Molecular profiling found to improve diagnosis and survival for children with high risk cancers

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Cancer is the leading cause of disease-related death in children in most developed countries, and at least a quarter of these patients are

diagnosed with aggressive high-risk or relapsed cancers, with an expected five-year survival rate of less than 30%. Accurate diagnosis can be difficult, and survivors often suffer life-long side effects because of the toxic treatments needed to cure them.

Now, researchers from Australia have shown that, by using precision medicine, it is possible not only to obtain more accurate diagnoses, but also that using precision-guided, targeted treatments earlier improves the two-year progression-free survival in young cancer patients. Their results will be presented to the annual conference of the European Society of Human Genetics.

Associate Professor Vanessa Tyrrell, Director of the Zero Childhood Cancer National Precision Medicine Program (ZERO), a joint initiative of Children's Cancer Institute, and Kids Cancer Center, Children's Hospital, Randwick, Australia, and colleagues at the nine child cancer centers around Australia, have enrolled over 1,600 children into the program since 2017.

Previously, ZERO was limited to children with high-risk cancers, but recently expanded to be open to all children diagnosed with cancer in Australia, a trial the team are calling ZERO2.

"Having found that over 70% of children with high-risk cancers were able to benefit from personalized medicine, we felt that we needed to see whether this benefit could be applied to other childhood cancers, too," says Prof Tyrrell.

"To date we have recruited over 700 children to this second trial, which we are aiming to continue for at least another four years."

ZERO's first national clinical trial, which ran from 2017 to 2022, has already produced results related to a child's predisposition to cancer

through gene variants in their germline (child genomic cancer risk).

These variants were found in around 16% of children with high-risk cancer. Utilizing whole genome sequencing (WGS) was more sensitive for the detection of germline cancer predisposition variants than standard clinical testing pathways; more than half had not been previously identified through standard clinical care, because the patients did not meet the testing criteria.

Paired tumor-germline molecular profiling increased the germline cancer predisposition diagnosis rate and aided in genetic counseling for the families receiving these results. The findings of cancer risk led to high (nearly 67%) referral rates to cancer genetic services and, subsequently, the detection of relatives at risk of cancer. All first-degree relatives took up testing where it was recommended.

"This is not surprising to me, given that these children have developed cancer so young," says Prof Tyrrell.

"We also found that close to 70% of these germline variants were not previously known to be associated with the cancer type the patients presented with. This, together with the fact that over half the genetic cancer risk findings conferred a higher susceptibility to developing second cancers after chemotherapy, has significant implications for both treatment choices and ongoing surveillance."

Of the newly-identified variants, 80% had cancer surveillance/risk reduction implications for relatives, too. This is a much higher yield than is found in standard clinical practice and has significant implications for both patients and families, the researchers say.

They now aim to continue to improve the application of precision medicine over time, focusing on the identification of new targets that

drive an individual cancer; matching those targets to more effective, less toxic treatments and working out more effective, less invasive ways of monitoring how a child's cancer is behaving; accelerating access to clinical trials as the ability to identify and match more targets to treatments is expanded; and transitioning precision medicine from research into standard health care systems.

"Only seven years ago, these aims seemed implausible to most people, and it was challenging in the beginning to encourage enrollment of children into ZERO. Today, clinicians and families are demanding this precision medicine model as standard of care for all their high-risk, relapsed, rare, and undiagnosable patients," says Prof Tyrrell.

As well as identifying treatable cancers, ZERO aims to identify new genomic features, molecular targets and biomarkers that can lead to the development of more effective treatments. The researchers have already been able to characterize new cancer drivers and identify targeted drugs that may be effective in specific patients with specific alterations in their tumors.

"Further, there have been cases where we have shown that novel alterations were also sensitive to another targeted drug that we did not expect, therefore potentially offering more therapeutic options to the patient."

"The tools needed to implement precision medicine more widely are not cheap, but its unquestionable promise in better stratifying the diagnosis and identifying the most likely effective targeted treatments for an individual's cancer, together with the reduction in costs as technologies, computational capabilities, and automation improves leads me to believe that, in the future, multiomic profiling driving research-guided clinical care will be the gold standard, not just in cancer, but in many other diseases too," Prof Tyrrell concludes.

Professor Alexandre Reymond, from the Center for Integrative Genomics, University of Lausanne, Lausanne, Switzerland, and chair of the conference, said, "Sequencing our genome in its entirety allows us to do much more than looking under the proverbial lamp post. As a human genetic society, ESHG should aim to make this standard clinical care."

More information: Abstract no. PL3.1 Zero Childhood Cancer National Precision Medicine Program: Improving outcomes for children with high risk cancer cancer utilising comprehensive, integrated multiomic profiling

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