Protocol for a comprehensive prospective cohort study of trio-based whole-genome sequencing for underlying cancer predisposition in paediatric and adolescent patients newly diagnosed with cancer: the PREDICT study

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ABSTRACT

Introduction Identifying an underlying germline cancer predisposition (CP) in a child with cancer has potentially significant implications for both the child and biological relatives. Cohort studies indicate that 10%–15% of paediatric cancer patients carry germline pathogenic or likely pathogenic variants in cancer predisposition genes, but many of these patients do not meet current clinical criteria for genetic testing. This suggests broad tumour agnostic germline testing may benefit paediatric cancer patients. However, the utility and psychosocial impact of this approach remain unknown. We hypothesise that an approach involving trio whole-genome germline sequencing (trio WGS) will identify children and families with an underlying CP in a timely fashion, that the trio design will streamline cancer risk counselling to at-risk relatives if CP was inherited, and that trio testing will not have a negative psychosocial impact on families.

Method and analysis To test this, we present the Cancer PREDisposition In Childhood by Trio sequencing study (PREDICT). This study will assess the clinical utility of trio WGS to identify CP in unselected patients with cancer 21 years or younger in New South Wales, Australia. PREDICT will perform analysis of biological parents to determine heritability and will examine the psychosocial impact of this trio sequencing approach. PREDICT also includes a broad genomics research programme to identify new candidate genes associated with childhood cancer risk.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Prospective multicentre study to investigate underlying cancer predisposition in children and adolescents with cancer using trio whole-genome germline sequencing (WGS) at diagnosis.
⇒ Every patient newly diagnosed with cancer will be offered enrolment allowing for improved generalisability of findings.
⇒ Ability to look at the challenges of incorporating the informed consent for trio WGS within the first one to 2 months of diagnosis, delivered by non-genetics clinicians.
⇒ Ability to establish psychosocial impact on the families participating in germline research at new diagnosis of cancer.
⇒ The primary limitation of this study is the selection bias of parents who do not consent to participate in the study, as these families will not be included in the interpretation of the psychosocial analysis.

INTRODUCTION

Childhood cancer was traditionally considered a largely sporadic disease, rarely caused by an underlying genetic predisposition. Recent evidence has challenged this notion, with 10%–15% of paediatric cancer patients carrying pathogenic/likely pathogenic (P/LP) variants in cancer predisposition genes.
This rate far exceeds the population background and suggests that germline cancer predisposition (CP) is a significant phenomenon in paediatric cancer and should be considered as part of optimal management. Despite the emerging importance of investigating germline CP in paediatric cancer, several key questions remain: what is the true incidence of CP in paediatric cancer patients?; what analytical approach is best suited to screen for CP risk in children?; which clinical features are most suggestive of a CP?; and what are the psychosocial implications of CP risk screening in childhood cancer?

Estimates of the prevalence of underlying CP in paediatric cancer depend on the analytical methodology used to identify pathogenic CPG variants. The diagnostic yield of monogenic conditions like CP improves as the test reportable range increases from focused panels to whole exome or genome. Additionally, moving from singleton sequencing to trios (in which the genomes of both the patient and parents are analysed together) has demonstrated an increase in diagnostic efficacy, and can aid in the detection of CP-relevant conditions such as parental mosaicism. This suggests that the ideal test for paediatric CP would be trio whole-genome germline sequencing (trio WGS), however its use to screen for CP in all paediatric cancer patients remains a research-only activity that is difficult and costly to implement in a healthcare setting. Determining the analytical approach most suited to diagnose childhood CP in the clinic remains an open question requiring cohort screening studies.

The investigation of underlying CP in children with cancer is presently reliant on identifying patients most likely to be affected by a CP based on clinical presentation, who can then be referred for genetic testing. Australian children with cancer are currently recommended referral to a cancer genetics service if they meet evidence-based guidelines (eviQ criteria) for suspicion of an underlying CP. These criteria include a family history of the same or related cancers; bilateral, multiple or multifocal cancers; earlier age at diagnosis than sporadic tumours of the same type; physical findings suggestive of a predisposition syndrome; and unexpected treatment-related toxicity. Despite this broad set of features suggesting the presence of a CP in a child, research suggests that current referral criteria do not accurately identify all patients with an underlying CP, ultimately limiting diagnosis rates.

For example, recent literature suggests 5% patients diagnosed with osteosarcoma harboured P/LP TP53 germline variant where half were de-novo. These patients will not be identified by clinical features as they do not fulfil the criteria for Li-Fraumeni syndrome (LFS) and universal germline testing is the only way to identify them. Furthermore, referral to a cancer genetics service often may not be in the same hospital and could occur months or even years later. Whether an agnostic approach of testing all patients newly diagnosed with cancer will be practical, cost-effective and psychologically acceptable, with an improved P/LP variant detection rate in CPG, has yet to be established.

Identifying an underlying CP in a child or adolescent is crucial as CP diagnosis may influence the treatment of primary disease as well as confer a significantly increased risk of developing subsequent cancers. For example, in a child with hypodiploid acute lymphoblastic leukaemia with underlying LFS, total body radiation-based conditioning and stem cell transplant could be potentially avoided, and CAR-T cell therapy could be considered. For children diagnosed with both constitutional mismatch repair deficiency (cMMRD) and brain tumours immunotherapy with immune checkpoint inhibitors is a treatment option. For children diagnosed with acute myeloid leukaemia detection of underlying CP can help in selection of an appropriate donor as family members could potentially harbour the same variant. Focused surveillance and/or risk-reducing strategies during the period of most significant risk aims to improve their outcome through early detection, risk reduction and/or prevention. This is well described for children with LFS. Durno and colleagues described benefit of surveillance in patients with cMMRD when this was initiated in childhood. For children with rhabdoid tumour predisposition syndrome the risk of brain tumour is maximum in early childhood and hence the recommended surveillance for brain tumours is more frequent in early childhood years. On the other hand, surveillance does not begin at least until the age of 10 years in most patients with familial adenomatous polyposis as the risk for polyps/colorectal cancer increases after then. Identification of underlying CP also has implications for the wider family, enabling cascade testing for at-risk relatives to identify those who would benefit from risk management and informing recurrence risk and reproductive decision-making. Such testing could be more precise if it is known whether the CP has been inherited and from which parent.

Despite the potential clinical benefits of underlying CP diagnosis, the impact of testing for CP immediately following a childhood cancer diagnosis is understudied, especially in the trio WGS setting. Potential psychosocial benefits arising from CP testing include reduced distress levels, relief from uncertainty and decreased anxiety about the future. Yet potential adverse psychosocial outcomes also exist, including increased distress and worry, guilt and relationship issues. A small body of literature investigating the impact of CP testing on children has identified a number of complexities, including significant increases in depressive symptoms for affected children, as well as unique emotional and relationship challenges. There is limited information about the short and long-term psychosocial impact of trio WGS on families affected by childhood cancer, and a lack of research examining families’ perceptions of the personal utility and the impact of undergoing testing shortly after a child’s cancer diagnosis. Some evidence suggests that parents may hold high hopes and expectations for genomic testing that does not reflect the actual outcomes. More broadly, research examining parents’ decision-making around precision medicine and early phase clinical trials suggests that informed consent may be complicated by therapeutic optimism and a misunderstanding of key
concepts, particularly differentiating between somatic and germline genomic testing.\textsuperscript{27}

Given the increasing understanding of the importance of identifying an underlying CP in children and adolescents diagnosed with cancer, and limitations of basing germline testing predominantly on clinical criteria, the cancer PREDisposition In Childhood by Trio-based whole-genome sequencing (PREDICT) study was conceived. PREDICT will offer trio WGS to all children and adolescents newly diagnosed with cancer in New South Wales (NSW), Australia, regardless of tumour type, other personal medical history or family history, and where possible will include both biological parents. By exhaustively analysing each genome for P/LP CPG variants and testing both parents to determine CP heritability, PREDICT aims to establish the prevalence of CP in paediatric cancer, inform clinical utility for the family, and quantify the expected diagnostic yield of different analytical approaches for CP.

The PREDICT design also allows for substudies to address outstanding questions in the management of childhood CP. PREDICT includes a psychosocial component, PREDICT-Impact, which aims to better understand families’ experiences and communication of, and attitudes toward, receiving genetic information about cancer risk via trio WGS shortly after a childhood cancer diagnosis. PREDICT-Impact will examine the perspectives of families and healthcare professionals towards family-based germline sequencing and establish their information and training needs.

STUDY AIMS

Hypothesis

Germline trio WGS in childhood and adolescent cancer patients will identify more patients with an underlying CP than current guidelines-based approaches, optimise referral to cancer genetics services and prompt changes in the medical management of these patients and at-risk relatives.\textsuperscript{10} Current guidelines recommend genetic testing for underlying CP in children diagnosed with cancer only if they meet certain diagnostic criteria.

Aims

PREDICT’s primary aim is to evaluate the utility of applying trio WGS to identify underlying CP in every child/adolescent newly diagnosed with cancer. Utility will be assessed as the proportion of patients diagnosed with underlying CP under the PREDICT all-comer WGS model, as compared with the expected diagnosis rate from standard-of-care.

In addition to this primary aim, PREDICT will address secondary objectives:

- Develop a pilot model-of-care for family-based WGS cancer risk screening offered to all children with cancer.
- Determine the proportion of newly diagnosed childhood and adolescent cancer patients with a reportable germline P/LP variant in a CPG.
- Determine the proportion of newly diagnosed childhood and adolescent cancer patients who harbour likely de novo versus inherited P/LP variants in CPG.
- Determine the proportion of participants with underlying CP who subsequently undergo cancer surveillance.
- Determine the psychosocial impact of the germline sequencing process on patients and parents/guardians and the information training needs of health professionals who care for them.

METHODS AND ANALYSIS

The study involves three paediatric oncology centres in NSW, Australia: (1) Sydney Children’s Hospital; (2) The Children’s Hospital at Westmead and (3) John Hunter Hospital. Although the regions that these three centres are located within have considerably different demographics, in terms of age distributions and ethnicities, together they provide care to all paediatric oncology patients diagnosed in the state (figure 1).\textsuperscript{28–30} In turn, NSW has comparable demographics to the nation, along with an age-standardised rate of cancer that is close to the Australian average, suggesting that findings from the study may be generalisable to the overall Australian population.\textsuperscript{31}

While it is expected that PREDICT will be generalisable in terms of demographics to the broader national context, our all-comers sampling approach means that our sample is nonetheless reflective of the case load at the recruiting hospitals rather than stratified by demographics. Taking this into account, we intend to evaluate ethnic distribution of the cohort through self-reported and genetically determined ancestry. Participants may nominate up to two cultural backgrounds of which they identify with for the purposes of the psychosocial study. Genetic ancestry will also be objectively evaluated using principal component analysis based methods. This approach, addressing diversity at both a cultural and genetic level, should help identify trends in psychosocial experiences and negate bias in genetic research findings. The study started recruitment in March 2021 and will continue at least until the final quarter of 2023. The target sample size for the study is to sequence at least 100 complete trios. This target was determined as being approximately the minimum required number of trios needed to reach statistical power for testing polygenic risk scores using traditional methods. However, not all enrolled families will involve full trio consent (ie, occasionally, some family members may not be present or choose to consent). Furthermore, we expect that not all blood samples will be collected from participants that have initially consented to participate in the study. For this reason, additional recruitment will be employed with the goal of having approximately 270 families enrolled in the study overall.

Criteria for study inclusion are shown in table 1; recruitment will occur within 60 days from the diagnosis of malignancy or later at the discretion of the study chair.
Enrolment

Patient enrolment

Patient enrolment is performed by paediatric oncologists. They are responsible for discussing the potential benefits and implications of participation in the study with the patient (if age appropriate) and parents. An example patient consent form is given in online supplemental appendix 1.

Parental enrolment

Individual informed consent is obtained from biological parents willing to participate in trio WGS. Separate consent forms (online supplemental appendix 2) are provided to each parent.

Opt-out

At the time of enrolment, patients and parents are given the choice of individually opting out of the following study components:

- Disclosure of cancer-related germline P/LP variants found in the child and one or both parents.
- Storage and use of samples, genetic data, and related health information for future ethically approved research.
- Participation in the health economics substudy.

Training and additional information

Training sessions regarding pretest and post-test counselling for germline WGS in the context of paediatric cancer were offered at study commencement to all recruiting clinicians. Training sessions were offered in person and online as part of the site initiation visit before study commencement. These sessions were divided into two parts: (1) pretest and post-test genetic counselling conducted by senior genetic counsellors (certified by the Human Genetics Society of Australasia); and (2) physical examination for features included on the study recruitment checklist conducted by a clinical geneticist and paediatric oncologist. Genetic counsellors’ input is provided at any time during the study if it is: (1) considered necessary by the treating clinician; (2) the genetic counsellors have an existing relationship with the family or (3) if requested by the family.
Data collection

Detailed demographic data including details of cancer diagnosis are collected at enrolment (online supplemental appendix 3). Physical examination is performed according to a study examination checklist. This examination checklist (online supplemental appendix 4) is designed to collect comprehensive phenotype data for genotype-phenotype correlations and is adapted from published examination lists.\textsuperscript{32-34} Examination is performed by the recruiting oncology physicians, who are offered training in dysmorphology. Images to help facilitate the training were obtained from the photo and definitions booklet developed by Postema et al and other medical literature.\textsuperscript{34}

Family history supplied by the patients and/or their parents is captured on a secure REDCap database. The study involves two modalities for family history collection: a paper form completed with input from the recruiting clinician, or an electronic form completed via REDCap by the patient/family. If family history is previously collected as part of a referral to a genetic cancer service, it will also be accessed.

Trio WGS and analysis

Peripheral blood is collected into EDTA vacuum tubes and DNA is extracted using the QIAamp DNA Blood Mini Kit. Extracted DNA is used to generate PCR-free WGS paired-end libraries, which are sequenced to a minimum mean depth of 30X per sample on the Illumina NovaSeq platform, yielding 2×150 bp paired end reads. Reads are mapped to the 1000 Genomes Project GRCh38 full analytical reference including decoys and HLA sequences (GRCh38_full_analysis_set_plus_decoy_hla.fa, accessed 14 Dec 2020), augmented with an additional decoy contig of FX174 (NC_001422.1), using bwa mem 0.7.17 with default options. Sorting and duplicate marking is performed using biobambam2 2.0.87, and molecular variants identified using DeepTrio 1.0.1rc for duos and trios, and DeepVariant 1.2.0 for simplex samples, before joint calling using GLNexus 1.2.7. Sequencing data quality control is implemented using samtools 1.14 idxstats and duplicate metrics for gross sequencing metrics, and Somatic tweak 0.2.13 to detect non-relatedness and sample swaps. All analytical steps are implemented on the Cavatica platform (Seven Bridges Genomics).

To reduce the chances of incidental findings in parental samples, family joint-called variants from GLNexus are postprocessed to suppress any haplotypes present in the parents which are not also shared by the child. Postprocessed variants are then loaded into the Alissa Interpret platform (V.5.3.3, Agilent), and within each family are used to run a familial analysis searching for inherited or de novo pathogenic variation in a curated list of CPGs. The curated list of CPGs currently has 191 entries (online supplemental appendix 5) but will be reviewed annually or earlier should the study team become aware of additional clinically significant CPGs.

Variants are curated according to ACMG-AMP/Sherloc criteria,\textsuperscript{35,36} incorporating parental sequence data to identify the inheritance pattern of variants and to assist with the classification of variants of unknown significance. Further molecular analysis may be performed on alternative platforms (eg, targeted sequencing, RNA sequencing) if indicated by the WGS result.

The variant reporting pathway involves three sequential stages (figure 2):

1. Curation of all variants identified by Agilent Alissa by a multidisciplinary genomics team (MGT). The MGT is tasked with identifying variants with potential clinical implications for subsequent review, and includes bioinformaticians, molecular scientists, genetic counsellors and clinicians.
2. Assessment of variants curated by the MGT for portability, by a multidisciplinary cancer genetic team (MCGT). The MCGT’s role is to assess if there is a high probability of a variant being implicated in the patient’s phenotype. It includes genetic counsellors, cancer genetics clinicians and paediatric oncologists.
3. Discussion of recommendations based on variants identified by the MCGT, by a regular multidisciplinary team (MDT). The goal of the MDT is to reach consensus on further investigations and recommendations for the patient, and to establish which genomic findings are clinically relevant and reportable. The MDT is attended by paediatric and AYA oncologists (including


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Table 1 Inclusion and exclusion criteria

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<thead>
<tr>
<th>Inclusion criteria</th>
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<tr>
<td>For trio whole-genome sequencing</td>
<td>New diagnosis of malignancy</td>
</tr>
<tr>
<td>Patient age ≤21 years</td>
<td>Written informed consent</td>
</tr>
<tr>
<td>Psychosocial component: biological parents</td>
<td>Give written informed consent</td>
</tr>
<tr>
<td>Speak/read conversational English</td>
<td>Severe depression and/or suicidality*</td>
</tr>
<tr>
<td>Able to provide details of a trusted health professional</td>
<td>Current psychotic episode*</td>
</tr>
<tr>
<td>Significant substance abuse*</td>
<td>Other significant difficulties which impact the ability to complete questionnaires</td>
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| Psychosocial component: patients | Age ≥12 years |
| Speak/read conversational English | Deemed too unwell by parent or doctor |
| Current psychotic episode* | Other significant difficulties which impact the ability to complete questionnaires |

*Identified through contact with the patient’s treating clinician or screening by the study psychologist.
the treating clinician when possible) and representatives from the MGT and MCGT.

Variants can be reclassified over time as new insights about genomics and genotype/phenotype correlation are discovered. As this arises, throughout this and other related studies, variant classification will be reviewed by the MDT and reported back to the treating clinician if a reclassified variant has new clinical implications.

**Delivery of results and recommendations**

Any P/LP variant identified in the curated list of CPGs is considered potentially reportable, regardless of variant zygosities and gene inheritance mode. If consent is given for return of results, information on reportable variants will be provided to the patient’s recruiting clinician in a research report that will include variant genomic coordinates and refSeq, the interpretation in the clinical context, and a recommendation from the study’s MDT.

Referring clinicians are responsible for returning results to families. The recommended procedure for return of actionable findings is consultation with the study genetic counsellor prior to results delivery to review implications and best approach for return of results. The option of a joint consultation with the genetic counsellor is available for all results delivered. The study genetic counsellor is available for the clinician or families prior to or post results delivery for additional support. While this is recommended, the study team, including research genetic counsellors, have developed a report within the germline report that ensures that there is enough information to support the clinician in return of results to families.

If no reportable variants are identified, a ‘no reportable findings’ report will be issued to the recruiting clinician for return to the family. This report will include a list of genes in the analysis and will be accompanied by a family-oriented, plain language leaflet explaining the meaning of ‘no reportable findings’ in the context of the study (online supplemental appendix 6).

**Enabling genomic research in a clinical reporting context**

The pan-cancer WGS design of PREDICT allows for research into new and emerging genomic mediators of cancer risk. However, conducting speculative genomic research in the context of a study that returns genetic results to patients presents ethical challenges around appropriate consent and the return of research findings. To address these concerns, PREDICT implements a research firewall design (figure 3). The key feature of the research firewall is a conceptual and information separation between PREDICT’s clinical and research arms.

The clinical arm of PREDICT has been previously described; it operates with an intent to report, considers only clinically reportable findings in a predefined and fixed set of cancer risk genes, and has access to patient identifying information. By contrast, the research arm of PREDICT operates with no access to patient identity or contact information, and no ability to report. This enables the research arm to investigate more speculative mechanisms of genomic cancer risk that do not meet the threshold for clinical reporting, while avoiding ethical dilemmas around reporting uncertain findings.

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**Figure 2** Sequential stages in curation of variants and reporting. MDT, multidisciplinary team; MGCT, multidisciplinary cancer genetic team; MGT, multidisciplinary genomics team.
In exceptional circumstances, a research investigation may discover a variant that meets the criteria for clinical reportability but was missed by the clinical arm analysis. To enable reporting in these situations PREDICT incorporates a path for information to flow from the research arm to the clinical arm: potentially reportable variants identified in the research arm are communicated to the clinical arm team, who curate and potentially report new variants via the standard reporting pipeline.

**Psychosocial evaluation (the PREDICT-Impact study)**

Through the psychosocial component of the PREDICT study, we will use a prospective, mixed-method, sequential explanatory design to track the experiences of parents/caregivers and patients who are ≥12 years over 5 years from the time of study enrolment. All eligible participants will be invited to participate in the psychosocial component of the PREDICT study, regardless of their WGS result. Parents will be invited to complete questionnaires (either online or paper-based), which include quantitative measures and open-ended response questions, after study enrolment (T0), 2–4 weeks after the return of the germline research results (T1), 1 year after study enrolment (T2) and yearly after that for a further 3 years (T3–T4). We will also administer a brief questionnaire to parents quarterly (ie, every 3 months) and invite them to participate in an optional short semi-structured qualitative interview after returning their results and yearly (on an opt-in basis). With their parents’ consent, patients will be invited to complete a questionnaire at baseline (T0) and after the return of results (T1). Online supplemental appendix 7 summarises the assessments included in the psychosocial component. Patient questionnaires will consist of a subset of the assessments in the parent questionnaires, adapted for younger participants.

Clinicians and other healthcare professionals involved in the care of families of children with cancer offered germline sequencing through the PREDICT study will be asked to participate in an online/paper survey yearly from the commencement to the end of the study. Healthcare professional questionnaires will include quantitative measures which assess knowledge, confidence and experiences with cancer genomics/CP and professional development needs. Questionnaires will also include open-ended response questions exploring barriers to participation and perceived advantages/disadvantages of the study. Both the qualitative and quantitative psychosocial data will be integrated during analysis, with both data types compared to ensure consistency and qualitative data used to provide further explanation and understanding of the quantitative data. Results will also be interpreted in the context of the family’s WGS result.
Patient and public involvement

This protocol is approved by Sydney Children’s hospital network human research ethics committee. This committee has consumer representatives who are keenly involved in the discussion about the scientific rationale and ethical basis of the study. Their feedback is also valuable in designing parent information sheets and consent forms.

This study involves germline testing to determine cancer risk for patients and their families, and it has a very important psychosocial component, where parents (and when appropriate patients) participate in interviews about their understanding and the psychosocial impact of the study. This feedback from patients and families is implemented in real-time to amend the parents/guardian information sheets and consent forms with clarifications added to them as identified. The result of the genetic test also includes a consumer-friendly document that explains the result in lay language. To ensure that the output from the research informs practice and thereby maximise the benefit to patients and the health system, various dissemination strategies will be used for translating the knowledge into practice.

Data management and oversight

Information about study patients is kept confidential and managed according to the requirements of the NHMRC Code for the Responsible Conduct of Research (2007, updated 2018). Study data, stored as re-identifiable are kept on secure storage, with access strictly limited to essential personnel. The documents will be retained for at least 15 years after publication or termination of the study. Records documenting the diagnosis of a genetic or inherited disorder will be kept indefinitely. Records will be sent to NSW State Archives for long-term retention as per NSW State Records General Disposal Authority (GDA17). Raw genomic data will be stored in secure databases, such as the European Genomics Archive.

ETHICS AND DISSEMINATION

PREDICT study is approved by SCHN-HREC (SCHN-HREC, Ethics approval 2020/ETH00634). An ethically defensible plan (EDP online supplemental appendix 8) following guidelines in the National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research (2007) is developed for PREDICT. This plan addresses ethical considerations for each component of the study.

The results from this study will be disseminated using multiple vehicles such as the development of a clinical practice guideline, decision aids, publication in peer-review journals, presentation at international meetings, and contribution to data repositories and public databases.

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Contributors

TAO and LDP conceived of PREDICT study and are the clinical co-leads of the project. BP, NAFB and MD designed and wrote the manuscript, with comments and contributions from all authors. KT, JK, MW, EC, SJ-T, FA and LMSL contributed to the design of the clinical pipeline, including informed consent and return of results. BP, NAFB and FA are clinical leads at recruiting centres and coordinate patient recruitment. KB-S and EC developed an ethically defensible plan. MP, MD, DS and MW-E designed the computational pipeline, study procedures and clinical/research interface. PB, PA, A-KA, YC and LMSL provided input into the methodology for analysis and interpretation of results. VJT contributed as the programme lead of Zero Childhood Cancer Programme. JH developed the psychosocial component of the study with the guidance of senior authors CW and KH. All authors edited and approved the final manuscript.

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