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When genetics and pediatric cancer collide: Understanding and optimizing families' experiences

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Abstract

Background. Advances in our understanding of the genetic basis of childhood cancer, including primary central nervous system cancers, are improving the diagnosis, treatment, and clinical management of pediatric patients. To effectively translate scientific breakthroughs into enhanced clinical care, it is essential we understand and learn from the experiences of patients, families, and health professionals.

Methods. This report summarizes findings from 4 Australian psychosocial substudies exploring the perspectives of patients, parents, clinicians, and scientists participating in research related to childhood cancer genetics. Specifically, these studies focus on the psychosocial impact of germline testing in children, surveillance for children with a cancer predisposition syndrome and the perspectives of healthcare professionals who deliver this testing and surveillance.

Results. Data presented highlight some of the opportunities and challenges associated with the changing context of genetic predisposition testing for children, adolescents and yound adults with cancer and illustrate how embedding psychosocial data collection in clinical research can answer important questions in the field and inform the design of patient-centric models of care, resources, and workforce training.

Conclusions. By embracing these perspectives, we can ensure that advances in genetic research translate into enhanced family experiences, and, ultimately, improved outcomes for children and young people with cancer, and their families.

Keywords

childhood cancer | genetic cancer risk | genetic testing and surveillance | precision medicine | psychosocial impact

Over the last 30 years, we have achieved major advances in our understanding of the genetic basis of cancer, improving our ability to identify and manage genetic cancer risk, including predisposition to primary central nervous system (CNS) cancers in children, adolescents, and young adults (AYAs). These advances continue to happen rapidly, presenting significant opportunities as well as challenges. To ensure scientific advances translate into improved clinical care, it is essential we understand and learn from the experiences of patients, families, and health professionals. In Australia, psychosocial substudies embedded within the ZERO Childhood Cancer Program's pediatric precision medicine trials, the Luminesce Alliance supported PREDICT trial, and Omico's Surveillance study in Multi-Organ Cancer predisposition syndromes in Pediatrics (SMOC-Junior), are helping to answer critical psychosocial questions in this field[1] (Table 1). These embedded psychosocial studies are providing insights into families' attitudes toward and experiences of undergoing genetic **testing**

Table 1. Summary of Embedded Psychosocial Studies (PSS)

Aim	To understand patients', parents', and health professionals' perspectives, experiences and support/training needs			
	ZERO PROGRAM			
Study	PRISM[a]	ZERO2[b]	PREDICT[c]	SMOC-Junior[d]
Testing and surveillance offered	Germline and somatic sequencing as part of a precision medicine program	Germline and somatic sequencing as part of a precision medicine program	Trio-based genomic sequencing to diagnose cancer predisposition	Surveillance involving WB-MRI
Patient population	Children (age < 21) with poor prognosis cancer at diagnosis, relapse, progression	Children (age < 25) with cancer at diagnosis, relapse, progression	Children (age < 21) with cancer at diagnosis	Children (age < 18) with a cancer predisposition syndrome
PSS participants	Patients (age ≥ 12), parents, health professionals			Patients (age ≥ 12) and parents
PSS methods	Longitudinal, mixed methods			

[a]The PRecISion Medicine for Children with Cancer (PRISM) study.
[b]ZERO2, the Next iteration of the PRISM study expanded to all diagnoses.
[c]The cancer PREDisposition In Childhood by Trio-based whole-genome sequencing (PREDICT) study.
[d]Surveillance study in Multi-Organ Cancer predisposition syndromes in pediatrics (SMOC-Junior).

and **surveillance programs** for conditions associated with increased cancer risk, and challenges faced by **health professionals** caring for children and families in this rapidly evolving setting.

Psychosocial Impact of Germline Testing

Advances in our knowledge of cancer risk-related germline variants in pediatric cancer, coupled with the increasing affordability of next-generation sequencing, are changing the context of genetic predisposition testing for children and AYAs with cancer. With the emergence of pediatric precision medicine programs, germline sequencing is being offered to unselected cohorts of patients with childhood cancer (and, in some cases, their parents). This often involves whole-genome sequencing and whole-exome sequencing, where germline sequencing is typically paired with tumor profiling and offered at the time of a child's cancer diagnosis, relapse, or progression. This directly impacts the amount and complexity of information families are presented with, and the emotional setting in which testing occurs. Providing germline testing as part of research rather than clinical care can also reduce the genetic counseling support available to patients and families.

In a recently published study, we explored parents' experiences of germline testing offered as part of the PRISM trial[2] (see Table 1), including their expectations of germline testing, preferences for the type of germline results received, and recall of any clinically relevant germline findings identified in the early period following delivery of results by the child's treating clinician. The parents who participated represented 144 patients, of whom close to 40% had been diagnosed with CNS cancer, and 17% had a clinically actionable germline finding, some in primary CNS cancer-predisposition genes (eg *TP53* and *VHL*). In our analysis of the PRISM psychosocial data (restricted to poor prognosis cancers), consistent with much of the psychosocial literature, McGill et al. found little evidence of differences in psychosocial outcomes by patient diagnosis. Given this, the data that follows includes the whole PRISM psychosocial sample.

When we explored parents' expectations of germline testing in this context, we found that close to two-thirds of parents believed it was at least "somewhat likely" that PRISM would identify a change in their child's genes. We found no statistically significant association between parents' expectations of testing and their family history of cancer, perceived knowledge of genetics, or history of genetic testing in the immediate family. However, qualitative data indicated that some parents' expectations were influenced by their own lived experience of cancer or cancer diagnoses in their family, leading to confusion when the results of their child's testing were not congruent with this. When we explored parents' preferences for the return of germline results, consistent with previous studies in other contexts, we found that most parents (>85%) wanted to receive a broad range of findings, including variants of uncertain significance and incidental findings. With regards to parents' recall of results, some parents lacked clarity. Among parents whose child received a clinically relevant finding, close to two-thirds of our sample accurately recalled this, with the remainder reporting being unsure. Among parents whose child or AYA did not receive a clinically actionable germline finding, 33% recalled this accurately, 38% reported being unsure, and 29% believed their child had received a clinically relevant finding when they had not. Lack of clarity was more common amongst parents whose child did not receive a clinically actionable germline finding, and in some cases was associated with confusion regarding the distinction between germline and tumor-related results.

Findings highlight the need to carefully design processes for testing to identify genetic cancer risk offered in the increasingly common context of pediatric precision medicine programs. Processes for obtaining consent and returning results need to ensure that families have realistic expectations of testing and can accurately recall results, and take

into consideration parents' preferences for the type of information they want returned. Building on these findings, the next iteration of the PRISM trial, ZERO2, will involve a 2-step consent process, separating tumor and germline testing-related information. Work is also underway on the development of resources to help patients and families understand precision medicine trials, particularly the distinction between somatic and germline testing, as well as resources to support the sharing of results. It is important that future work continue to inform the design and implementation of patient-centered processes and resources to support germline testing.

Psychosocial Impact of Surveillance

The expansion of germline testing in children and AYAs is increasing the identification of cancer predisposition syndromes and presenting opportunities to manage cancer risk from a younger age. Historically, children were only tested for genetic cancer risk if the risk of developing cancer in childhood was high and an effective intervention was available. Children with genetic cancer risk are sometimes recommended extensive, life-long surveillance to identify new cancers at an earlier and more treatable stage. Yet, few studies have explored young peoples' experiences of such surveillance. The available data suggests young people and parents report a mix of perceived benefits and concerns. They report feeling reassured by the potential for earlier detection and improved outcomes, which can bring a sense of control. Alongside these benefits, families report practical and logistical challenges and worries related to procedure-related risks and the risk of developing cancer, which surveillance can be a reminder of. Given the burdens associated with surveillance, adherence can be difficult. We are currently exploring families' experiences of surveillance through the SMOC Junior study. Knowledge of families' experiences of pediatric surveillance programs is essential to designing models of care which maximize benefits and minimize potential burdens, particularly as the number of young people identified with genetic cancer risk continues to grow.

Health Professional Perspectives

Changes to testing and surveillance programs for children and AYAs with genetic cancer risk also impact the roles of professionals tasked with delivering this care. The PRISM psychosocial substudy has enabled us to explore clinicians' (including oncologists and genetics professionals) and scientists' experiences.[3] While clinicians' and scientists' early experiences of PRISM were characterized by cautious optimism and appreciation of the multidisciplinary tumor board (MTB), they also described needing to adapt their usual practice. One challenge which clinicians reported experiencing was difficulty understanding and communicating trial results, with one example shared by a genetics professional who explained: "There was one family that didn't consent to germline findings, but we actually did find the pathogenic mutation in that child … I don't know what to do with that."

Related to the challenge of understanding and communicating results, clinicians reported varying levels of knowledge and confidence. For example, while most clinicians felt their knowledge of hereditary genetics in childhood cancer was good or very good, only a minority felt very confident' in interpreting, explaining, and making treatment recommendations using germline genetic information. We recently extended this study to explore the experiences of a broader range of professionals in both patient-facing and nonpatient-facing roles.[4] While professionals across all groups expressed positive attitudes toward precision medicine, many described how it added complexity to their role and at times resulted in less certain outcomes for families. Most professionals reported navigating the changes without formal training. Findings highlight the need for future work to focus on developing models of care that promote multidisciplinary involvement, training (particularly for nongenetics professionals) and an ethically defensible plan to guide practice when challenging situations arise.

Value of Embedding Psychosocial Data Collection

There is growing recognition of the value of embedding the collection of patient-reported outcomes within clinical studies. The collection of such data offers several advantages, including an increased understanding of stakeholders' experiences of evolving care, informing the development of models of care, and workforce training. Knowledge gained can guide patient care over the medium term and iteratively in the short term. The PREDICT study[5] provides an example of how the embedded collection of psychosocial data can improve patient care in the short term. In the PREDICT study, analysis of data from the first five parent interviews, coupled with observations by the psychosocial and clinical teams, led to changes to study processes. This included the development and implementation of a study process infographic and a resource to support the return of results.

One potential barrier to embedding the collection of psychosocial data within research studies is the concern that participation may burden families at an already difficult time. In the PRISM study, we have been able to assess parents' perspectives on participation in the psychosocial substudy and found that most report little to no burden (>93%, with >75% in the no burden category), and >30% report some benefit.[6] When asked whether participating in the psychosocial substudy impacted their willingness to participate in the main PRISM study, 72% reported it had no effect, with 21% reporting that it made them more eager. Reasons for being more eager included feeling like their input was being respected and appreciating a holistic approach.

Limitations and Future Directions

Psychosocial data also has limitations. It can be challenging to recruit representative samples, with certain groups often underrepresented. Participation in PRISM-impact required

patients and parents to read and speak English, limiting understanding of the experiences of culturally and linguistically diverse families. The PRISM-impact study[6] also highlighted how longitudinal studies can have significant attrition, making it difficult to conduct an in-depth analysis of change over time. Confounding factors may also impact on family experiences, such as the child's clinical situation or other external psychosocial pressures which can be difficult to account for. Future work aimed at understanding the perspectives of underrepresented groups is needed to guide equitable translation into care.

Conclusion

Progress made over the last 30 years in understanding the genetic basis of childhood cancer, including primary CNS cancers, has paved the way for groundbreaking advances in treatment and clinical management. Incorporating psychosocial substudies within clinical studies, such as those in the ZERO Childhood Cancer Program, the PREDICT trial and SMOC Junior, provides a significant opportunity to capture the perspectives of participating patients, families, and healthcare professionals. The resulting insights shed light on the psychosocial aspects of genetic cancer risk testing and surveillance, and can inform the design of patient-centric models of care. By embracing these perspectives, we can ensure that advancements in genetic research translate into enhanced family experiences, and, ultimately, improved outcomes for children and young people with cancer, and their families.

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Conflict of interest statement

D.S.Z. reports consulting/advisory board fees from Bayer, Astra Zeneca, Accendatech, Novartis, Day One, FivePhusion, Amgen, Alexion, and Norgine. All other authors have no potential conflicts of interest to declare.

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