW Government will be delivered through the creation of Enabling Platforms - functional specialisations that cross disease areas and organisations to deliver collaborative, multidisciplinary, contemporary research and clinical health programs.

Leading clinicians and researchers, from across our partner organisations, will focus on improving the understanding and application of paediatric precision medicine across five Enabling Platforms:

Functional Genomics

Identifying and understanding disease-causing genes and new treatments.

Data

Translating rich and complex data to improve detection, treatment, prevention and clinical impact.

Precision Therapy

Delivering new drugs and novel medical technologies that will support early phase clinical trials.

Psychosocial

Developing world-leading best practice for psychological, emotional, social, and educational support of patients and their caregivers.

Health systems implementation and economics research

Translating research discoveries into new models of care.

www.luminesce.org.au

LUMINESCE Alliance

The Sydney Children's Hospitals Network

Children's Cancer Institute

Children's Medical Research Institute

Jeans for Genes

The University of Sydney

UNSW Sydney