

BMJ Open 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

Noemi Auxiliadora Fuentes Bolanos ^{1,2}, Bhavna Padhye,^{3,4} Macabe Daley,² Jacqueline Hunter,^{5,6} Kate Hetherington,^{6,7} Meera Warby,^{2,8} Eliza Courtney,^{1,2} Judy Kirk,^{9,10} Sarah Josephi-Taylor,^{11,12} Yuyan Chen,⁴ Frank Alvaro,¹³ Kristine Barlow-Stewart,^{2,5} Marie Wong-Erasmus,^{2,6} Paulette Barahona,^{2,6} Pamela Ajuyah,^{2,6} Ann-Kristin Altekoester,^{2,6} Vanessa J Tyrrell,² Loretta M S Lau,^{1,2} Claire Wakefield,^{5,6} Dianne Sylvester,⁴ Katherine Tucker,^{1,8} Mark Pinese,^{2,6} Luciano Dalla Pozza,³ Tracey A O'Brien¹

To cite: Fuentes Bolanos NA, Padhye B, Daley M, *et al*. 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. *BMJ Open* 2023;**13**:e070082. doi:10.1136/bmjopen-2022-070082

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2022-070082>).

NAFB, BP, MD, MP, LDP and TAO'B contributed equally.

Received 11 November 2022
Accepted 09 May 2023



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For numbered affiliations see end of article.

Correspondence to

Dr Bhavna Padhye;
bhavna.padhye@health.nsw.gov.au

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.

Ethics and dissemination By evaluating the feasibility, utility and psychosocial impact of trio WGS to identify CP in paediatric cancer, PREDICT will inform how such comprehensive testing can be incorporated into a standard of care at diagnosis for all childhood cancer patients.

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.

Trial registration number NCT04903782.

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



(CPGs).¹⁻⁴ This rate far exceeds the population background⁵ 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.⁶ 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.⁷⁻⁹ 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 health-care 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.¹⁰ 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.⁴ For example, recent literature suggests 5% patients diagnosed with osteosarcoma harboured P/LP TP53 germline variant where half were de-novo.¹¹ 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.¹² 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.¹³ 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.^{14 15} Durno and colleagues described benefit of surveillance in patients with cMMRD when this was initiated in childhood.¹⁶ 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.¹⁷ 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.¹⁸ 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.^{19 20} Yet potential adverse psychosocial outcomes also exist, including increased distress and worry,^{19 20} guilt,^{20 21} and relationship issues.²² 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^{23 24} as well as unique emotional and relationship challenges.²⁵ 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.²⁶ 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.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.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).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.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.



Figure 1 Regional demographics of the PREDISposition In Childhood by Trio-based whole-genome sequencing (PREDICT) recruiting sites compared with the state of New South Wales (NSW) and the overall Australian population, according to the 2021 Australian census. (A) The age distribution of recruiting sites for PREDICT, in relation to NSW and Australia. (B) The top five ancestries of each recruiting site in PREDICT, in relation to NSW and Australia. Ancestry is self-reported and not mutually exclusive; each census respondent could select up to two ancestries.

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.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
For trio whole-genome sequencing	
New diagnosis of malignancy	
Patient age ≤ 21 years	
Written informed consent	
Psychosocial component: biological parents	
Give written informed consent	
Speak/read conversational English	Severe depression and/or suicidality*
Able to provide details of a trusted health professional	Current psychotic episode*
	Significant substance abuse*
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.	

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.^{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.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 2×150bp 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 Φ X174 (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 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,^{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 reportability, 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

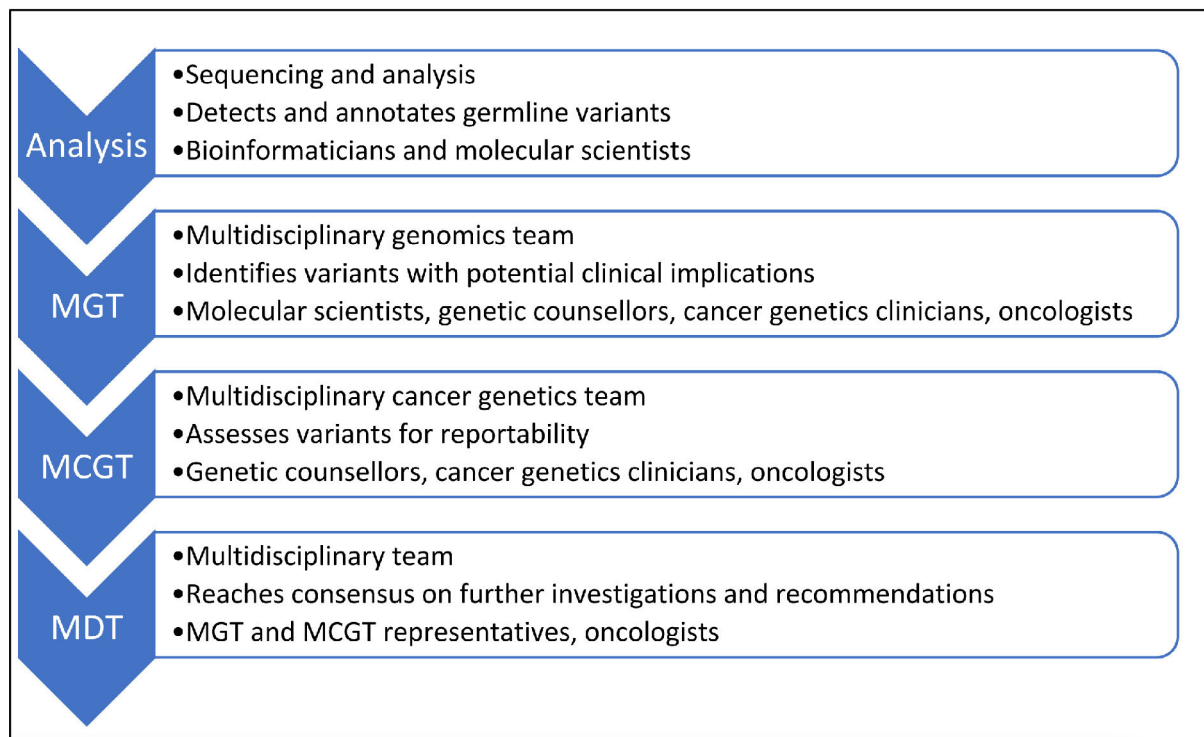


Figure 2 Sequential stages in curation of variants and reporting. MDT, multidisciplinary team; MCGT, multidisciplinary cancer genetic team; MGT, multidisciplinary genomics team.

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 zygosity 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.

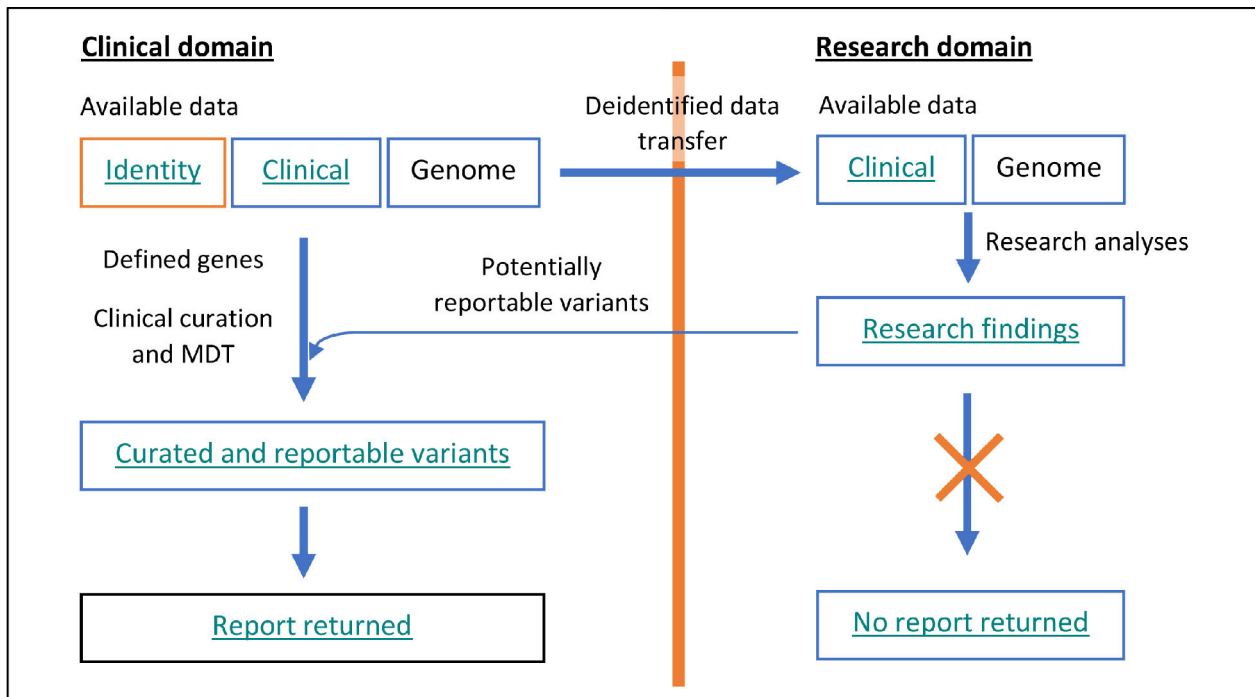


Figure 3 The research firewall concept for clinical-research separation in PREDisposition In Childhood by Trio-based whole-genome sequencing. Genomic, clinical and patient identity data proceed through the clinical domain, with variants curated and ultimately reported following expert review (left panel). Separately, deidentified clinical and genomic data are passed to the research domain (right panel), where broad-ranging research analyses are performed with no pathway to report. In exceptional circumstances, variants of potential clinical relevance identified in the research arm will be returned to a designated expert review panel comprising clinical and laboratory representatives. This review panel will assess the potential reportability of the variant, and if reporting is advised, the sample will be reidentified and details forwarded to the clinical arm for second review and potential reporting. MDT, multidisciplinary 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.

Author affiliations

¹Kids Cancer Centre, Sydney Children's Hospitals Network Randwick, Randwick, New South Wales, Australia

²Children's Cancer Institute, Lowy Cancer Centre, UNSW, Randwick, New South Wales, Australia

³Cancer Centre for Children, The Children's Hospital at Westmead, Westmead, New South Wales, Australia

⁴Kids Research, Children's Cancer Research Unit, The Children's Hospital at Westmead, Westmead, New South Wales, Australia

⁵Behavioural Sciences Unit, Kids Cancer Centre, Randwick, New South Wales, Australia

⁶School of Women's and Children's Health, University of New South Wales, Sydney, New South Wales, Australia

⁷Behavioural Sciences Unit, Sydney Children's Hospital Randwick, Randwick, New South Wales, Australia

⁸Hereditary Cancer Centre, Prince of Wales Hospital Nelune Comprehensive Cancer Centre - NCCC, Randwick, New South Wales, Australia

⁹Familial Cancer Service, Westmead Hospital, Westmead, New South Wales, Australia

¹⁰Sydney Medical School, The University of Sydney, Sydney, New South Wales, Australia

¹¹Department of Clinical Genetics, The Children's Hospital at Westmead, Westmead, New South Wales, Australia

¹²Discipline of Genomic Medicine, Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales, Australia

¹³Paediatric Oncology Service, John Hunter Children's Hospital, Hunter Region Mail Centre, New South Wales, Australia

Acknowledgements We sincerely thank patients and their families and clinicians, and health professionals involved in the development of this protocol and consumer representative groups. Thanks to all the collaborating partners in the PREDICT study: Children's Cancer Institute, Lowy Cancer Research Centre, UNSW; Children's Cancer Research Unit, University of Sydney Discipline of Child and Adolescent Health; Kids Cancer Centre, Sydney Children's Hospital, Sydney Children's Hospitals Network; Cancer Centre for Children, The Children's Hospital at Westmead, Sydney Children's Hospitals Network; Children's Cancer & Haematology Service, John Hunter Children's Hospital, Newcastle; Hereditary Cancer Clinic, Prince of Wales Hospital, and Children's Hospital Westmead; Familial Cancer Service, Westmead and Behavioural Sciences Unit, Kids Cancer Centre, Randwick, UNSW and University of Sydney, The New South Wales State Government, the Australian Federal Government Department of Health, the Medical Research Future Fund, the Munderoo Foundation, other contributors; as well as funds raised through the Zero Childhood Cancer Capacity Campaign, a joint initiative of the Children's Cancer Institute and the Sydney Children's Hospital Foundation, supported the national clinical trial and associated clinical and research personnel. We are sincerely grateful to Dr Floor A M Postema, Dr Johannes H M Merks, and the TuPS study group for their willingness to share the 'Tumour Predisposition syndrome in Childhood Cancer Screening Instrument, part II: definitions and pictures' booklet.

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.

Funding The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by Luminesce Alliance – Innovation for Children's Health for its contribution and support. Luminesce Alliance - Innovation for Children's Health, is a not-for-profit cooperative joint venture between the Sydney Children's Hospitals Network, the Children's Medical Research Institute and the Children's Cancer Institute. It has been established with the support of the NSW Government to coordinate and integrate paediatric research. Luminesce Alliance is also affiliated with the University of Sydney and the University of New South Wales Sydney. We thank the National Health and Medical Research Council of Australia (grant number APP1176265 to CW and APP2008300 to MP).

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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ORCID iD

Noemi Auxiliadora Fuentes Bolanos <http://orcid.org/0000-0001-6880-5428>

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Supplemental material

APPENDIX 1: Patient/guardian information sheet

Parent/Guardian Information Sheet

(For Parent/Guardian providing consent for the participant)

Introduction

Your child is being invited to take part in the PREDICT study because they have been diagnosed with cancer. The PREDICT study aims to understand the genetic cause of cancer affecting children and young people who are 21 years old or younger.

This Parent/Guardian Information Sheet and Consent Form tells you about this research study. It explains the tests and research involved. Knowing what is involved will help you decide if you want your child to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not your child can take part, you may wish to discuss this with your child, a relative or friend, and your child's doctor.

If you decide you want your child to take part in the PREDICT study, you will be asked to sign the consent section. By signing consent you are telling us that you:

- Understand what you have read
- Consent to your child taking part in the PREDICT study
- Consent to your child undertaking tests, which are outlined in this information sheet for the purpose of this study
- Consent to the use of your child's personal and health information as described.

You will be given a copy of this Parent/Guardian Information and Consent Form to keep.

Your child's participation is voluntary

Your decision to have your child participate in this study is completely voluntary and there will be no cost to you. If you do not want your child to take part in this study you do not have to. You should feel under no obligation to have your child participate in this study. Choosing for your child not to take part in this study will not affect your child's current and future medical care in any way. Whatever your decision, please be assured that it will not affect your child's medical treatment or your relationship with the staff who are caring for your child.

Your child's withdrawal from the study

You are under no obligation to have your child continue with the research study. You may change your mind at any time about your child's participation in the research. People withdraw from studies for various reasons and you do not need to provide a reason. You can withdraw your child from the study at any time by completing and signing the "Withdrawal Form" included with this Information Sheet.

If you withdraw your child from the study, you will be able to choose whether the study will destroy or retain the information it has collected about your child. You should only choose one of these options. Where both boxes are ticked in error or neither box is ticked, the study will destroy all information it has collected about your child.

If you withdraw your child from the study, information collected about your child that has already been analysed and/or included in a publication may not be able to be withdrawn or destroyed. In such circumstances, your child's personal information will continue to form part of the study's records and results. Your child's privacy will continue to be protected at all times

What is the purpose of this research?

Genes are what make up DNA – the chemical structure carrying your genetic information that determines many human characteristics such as the colour of your eyes or hair.

Researchers study genes to understand why some people have a certain condition, like cancer, and why some people do not. Understanding why cancer occurs in some people may help explain why some people respond to a treatment, while others do not, or why some people experience a side effect and others do not.

This study is focused on **Cancer Predisposition Syndromes (CPS)**, which are linked to an increased risk of developing certain types of cancer. Changes in a gene which affected their function are called 'gene faults' or 'mutations' and if the fault is in a cancer predisposition gene, this change can be linked to a CPS.

The PREDICT study will collect a blood sample and test the DNA of newly diagnosed cancer patients to look for CPS. If we find that your child has a CPS, it may mean they have an increased chance of other cancers. It may tell your child's doctor:

- If there are ways to check for cancers early
- How to help stop cancer happening
- About treatments that may help and which ones might not help

The purpose of this study is to:

- Show that this type of genetic test is useful and will accurately benefit patients at increased risk of cancer
- Improve the outcome for children with cancer and their families

Was my child's CPS inherited?

CPS can be passed down to a child from one or both of their parents (inherited) or may not be inherited at all and occur in a child for the first time when they are born.

If you agree for your child to join the study, we will also ask you, as his/her parent(s) to provide a blood sample. We will use your sample as a comparison tool in the analysis process of your child's sample. We will collect your DNA from the blood sample. If after two weeks your blood has not been collected, you will receive a reminder email. We recommend that you have your blood collected within 4 weeks of consenting.

If we find a CPS in your child, then we would test your DNA for the **same** gene fault found in your child. However, we only look for faults in parents' DNA if their child has been found to have a CPS.

If we find the same gene fault in one or both of you, you may also have a CPS. If you have CPS, it means:

- Your child has inherited the CPS from you
- You may have an increased chance of cancer
- Your blood relatives (sisters, brothers, nieces, nephews) may also have a CPS. If they want to find this out, they will be offered a referral to a specialist.
- It may also help you (as parents) to see if there are ways to avoid cancer in any future children.

What does participation in this research study involve?

Let us collect your child's health information from their hospital medical record

This information will include general information about your child (such as date of birth, sex, hospital) and details of their cancer (such as test reports and treatment).

Let us collect information about your child's relatives

This information will include details of any relatives who have had cancer or health problems at birth. To collect this information, you will be asked to fill out a web-based (or paper-based if you prefer) questionnaire for each family member. You may receive a call from the study genetic counsellor to clarify or expand some of your family history.

You may have previously provided your family history of cancer during attendance at the Family Cancer Clinic. To avoid repetition for you, we will access your clinic file and collect family history for use in this study.

Let us collect your child's DNA

We will need to get a sample of your child's healthy (non-cancer) cells from which to collect their DNA. These healthy cells can be taken from about 5ml (about 1 teaspoon) of blood. Where possible, the blood sample required for this study will be taken at a time when blood is taken as part of routine medical care so no extra needle puncture would be required. Blood can either be taken from a vein in the arm or from a central line if your child has one. In some situations normal (non-cancer) cells will need to come from a skin biopsy.

Let us test your child's DNA for faults in genes linked to cancer to look for a CPS

The study test looks for change in your child's genes but only those genes known to be linked to CPS. The detected changes will first be checked by a panel of specialists who will review if these changes are relevant or not. The relevant changes will be given to you by your child's doctor.

Where possible, we would also like to test DNA from both parents. This is to help us understand the findings in your child. If we find a gene fault in your child, this will also help us to see if one or both parents have the same gene fault. If one or both of you have the same gene fault as your child, then this may suggest that your child's CPS is inherited.

Help us understand your family's experience with being part of this study

To do this, we have developed some brief surveys that will be given to you throughout the study:

- I. At study enrolment, after you receive your child's results from the study (if you choose to), and then every year for three years. These will take about 15-20 minutes.
- II. We will also send you some other very brief surveys, every 3 months. These will only take about 2-5 minutes.

Our surveys will ask you:

- How your child is feeling physically (e.g., whether they are feeling well and have enough energy);
- How your child is feeling emotionally (e.g., whether they are feeling happy or stressed);
- What your child thinks of the study and about taking part (e.g., their satisfaction, any regrets); and
- If we can do anything to improve the study for future families.

Your child can participate in these surveys even if you do not wish to, and vice versa. We also understand that you may not wish to do all or some of these surveys. So, we will contact you before each survey is sent to see if you want to complete it. If you don't want to be contacted about completing surveys, we will send you a form to withdraw from this part of the study. Your child can still participate in the other parts of the study. Whatever you decide your decision will not affect your child's care in any way.

Let us follow up with your child's doctor after the testing has been done

If we find your child has a CPS, we will collect the following information for a period of up to 5 years:

- How your child's doctor used the genetic results in their treatment

- If your child's doctor referred you and your child to a Genetics Service to talk about the research results. If not, we would like to understand the reason.
- As part of this study, we will also collect information from the Genetics Services.

If we do not find a CPS in your child, we will still collect clinical information (e.g., treatment information) to understand the implications of these findings.

What might the genetic test result say?

I. We did not find that your child has a gene fault linked to CPS

This is the most likely result. However, your child may still have a CPS gene fault that we were not able to find with the current knowledge.

II. We found your child has a gene fault known to be linked to a CPS

Your child's doctor will talk to you about whether knowing this result can help their treatment. You and your child may be referred to a group of specialists who works at a Genetics Service.

III. We found a fault in one of your child's genes that we looked at but we do not know if it is linked to a CPS

We need to do more research. So, we won't usually tell your child's doctor about this result.

Do we have to get the results of my child's genetic testing?

When the results are ready, you and your child can talk to your child's doctor about what the test found. Even if a CPS is found, you may choose not to know. During the study, at any time, you can also tell us not to re-contact you to receive the result. We will still check with you when the results are available just in case you have changed your mind.

Are there possible benefits from being part of the study?

If your child is found to have a CPS, it may mean they have an increased chance of getting another cancer in the future. So, your child's participation in this study may allow them to undergo some additional screening, which can assist in the early detection of another cancer in them.

If your child has inherited a CPS, this study might also:

- Help you (as parents) and your blood relatives find out if you have a CPS.
- Be helpful to others in the future with the same cancer as your child.
- Help to make tests to find cancer and find new forms of treatment.
- Tell us how we can work with you and families like yours when we do genetic testing.

By testing your DNA it may also help to find out more about the genetic cause of cancer.

Are there possible risks from being part of the study?

Blood collection

Any complications with getting a blood sample from your child or you for this study will be small. Where possible, the sample will be taken from your child at a time when blood is taken as part of their routine medical care. If a central line is in place, we will draw blood samples from the line.

When getting the blood sample there can be:

- Slight pain where the needle is put in and/or some minor bruising, which may last one to two days.
- A small chance of bleeding or infection.

These complications would also apply to you when giving a blood sample.

Genetic testing

If your child (or you) is found to have a CPS, it may be upsetting and the findings may affect family relationships. Genetic counsellors working in the Genetics Service will be there to support you and your family. On the other hand, some families experience relief from knowing what is behind the cancer that has happened to your child.

It is possible that the study may not find any gene fault related to your child's cancer diagnosis. Some people may find not getting an answer upsetting.

If your child has a CPS, we look at both your child's and your genes (where possible). In doing this, there is a small chance that the test could identify family relationships that are different from expected. We will not report these findings.

Incidental findings

There is a small chance, thought to be less than 10%, that the study test may identify a genetic change (also called a mutation) in your child's normal cells which might be associated with an increased risk of developing other health problems.

Sometimes these health problems might be important for your child's future care and for your family. This is called an incidental finding. If an incidental genetic change is found in your child's normal cells, the finding will be reviewed by an appropriate panel of specialist doctors including laboratory and clinical geneticists.

The specialist review will determine whether the genetic change is known to be significant for your child's health. If so, this will be reported back to your child's doctor. It will also be recommended that your child and your family be referred to a Genetics Service for counselling and a specific management plan, and, if appropriate, to confirm this research finding in an accredited laboratory.

What will happen to my and my child's blood and DNA samples?

During the study, samples will be stored at the Children's Cancer Institute in Sydney. Personal details linked to the samples are stored separately. At any time, you can withdraw your child or yourself from this study or request the samples be destroyed. This can be done by completing the "Withdrawal Form" included with this Information Sheet.

Genomic analysis will be carried out on a validated industry-standard pipeline that is compliant with all privacy and security regulations. Blood and/or DNA samples may be sent for related testing to other laboratories. These may be in Australia or overseas. Before sending, any linked personal details will be removed.

You can choose to let us store any of your child's samples and your samples (if collected) left over after the testing has finished for this study. The samples would be stored for at least 15 years from when the study publishes its final report at the Children's Cancer Institute for future research studies.

All proposals for future research on the stored samples will be reviewed for scientific merit. They must also have approval from a Human Research Ethics Committee. Researchers who use your child's samples in these research studies may need to have information about your child's cancer, such as treatment response and outcome. However, this information will be shared in a de-identified manner to protect their privacy.

What will happen to my child's personal and health information?

By signing the consent, you agree to allow study investigators and relevant clinical and laboratory research staff involved in the study to collect and access your child's personal and health information. Your child's personal and health information will be accessed, used and stored in accordance with Australian privacy laws. Additionally, any personal and health information we obtain from you for the purposes of this study will be managed in the same way.

Any information obtained in connection with this research study that can identify your child will remain confidential. Access to this information will be strictly restricted to researchers involved in the PREDICT research study at the Children's Cancer Institute, the Sydney Children's Hospital, the Children's Hospital at Westmead and their delegates under which the research study is conducted.

Information about your child which is specifically related to the study will be collected using the RedCap database, hosted by UNSW. All information will be stored and backed up on their server, which is located within Australian borders, in the form of a computer file. Research report forms will be kept in paper hard copies and archived to a secondary storage facility on completion of the study. After the completion of the study, all study participant information will be kept in a secure secondary storage facility.

Within a period of up to 15 years of the publication of the study's final report, all soft copies of study participant information will be destroyed. Additionally, all hard copies will be

shredded and destroyed by a secured destruction service provider. However, non-identifiable data will be stored indefinitely, with the possibility that this data may be used for future related or unrelated studies.

Clinical information and genetic data from both your child's DNA and your DNA (if tested) will contribute to research databases or registries either in Australia or overseas. This allows researchers from all over the world to share data and accelerate cancer research. This can be a public database where the public can access limited de-identified information such as cancer type, age group and gender, and specific changes in the genes. It can also be a controlled database where doctors and scientists will apply for access to more detailed but de-identified clinical and genetic information for the purpose of answering specific research questions, which may or may not be related to this study.

It is anticipated that the results of this research study will be published and/or presented in a variety of forums. However, identifiable information (e.g. name, date of birth, photographs) will *not be* included, except with your permission that is separate to this consent. Given the nature of the medical information that may be included, it *may* be identifiable to you, some healthcare providers involved in your child's care, and possibly close relatives.

Measures used to secure this information have been approved by the Human Research Ethics Committee. Information gathered for the study will only be used for the purpose of this research study and it will only be disclosed for other purposes with your permission, except as required by law. Your child's information will remain confidential except in the case of a legal requirement to pass on personal information to authorised third parties. This requirement is standard and applies to information collected both in research and non-research situations. Such requests to access information are rare; however we have an obligation to inform you of this possibility

In accordance with relevant Australian privacy laws, you have the right to access the information collected and stored by the research team about your child. You also have the right to request that any information with which you disagree be corrected. Please contact the researchers named at the end of this document if you would like to access your child's information.

What will happen to my child's family history information?

Family history information will be stored along with your child's clinical and genetic information in a secure and confidential database (registry) held jointly by the Children's Cancer Institute and the Sydney Children's Hospital Network. Research results have the potential to influence and inform clinical management. This information may be used for your child's medical management, research purposes and to better understand how cancer predisposition syndromes present clinically. This information may also be important for the healthcare of other relatives in the family. No identifying data will be released or made public.

This information may be useful for your child's future health management. This information may be transferred to a clinical database to assist in your child's management.

Will the study cost me anything?

There are no additional costs associated with participation in this research study, nor will you or your child be paid for participating.

A sub-study that looks at associated costs and benefits of finding a CPS

You can choose whether or not you and your child wish to also take part in this sub-study. There will be an option on the consent form where you can choose for you and/or your child not to participate in this sub-study. If you choose not to, your child can still be part of the main study looking for a CPS.

What is this sub-study doing?

We want to understand the costs and benefits of using genetic testing in everyone diagnosed with a childhood cancer aged 21 or under.

What do I have to do on behalf of my child to take part in the sub-study?

1. Let us use your child's identifying information (e.g. name, date of birth, address) so that we can collect health-related data about them from a range of sources

In these datasets, your child's health information is de-identified (data is made anonymous). This is to ensure their personal privacy is protected. That is why we need their identifying information to be able to access their health information. Being able to access information using these data sources avoids us having to contact you in the future to ask you further questions. The information will be treated completely confidentially and used **only** for the purposes of this research study. The information sources include those held by hospitals, NSW and Commonwealth health departments and other groups or organisations that provide health services or collect health data such as the Cancer Institute NSW.

2. Let us collect your child's Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits Scheme (PBS) data

You will be asked to sign a consent form authorising the study to access your child's complete Medicare Benefits Schedule (MBS) and/or Pharmaceutical Benefits Scheme (PBS) information as outlined in the Medicare and PBS consent form. Medicare collects information on your child's doctor visits and the associated costs, while the PBS collects information on the prescription medications you have filled at pharmacies. The consent form is sent securely to Services Australia who holds MBS and PBS data confidentially.

- Where children under the age of 14 are being recruited, a separate child Medicare and PBS consent form will need to be used. If a child turns 14 years of age during the recruitment process, they will need to complete and sign the Medicare and PBS

consent form themselves. Alternatively, the form can be signed by a power of attorney or legal guardian. A certified copy of any authority to sign on behalf of a child must be provided with the consent form. This may mean some children will require more than one consent form to be completed for the purposes of the study. Please note, adolescents who turn 14 years of age during the study are only required to complete and sign the Medicare and PBS consent form as per Services Australia's policy. This is not applicable to the main study where participants must be 18 years old to consent as per the approving ethics policy.

- Where a child under 14 years of age is on two Medicare cards, both card numbers and the signatures of both primary card holders will need to be on the child's consent form. Data relating to a child's Medicare card will only be supplied where the primary card holder of that card has consented.

Medicare and PBS data collected from Services Australia will be stored on the Children's Cancer Institute secured server, which is physically located within Australian borders, and access to the data will be limited to authorised researchers in this study via assigned login password. Data collected from Services Australia will be securely destroyed within a period of 5 years of the publication of the study's final report, and will not be used for future related or unrelated studies.

Where is the research being done?

The study is a partnership between Sydney Children's Hospital, Westmead Children's Hospital and Children's Cancer Institute supported by research grants from the NSW Ministry of Health's Luminesce Alliance Fund.

What will happen once my child turns 18 years of age?

It is the law that a person who is 18 years of age and older must give their own permission to be part of a research study. Although you may have given this permission to the PREDICT study now, once your child turns 18 years old, the study team may get in touch with them again to make sure they still agree with being part of this research.

Who has reviewed the research study?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research study have been approved by the HREC of The Sydney Children's Hospital Network.

This study will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

Who can I contact if I need further information?

If you would like more information about the study or you need to speak to a member of the research team, please contact:

Clinical contact person

Name	[Name]
Position	[Position]
Telephone	[Phone number]
Email	[Email]

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Research Governance Officer Details

Name	[Name]
Position	[Position]
Telephone	[Phone number]
Email	[Email]

If you have any complaints about any aspect of the study, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer Details

Reviewing HREC name	
Study Reference number	
Position	
Telephone	
Email	

What do I do if I have a privacy complaint?

If you have a privacy complaint in relation to this study, contact the Office of the Australian Information Commissioner. You will be able to lodge a complaint with them.

Website	
Telephone	
Email	
Mail	

Thank you for considering this invitation

Supplemental material

Appendix 2: Parent Consent form

Parent Participation Consent Form (Parent providing consent for their own participation)

Declaration by the Participant

The study

I have read or had read to me in a language that I understand, the Participant Information Sheet. I understand its contents.

I understand the purposes, procedures and possible risks of my involvement in this study.

If my child has joined the research study, I understand that:

- I will also be asked to provide a blood sample from which my DNA will be collected.
- The genetic test may find a gene fault linked to a cancer predisposition syndrome (CPS) in me. The results of this test will be given to me by my child's treating doctor.
- If I am found to have a CPS it may mean I have an increased chance of cancer. This may have implications for my future.
- As we are looking at both my child's and my DNA, there is a small chance that the test could identify family relationships that are different from expected. These results will not be reported to my child's doctor or to me.
- There is a small chance that the test could unexpectedly identify other genetic information. This may be about a condition that I have now or may develop in the future (incidental findings). My DNA may be tested for genes which may be linked to cancer but at this stage we still don't know. These research results will not be reported to me.

I understand that:

- I am consenting to provide a blood sample from which my DNA will be collected, for the purposes of this study.
- I am free to withdraw my consent at any time by completing the Withdrawal Form during the study. I know this will not affect my child's current or future care.
- The genetic test results may have implications for the health/genetic risks of my blood relatives, now or in the future.
- My information will be available to health professionals involved in my child's care.
- Results are confidential and may be released to others only with my consent, or as required by law.
- My personal and health information may be held by the study for a period of up to 15 years from the publication of the study's final report. After this period of time, this information will be securely destroyed.

I understand I will receive a copy of the Participant Information Sheet and Consent Form.

Consent to take part

I do consent I do not consent

Optional consent

I do I do not consent to the disclosure of cancer-related gene faults and relevant incidental findings found in the study to my child's treating doctor and to me.

I do I do not consent to the storage and use of my sample and genetic data for future ethically and scientifically approved research, provided that I cannot be identified.

Name of Participant (please print)	_____	
Signature of Participant	_____	Date _____
Signature of Interpreter (if applicable)	_____	Date _____

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the parent/guardian has understood that explanation.

Name of Study Doctor/ Senior Researcher† (please print)	_____	
Signature	_____	Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature

PREDICT Study FORM01: Case Report

Ethics approval: SCHN 2020/ETH00634

Contact: -----

Study admin use only

REDCap ID -

General

- 1) Enrol date
- 2) Hospital

Patient information

If available, place patient sticker over dashed outline.

PLACE PATIENT
STICKER HERE

- 3) First name
- 4) Last name
- 5) Other names
- 6) Date of birth
- 7) Sex at birth Male Female

Primary patient parent / caregiver

This will be the family's primary contact for this study.

- 8) Name
- 9) Relationship to patient
- 10) Postal address with postcode
- 11) Phone
- 12) Email

Treating physician

- 13) Name
- 14) Email

A note for Demographics

Please note that the demographic questions in this form are for the purposes of the psychosocial study.

Cultural background refers to the main cultural group(s) to which a person feels they belong. This may be the same as a person's family members or it may be the country to which they feel closely tied to. This may be the same or different to their country of birth. A person may identify with more than one cultural group.

Please do not prompt the Patient or Carers with response options to the cultural background questions, provide the above definition instead (i.e. do not suggest that they are Australian or otherwise).

Demographics: Patient's CARER 1

For this section, please provide answers for the patient's carer, even if this carer is **not** a biological parent of the patient.

- 15) Full name
- 16) What is the relationship of **Carer 1** to the patient?
- Mother
- Father
- Other:

Demographics: Patient's CARER 1 (cont.)

- 17) What is the cultural background of **Carer 1**?

Mark all that apply.

- Australian
- Other:

- 18) Is **Carer 1** of Australian Aboriginal or Torres Strait Islander descent?

Mark all that apply.

- No
- Yes, Australian Aboriginal
- Yes, Torres Strait Islander

- 19) What is the first language of **Carer 1**?

- 20) Is this the preferred language of **Carer 1**?

If no, please specify the preferred language of Carer 1.

- Yes
- No:

Demographics: Patient's CARER 2

For this section, please provide answers for the patient's carer, even if this carer is **not** a biological parent of the patient.

- 21) Full name

- 22) What is the relationship of **Carer 2** to the patient?

- Mother
- Father
- Other:

- 23) What is the cultural background of **Carer 2**?

Mark all that apply.

- Australian
- Other:

- 24) Is **Carer 2** of Australian Aboriginal or Torres Strait Islander descent?

Mark all that apply.

- No
- Yes, Australian Aboriginal
- Yes, Torres Strait Islander

- 25) What is the first language of **Carer 2**?

- 26) Is this the preferred language of **Carer 2**?

If no, please specify the preferred language of Carer 2.

- Yes
- No:

Demographics: Patient

- 27) What is the patient's cultural background?

Mark all that apply.

- Australian
- Other:

PREDICT Study FORM01: Case Report

Ethics approval: SCHN 2020/ETH00634

Contact: -----

Study admin use only

REDCap ID - **Demographics: Patient (cont.)**

28) Is the patient of Australian Aboriginal or Torres Strait Islander descent?

Mark all that apply.

 No Yes, Australian Aboriginal Yes, Torres Strait Islander

29) What is the patient's first language?

If unsure, leave blank and go to question 31.

30) Is this the patient's preferred language?

If no, please specify the patient's preferred language.

 Yes Unsure No: **Cancer diagnosis**

31) Diagnosis

32) Date of diagnosis DD / MM / YY

(Date when biopsy or BM aspiration is done, or date of imaging when tissue diagnosis is not required)

33) Risk stratification

 Low / standard Medium / intermediate High Unknown at enrollment Not applicable

34) Metastasis

 Not assessed, or unknown No Yes Not applicable to this cancer type**Patient kinship and perinatal history**

35) Are the parents related (consanguineous)?

If yes, please specify degree of relatedness: first (e.g. siblings) / second (e.g. uncle-niece) / third (e.g. first cousins) / not specified, etc.

 Yes: No

36) Type of birth

 Single Twin Unknown

If Single or Unknown, proceed to question 39.

37) Type of twin

 Identical Fraternal Unknown

If Identical, proceed to question 39.

38) Twin's birth sex Male Female**Patient kinship and perinatal history (cont.)**

39) Assisted reproductive technology used

Mark all that apply.

 None IVF (In vitro fertilisation) ICSI (Intracytoplasmic sperm injection) PGD (Preimplantation genetic dx)40) Gestational age at birth wk41) Birth weight g42) Length at birth cm43) Head circumference at birth cm

44) Prenatal or perinatal complications

45) Congenital abnormalities

Patient development46) Motor Age-appropriate Delayed47) Cognition Age-appropriate Delayed48) Puberty Prepubertal Pubertal**Patient medical history**

49) Previously diagnosed genetic syndromes

50) Previously diagnosed autoimmune disease

Cancer genetics referral

51) Prior to this cancer diagnosis, has this patient been referred to a genetics service (whether attended or not, for suspicion of either a cancer or non-cancer genetic syndrome)?

If yes, please list which genetic service/s the patient has seen.

 No Yes:

Version 1.4 (20211217)

Last author: -----

Page 2 / 3

PREDICT Study FORM01: Case Report

Ethics approval: SCHN 2020/ETH00634

Contact: -----

Study admin use only

REDCap ID - **Cancer genetics referral (cont.)**

52) Following this cancer diagnosis, would a direct referral to cancer genetics be recommended on the basis of clinical features?

- No Unknown
 Yes, based on eviQ guidelines (v1)
 Yes, based on MIPOGG (v1.0.2)
 Yes, based on other criteria

Please specify other criteria or guidelines used:

53) If yes, have you referred, or do you intend to refer, this patient to cancer genetics?

- Yes Not applicable
 No

Family history collection method

54) How would the family like to supply their health history? Choose **ONLY ONE** option

- Online via emailed survey
Survey will be emailed to the address in Question 12
 In person via FHx interview

Informed consent led by:

55) Name

56) Role

If other, please specify the role of the person.

- Paediatric/Adolescent and Young Adult (AYA) oncologist
 Oncology fellow
 Oncology Research fellow
 Other:

End of document

PREDICT Study FORM02: Phenotype

Ethics approval: SCHN 2020/ETH00634

Contact: -----

Study admin use only

REDCap ID - **General**1) Date of exam DD / MM / YY**Patient information**

If available, place patient sticker over dashed outline.

PLACE PATIENT
STICKER HERE

2) First name

3) Last name

4) Other names

5) Date of birth DD / MM / YY

Examiner information

6) Name

7) Position

JMO

Fellow

Consultant

Other:

Anthropometrics

8) Height cm

9) Weight kg

10) Head circumference cm

Asymmetry

11) Asymmetry

None

Head

Face

Limbs

Cranium

12) Scalp tumours

Yes

No

13) Hair type

Mark all that apply

Normal

Brittle

Sparse/fine

Coarse

14) Frontal bossing (prominent forehead)

Yes

No

Eyes

15) Cataract

Not examined

Yes

No

16) Visible nerve fibers on cornea

Not examined

Yes

No

17) Photosensitivity

Mark all that apply

No

Yes, eyes

Yes, skin

18) Eye spacing

Normal

Orbital hypotelorism

Orbital hypertelorism

19) Eye size

Normal

Microphthalmia

Macrophthalmia

20) Palpebral fissure slant

Normal

Downslanted

Upslanted

21) Epicanthal folds

Yes

No

22) Ptosis (drooping eyelid)

Yes

No

23) Abnormalities of eye control

Not explained by primary tumour. Check all that apply.

None

Strabismus

Nystagmus

Amblyopia

Other:

24) Vision loss

Not explained by primary tumour. Check all that apply.

None

Colour vision deficiency

Partial vision loss (bilateral)

Hemianopsia

Complete blindness

PREDICT Study FORM02: Phenotype

Ethics approval: SCHN 2020/ETH00634

Contact: -----

Study admin use only

REDCap ID - **Ears**

25) Ear lobule creases or pits

- Yes
 No

26) Posterior helical ear pits

- Yes
 No

27) Abnormal ear shape

If yes, please describe

- Yes:
 No

Oral region

28) Jaw position

Mark all that apply

- Normal
 Micrognathia
 Retrognathia
 Prognathia

29) Lips

Mark all that apply

- Normal
 Periorificial papilloma
 Perioral hyperpigmentation
 Mucosal neuromata

30) Oral cavity

Mark all that apply

- Normal
 Short superior frenulum
 Cleft palate
 Hard palate high/short/narrow

31) Oral mucosa

Mark all that apply. If other, please comment.

- Normal
 Leukoplakia
 Gingival overgrowth
 Papilloma / neuroma
 Papular fibromatosis
 Cobblestone
 Other:

32) Tongue

Mark all that apply

- Normal
 Macroglossia
 Geographic
 Lobulated
 Glossoptosis
 Ankyloglossia

Oral region continued on right

Oral region (continued)

33) Oral pigmentation

Mark all that apply. If other, please comment.

- Normal
 Mucocutaneous pigmentation
 Other:

34) Dental abnormalities

Mark all that apply. If other, please comment.

- Normal
 Hypodontia (congenital)
 Hyperdontia
 Unerupted teeth
 Impacted teeth
 Enamel pits
 Other:

35) Has a mouth X-ray been performed?

Mark all that apply. If other, please comment.

- No, or not known
 Yes, with no abnormalities identified
 Yes, with odontogenic keratocysts detected.
 Yes, with other abnormalities detected:

Thorax

36) Supernumerary or widely-spaced nipples

- Yes
 No

37) Gynaecomastia (in males)

- Yes
 No
 Not applicable (patient is female)

Abdomen

38) Umbilical hernia

- Yes
 No

Joints and skeleton

39) Neck

Mark all that apply

- Normal
 Short neck
 Pterygium colli
 Redundant neck folds

Joints and skeleton continued on next page

PREDICT Study FORM02: Phenotype

Ethics approval: SCHN 2020/ETH00634

Contact: -----

Study admin use only

REDCap ID - **Joints and skeleton** (continued)

40) Chest wall deformities

Mark all that apply. If other, please comment.

- None
- Pectus excavatum
- Pectus carinatum
- Cleft sternum
- Other:

41) Scoliosis of spine

- Yes
- No

42) Limbs

Mark all that apply

- Normal
- Reduced range of movement
- Hypermobile joints
- Absent radius
- Other limb abnormalities:

Hands and feet

43) Digit abnormalities

Mark all that apply

- None
- Polydactyly
- Syndactyly
- Clinodactyly
- Camptodactyly
- Other:

44) Palm / plantar

Mark all that apply

- Normal
- Palmar/plantar pits
- Single palmar crease
- Single plantar crease

45) Nails

Mark all that apply

- Normal
- Hypoplastic
- Nail pits

Genitalia

46) Precocious puberty

- Not applicable (prepubertal)
- No: puberty is age-appropriate
- Yes: precocious puberty present
- Not examined

Genitalia continued on right

Genitalia (continued)

47) Abnormal genital pigmentation

- Yes
- No
- Not examined

48) Ambiguous genitalia

- Yes
- No
- Not examined

49) Undescended testicle (if patient is male)

- Yes
- No
- Not examined

Skin

50) Telangiectasia

- Yes
- No

51) Tumours

Mark all that apply

- None Neurofibromas
- Lipomata Schwannomas
- Pilomatrixomas
- Sebaceous Adenomas
- Other:

52) Blue naevus

- Yes
- No

53) Pigmentation

Mark all that apply. If other, please comment.

- Normal
- Café-au-lait spots
- Axillary freckling
- Hyperpigmentation
- Hypopigmentation
- Inguinal freckling
- Other:

If Café-au-lait spots, please comment on number and size

54) Palmoplantar hyperkeratosis

- Yes
- No

55) Thin skin, or generalised skin atrophy

- Yes
- No

PREDICT Study FORM02: Phenotype

Ethics approval: SCHN 2020/ETH00634

Contact: -----

Study admin use only

REDCap ID - **Neurological signs**

(Not explained by primary tumour)

56) Ataxia

 Yes No

57) Cranial nerve palsies

 Yes No**Endocrine**

58) Enlarged thyroid

 Yes No

End of document

Supplemental material

APPENDIX 5: Virtual gene panel for WGS analysis and interpretation

ACD	EXT2	NHP2	RPS28
AIP	FAAP100	NOP10	RPS29
ALK	FANCA	NRAS	RPS7
ANKRD26	FANCB	NSD1	RTEL1
APC	FANCC	NTHL1	RUNX1
ATM	FANCD2	PALB2	SAMD9
AXIN2	FANCE	PARN	SAMD9L
BAP1	FANCF	PAX5	SBDS
BARD1	FANCG	PDGFRA	SDHA
BLM	FANCI	PHOX2B	SDHAF2
BMPR1A	FANCL	PMS2	SDHB
BRAF	FANCM	POLD1	SDHC
BRCA1	FAS	POLE	SDHD
BRCA2	FGFR2	POT1	SETBP1
BRIP1	FH	PRF1	SH2B3
BUB1B	FLCN	PRKAR1A	SHOC2
CBL	GATA1	PTCH1	SLX4
CDC73	GATA2	PTEN	SMAD4
CDH1	GPC3	PTPN11	SMARCA4
CDK4	GPR161	RAD51	SMARCB1
CDKN1B	GREM1	RAD51C	SMARCE1
CDKN1C	HAVCR2	RAD51D	SOS1
CDKN2A	HAX1	RAF1	SPRED1
CEBPA	HOXB13	RB1	SPRTN
CHEK2	HRAS	RECQL4	SRP72
CREBBP	IKZF1	REST	STAT3
CTC1	KCNQ1OT1	RET	STK11
CTR9	KIT	RFWD3	STN1
CXCR4	KRAS	RHBDF2	SUFU
CYLD	LZTR1	RIT1	TERC
DDB2	MAD2L2	RMRP	TERT
DDX41	MAP2K1	RPL11	TINF2
DICER1	MAP2K2	RPL15	TMEM127
DIS3L2	MAX	RPL23	TP53
DKC1	MBD4	RPL26	TRIM28
EGFR	MEN1	RPL27	TSC1
ELANE	MET	RPL31	TSC2
ELP1	MITF	RPL35A	TSR2
ENG	MLH1	RPL36	UBE2T
EP300	MPL	RPL5	VHL
EPCAM	MSH2	RPS10	WAS
ERCC1	MSH6	RPS15	WRAP53
ERCC2	MTAP	RPS17	WRN
ERCC3	MUTYH	RPS19	WT1
ERCC4	NAF1	RPS24	XPA
ERCC5	NBN	RPS26	XPC
ETV6	NF1	RPS27	XRCC2
EXT1	NF2	RPS27A	

PREDICT Protocol_Appendix 5

Supplemental material

APPENDIX 6: Family-oriented leaflet explaining the meaning of ‘no findings’ in the context of the study

My Child’s Testing *Did Not* Find Any Genetic Changes

What does this result mean?

- Testing did not find any changes (variants) in the tested genes that can cause cancer
- As no genetic changes were found in your child, your (parent) samples were not checked

This result **does not** exclude a genetic cause, given the following

- There is a small chance that your child has a genetic change that cannot be found with current testing methods
- A genetic change may have been found but we do not know what it means – these are not reported
- There may be genetic causes of cancer that we have not yet discovered and were not checked with this testing

Will the PREDICT Study re-check my child’s testing?

- The PREDICT Study Team *may* re-check your child’s sample if new genetic causes of cancer are discovered during the study period
- Your child’s doctor will update you if the result changes, but the chance of this is low

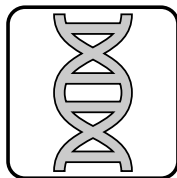
What is the chance of another childhood cancer happening in our family?

- Your child’s cancer could be a ‘one-off’ event, also known as a *sporadic* cancer
- This usually means the chance of a close family member getting the same cancer is **not** high
- *However*, this can depend on your child’s cancer type and family history
- An appointment with a clinical cancer genetics service might be useful
- *Most* children *do not* need to be referred and so your child’s doctor will discuss with you if this is recommended

We have been referred to a clinical cancer genetics service – what does this involve?

- They will look at your child’s health history and family tree in more detail
- In *rare* cases, more genetic testing might be useful
- Genetic testing by a *clinical* service can sometimes use different testing methods to a *research* study

Supplemental material

What are some important points to keep in mind?**We may discover new cancer genes over time**

- Ask your child's doctors every 3-5 years during their long-term follow-up if a referral to a clinical genetics service is needed
- Once your child is an adult, they can seek updated advice from their doctor/GP if planning a family

**Family history information can change over time**

- Update your child's doctor about any family history changes
- This *may* change the recommendations given by your child's doctor

Who can I contact if I have more questions?

- If you would like to discuss your child's testing in the PREDICT Study further, your child's doctor can arrange for you to speak to a PREDICT Study Genetic Counsellor
- Genetic Counsellors are specially trained health professions who can provide information about genetic testing and genetic results
- You can also contact the PREDICT Study Team by email: schn-predict@health.nsw.gov.au

Supplemental material

Appendix 7: Assessment schedule for the psychosocial component**Assessment schedule for the psychosocial component**

Measure	Intake	Case report form	T0	T1	T2-T4	T2b	Brief Q
Semi-structured interview	-	-	-	X	X	-	-
Demographic data	-	X	X	-	-	-	-
Decision to participate ¹	-	-	X	-	-	-	-
PIPseqKQ adapted[21]	-	-	X	-	-	-	-
Distress ratings	-	-	X	X	-	-	-
Family communication	-	-	X	X	X	-	-
Family surveillance	-	-	-	X	X	-	-
Trust in Physician scale[22]	-	-	X	X	X	-	-
Understanding ²	-	-	X	-	-	-	-
Hopes and concerns ² [14]	-	-	X	X	X	-	-
Perceived benefit ² [14]	-	-	X	-	-	-	-
Who will benefit most ²	-	-	X	X	X	X	-
Satisfaction with Decision scale	-	-	X	X	X	X	-
Satisfaction rating ²	-	-	X	X	X	X	-
Decisional Regret scale[23]	-	-	-	X	X	X	-
Patient QoL EQ-5D-5L ² [24]	-	-	X	X	X	-	X
Parent wellbeing[24]	-	-	X	X	X	-	X
Emotion Thermometers Tool ² [25]	X	-	X	X	X	X	X
Change to health status	-	-	X	X	X	-	X
Impact of participation ¹	-	-	X	X	-	-	-
Impact of COVID-19	-	-	X	X	X	-	-
Recommend to others ²	-	-	X	X	X	X	-
Open-ended comments ²	-	-	X	X	X	X	-

T0 = Baseline; T1 = following receipt of results; T2 – T4 = annually following enrolment; Brief Q= Quarterly.

¹Assessed in patient questionnaires only.

²Assessed in patient questionnaires (T0 and T1 only) and parent questionnaires.

PREDICT Protocol_Appendix 7

Supplemental material

APPENDIX 8: Ethically defensible plan

Determination of findings that will be returned and actions (*National Statement Guidelines 3.3.36, 3.3.43, 3.3.44*)

Only P/LP variants in known CPGs are considered reportable, and results will be distributed to the treating oncologist in the form of a report, if consent for return of results is obtained. The report will contain a summary and interpretation of laboratory results, a determination that the variant is inherited or de novo (where possible), and a recommendation for genetic counselling referral based on the reportable findings and/or reported clinical/family history features. Ethically approved, patient-friendly leaflets will accompany the report to facilitate results discussions. A multi-pronged approach mitigating the risk of revealing incidental findings (IF) will be implemented, however, reportability will be reviewed on a case-by-case basis if an IF is identified considered clinically actionable during childhood. Where reported, referral will be made to the local genetics service for genetic counselling and management of the condition identified.

Validation and assessment of findings (*National Statement Guidelines 3.3.45 and 3.3.46*)

Genomics and multidisciplinary clinical teams will review the variants via a three-step pathway. Variants can be reclassified over time, and this will be periodically reviewed, and a new report will be issued as required. The result report will clearly state the findings were generated as part of the research, and clinical confirmation of reportable variants in an accredited laboratory is necessary before any changes in clinical management. The study team encourages PREDICT results to be delivered in a joint appointment with the treating clinician and a study genetic counsellor.

Consent to disclosure of findings and notification requirements (*National Statement Guidelines 3.3.47– 3.3.57*)

To facilitate the involvement of the child or adolescent in the pre-test consent discussion, age-appropriate patient information sheets have been developed. A two-step consent process will be implemented, including (1) preliminary discussion regarding the study aims and requirements of participation, followed by the offer of further discussion with the study genetic counsellor (strongly encouraged in certain scenarios including significant distress, limited health literacy, or where there are differing preferences between family member participants); and (2) the consent form is reviewed between the treating clinician and/or study genetic counsellor and the participating family. All attempts will be made to re-consent participants upon reaching the age of majority during the study at their next scheduled visit if they have not previously consented for themselves. The decision for individuals declining return of results will not be routinely checked (as per *National Statement* guideline 3.3.53). However, families will be made aware during the pre-test discussion that they can update their decision at any time during the study and will be provided with study contact details to facilitate this. Special considerations for disclosing findings and other correspondence regarding the study will be made for bereaved families. Requests for the return of raw data and/or biospecimens will be facilitated, where possible.

PREDICT Protocol_Appendix 8