# 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

# 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."