The contribution of genetic predisposition to pediatric cancer: a study integrating extensive phenotyping and state of the art genotyping.

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To evaluate the performance of a *genotype first approach* (WES-based panel analysis) in diagnostics of genetic predisposition in children with cancer or neoplasms, compared to the current *phenotype first approach* (standard of care). In particular…

Ethical review	Approved WMO
Status	Completed
Health condition type	Congenital and hereditary disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON52506

Source
ToetsingOnline

Brief title
PrediCT - Predispostion to Childhood Tumors

Condition

- Congenital and hereditary disorders NEC
- Miscellaneous and site unspecified neoplasms benign

Synonym
childhood tumors, pediatric cancer

Research involving
Human

Sponsors and support

Primary sponsor: Prinses Máxima Centrum voor Kinderoncologie
Source(s) of monetary or material Support: Stichting Kinderen Kankervrij (KiKa) - KiKa project nummer 355 & 403

Intervention

Keyword: decision-support tool, genetic predisposition, pediatric cancer, whole exome sequencing

Outcome measures

Primary outcome

Pediatric cancer predisposition syndromes diagnoses (molecular and/or clinical). We will compare the number of cancer predisposition syndromes diagnosed by the genotype first approach (molecular diagnosis based on WES panel analysis) to the phenotype first approach (clinical diagnosis and/or molecular diagnosis based on targeted tests).

Secondary outcome

We will evaluate the number of pediatric CPSs diagnosed by the genotype first approach and the phenotype first approach for different groups of tumor types.

Other secondary study parameters are:

- The number of patients referred to a clinical geneticists
- The number of children who already have a molecular confirmed cancer predisposition syndrome at the time of cancer/neoplasm diagnosis.
- The total number of pediatric cancer predisposition syndromes
- The number of variants of unknown significance (VUSs) detected by WES panel analysis.

- The number of children with hematological malignancies who have an underlying PID or IBMFS as cancer predisposition syndrome
- The performance of the decision-support questionnaire (MIPOGG tool; standard of care) (positive predictive value, negative predictive value, sensitivity and specificity); The MIPOGG tool serves as a decision-support tool to help streamline referrals to clinical genetics services and assists the pediatric oncologist to assess whether a referral would be appropriate for the patient
- The number of children who refuse to participate in our study and the reasons why children/parents refuse to participate
- The motivations and concerns of families who participate in our study
- The impact of participating in the study and receiving genetic test results
- The knowledge families have on genetic concepts
- How families made a decision on participating in the study and how they experienced the counseling

Based on these endpoints we will develop guidelines for best strategy to detect cancer predisposition syndromes in a routine clinical setting. Furthermore, this study will contribute to improving the counseling and support offered to future families.

Study description

Background summary

Recognition of genetic predisposition in children with cancer or neoplasms is of high clinical significance since it might influence therapy choices, surveillance policies and counseling of relatives. Cancer predisposition syndromes (CPSs) can be suspected based on specific hallmarks such as a positive family history or the presence of congenital anomalies. Due to the expanding phenotypic diversity, the upfront *phenotype based* recognition of CPSs is becoming more challenging for clinicians. Furthermore, next-generation sequencing (NGS) studies have revealed mutations in pediatric cancer predisposition genes in patients without any clinical features suggestive for genetic predisposition. Additionally, patients with genetically-determined defects in the production and/or function of (white) blood cells can have an increased risk of hematological malignancies. These include inherited bone marrow failure syndromes (IBMFS) and primary immunodeficiencies (PID), with important genetic overlap between the two disease groups.
From previous research it is known that participating in NGS and receiving genetic test results can be psychologically impactful. Little is known about the experiences with NGS of parents and children in a pediatric oncology setting

Study objective

To evaluate the performance of a *genotype first approach* (WES-based panel analysis) in diagnostics of genetic predisposition in children with cancer or neoplasms, compared to the current *phenotype first approach* (standard of care). In particular we will focus on discrepancies in CPS diagnoses between these two approaches. Furthermore, we will obtain insight into the prevalence of germline mutations in PID- and IBMFS-associated genes in children with hematological malignancies. In addition we will evaluate the psychosocial aspects of participating in NGS in a childhood cancer setting to improve counseling of future families.

Study design

Prospective nationwide cohort study. We will use WES-data generated routinely from all children diagnosed with cancer or neoplasms in the Prinsess Máxima Center. After informed consent, a panel of known pediatric cancer predisposing genes will be analysed in the germline data. In the Hemato add-on study, children with hematological malignancies will be additionally analysed for a panel of potentially relevant PID- and IBMFS-associated genes (separate informed consent requested retrospectively for already included patients, or prospectively for newly recruited patients). In addition, patients > 12 yrs. and parents who participate in NGS will be asked to complete questionnaires and interviews (children >12yrs).

Study burden and risks

Burden and risks: the burden for patients is minimal since for most of them no additional interventions are needed. In patients from whom a germline DNA sample is not available, venipuncture will be combined with a puncture as part of the cancer diagnostics/treatment. To minimize the chance of detecting *unsolicited findings* WES data will be analysed using a gene-specific filter of known pediatric cancer predisposing genes and a panel of potentially relevant PID- and IBMFS-associated genes.

Benefit: knowledge of a cancer-predisposing mutation in a child can be beneficial in terms of treatment choices, surveillance protocols, and genetic counseling of family members.

Group relatedness: pediatric tumors are genetically and biologically different form tumors in the adult population.

Burden of the psychosocial part of the study remains limited to the time needed to complete questionnaires and/or interviews.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)
Newborns
Premature newborns (<37 weeks pregnancy)

Inclusion criteria

Inclusion criteria for the main study PrediCT:
- Children (age < 19 years) newly diagnosed with cancer or neoplasms at the Princess Máxima Center (in a period
of three years)
- Written informed consent (by patient when aged 16 years or older, by patient and parent(s) when aged 12-16
years, by parent(s) when younger than 12 years)

Additional inclusion criteria for REFLECT:
- Consent for participation in PrediCT
- Written informed consent for REFLECT. This can include:
• Parents (of children 0-19 years)
• Children aged 12-16 years (additional consent by their parents needed)
• Children aged 16-19 years.

Additional inclusion criteria for the Hemato add-on study:
- Consent for participation in PrediCT
- Children (age < 19 years) diagnosed with hematological malignancies (including myelodysplastic syndromes) at the Princess Máxima Center
- Written informed consent for the Hemato add-on study (by patient when aged 16 years or older, by patient and parent(s) when aged 12-16 years, by parent(s) when younger than 12 years).

Exclusion criteria

Children and/or their parents who don't want to know the results of the DNA test (pediatric cancer gene panel
analysis).
Additional exclusion criterion for REFLECT: Insufficient proficiency in Dutch.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	21-09-2020
Enrollment:	843
Type:	Actual

Ethics review

Approved WMO Date:	08-07-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	08-04-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-07-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-03-2022
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 20548
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL70480.041.20
Other	Trial NL8456

Study results

Date completed: 02-05-2024

Results posted: 18-09-2024

First publication
18-09-2024