Medizinische Hochschule Hannover

KiTZ Hopp-Kindertumorzentrum Heidelberg
Deutsches Krebsforschungszentrum
Universitätsklinikum Heidelberg
Universität Heidelberg

ADDRess
Translational Research for Persons with Abnormal DNA Damage Response

**Krebsprädispositionssyndrom-Register 01**

Registerleitung:
Prof. Dr. med. Christian Kratz
Prof. Dr. med. Stefan Pfister

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Carl-Neuberg-Straße 1, 30625 Hannover

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Hopp-Kindertumorzentrum Heidelberg
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**Information for adolescents 12-17 years of age**

Liquid Biopsy as a part of

Cancer-Predisposition-Syndrome-Registry-01

Dear _____,

in conversation with your parents and your physician, you have just noticed that you and your parents are being asked to participate in a scientific project. These forms will inform you about the project. You can read them, think about it and discuss it with your parents and your physician whether you would like to participate.

You have a very rare kind of disease. It is still very much unknown in children and teenagers. That is why a number of physicians have joined forces to research this disease. This is only possible through a very large network of physicians because it is not easy to find out anything about rare diseases.

You already agree to participate in the Cancer-Predisposition-Syndrome-Registry-01.

In a further project we want to investigate, whether and when indications for cancer are presented in the blood. We want to identify cancer diseases as early as possible, which will eventually lead to milder and more successful therapies. Additionally we want to improve early detection strategies for patients with diseases as yours.

In this project we want to take blood from all participating children and adolescents every 6 months (which is equivalent to a tablespoon). If a blood sample is taken for your medical care anyway, the blood samples required for this project can be taken at the same time, so that we have to prick you as rarely as possible. The samples taken are first collected at the Children's Oncology Department of Hannover Medical School, then transferred to the Hopp Children's Tumor Centre in Heidelberg, where specific investigations are performed.

Your samples and your medical history will be treated confidentially and in accordance with the data protection process. This means, that only we can see your name in connection with your medical history and we will not tell your story in connection with your name or address. If we share our experiences in the treatment of your illness with other physicians (e.g. in a publication), your name and address will be deleted, i.e. it is not possible to see that you are meant.

We would be very happy if you would like to help us and other patients with this disease and we could analyze your samples. If you do not want to participate or if you want to withdraw your consent, this is not a problem. Your medical treatment will continue normally and for your best.

As soon as you are of legal age, we will contact you again to ask if you would like to continue participating in the study.

You can ask your physicians if there is something you do not understand. They will gladly help you.

Thank you very much.

Your team of physicians

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**Informed Consent for patients 12-17 years of age**

Liquid Biopsy as a part of

Cancer-Predisposition-Syndrome-Registry-01

_____ _____
Surname, first name of the patient Date of birth

_____
Treating hospital

I agree that information about my illness as well as blood samples as described in the information form, may be passed on to the Liquid Biopsy project as a part of CPS-R01 so that research can be conducted on my illness. The aim of the research is to learn more about the disease in the long term. With the knowledge gained in this way, it should be possible to treat those affected better in the future.

The study was explained to me personally and I read the information form. I had the opportunity to ask questions. I know that my participation is voluntary and that I can withdraw my consent at anytime without giving reasons and without any disadvantages. I understand that I will be contacted again as soon as I am 18 years old so that I can then decide whether I want to continue participating in the study.

**CONFIRMATION OF THE PARTICIPANT**

_____

Surname, first name of the patient

_____ _____

Place, date Signature of the patient

**CONFIRMATION OF THE ATTENDING PHYSICIAN**

I have discussed the Liquid Biopsy project as a part of CPS-R01 and the accompanying research including the patient information and the declaration of consent with the patient. All questions were answered comprehensively. I explained to the participant that participation is voluntary. I have obtained the patient's consent.

_____

Name of physician

_____ _____

Place, date Signature of physician

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**Information for parents/guardians**

Liquid Biopsy as a part of

Cancer-Predisposition-Syndrome-Registry-01

Dear Parents/Guardians,
The physician of your child has informed you that your child has been diagnosed with a cancer predisposition syndrome (CPS). One main feature of this genetic condition is an increased cancer risk.

You have already agreed to your child's participation in the Cancer-Predisposition-Syndrome-Registry-01.

In order to detect CPS-associated malignancies as early as possible and to improve the monitoring of the course of malignant processes, we want to support the establishment of the so-called Liquid Biopsy. This involves the detection of small fragments of the genetic information (DNA) of tumors and other biomarkers in blood.

Within this research project we pursue the following aims:

- We want to understand in which cases of CPS circulating tumor DNA and other biomarkers can be detected and whether liquid biopsy is suitable for the diagnosis, early detection and progression of tumors as well as a diagnostic tool for the follow-up care of cancer patients.
- We want to identify the occurrence of malignant processes as early as possible. By detecting tumors at an early stage, the intensity of therapy should be minimized in long term.
- By comparing the results with the early detection tests recorded in CPS-R01, we hope to be able to draw conclusions about the temporal relationship between markers measurable in blood and the occurrence of physical symptoms, radiological evidence of a tumor or changes in other laboratory values.

- We want to establish early detection strategies, which are characterized by high-effectiveness, low-invasiveness and therefore as uneventful as possible. This should lead to a greater willingness to undergo regular checks.

**Brief Overview**

**Current state of knowledge**: In recent years, it has become increasingly possible to detect smallest fragments of the genome of healthy cells, but also of tumor cells and other cancer-associated biomarkers in the blood. The analysis of this so-called Liquid Biopsy should make it possible to detect the development and progress of malignancies early and with as little invasiveness as possible. In the future, it is imaginable that this form of liquid diagnostics will also be used for therapy monitoring and aftercare. In addition, there are other markers measurable in the blood that can predict the presence of a tumor. This blood-based and less invasive form of cancer detection is particularly promising for patients with a cancer predisposition syndrome.

**Study design:** Within this study we are collecting blood of patients with underlying CPS every 6 months, to analyze the samples for freely circulating tumor-DNA. The results of these checks will be compared with the results of the screening tests recorded in CPS-R01.

**Procedures and processes**: Blood samples should be taken every 6 months and, if possible, as part of other diagnostic or routine blood draws that are normally completed for your child's medical care. For children, approximately 10 ml per blood sample is required, for adults - if possible - 45 ml of blood should be collected. The blood samples are processed at the Clinic for Paediatric Haematology and Oncology at Hannover Medical School and at the Hopp Children's Tumor Centre in Heidelberg. The findings are transferred to the CPS Registry. Since this is a long-term investigation that addresses the course of a condition over several years, the study has no defined duration.

**The Risks and Benefits of Participation**

**Expected individual benefit:**
Donating your child's biospecimen and medical data will not necessarily lead to a direct benefit to your child. Our analysis serves primarily as scientific research and is not intended as actionable conclusions for your health. Nevertheless, the research may lead to findings that may be of importance to your child's health. In the situation, when an analysis reveals evidence of a severe previously unknown condition, that can potentially be treated or prevented, we may want to contact you in order to give you this information (see below).

In case you do not wish to receive this type of feedback, please check the box containing "no" on the informed consent. Any time, you can change your decision for or against this feedback option by letting us know. However, please note that you may be obligated to disclose health related information that you receive through our registry, if you prefer this option, to other parties such as health- or life insurance companies. This may be a disadvantage for your child.

The statement above is also relevant to genetic analyses and the discovery of genetic conditions. Therefore, this information may be relevant for your child's family members and family planning.

In the long-term, biospecimen and data collected through our registry is meant eventually to improve the care of patients with cancer predisposition syndromes, which contains DNA repair defects (possibly including participants of the registry). For example, we would like to explore the role of regular evidence-based surveillance strategies and if they may be improved by using liquid biopsies.

**General Benefit of the Registry:**
Medical studies of this kind aim at a better understanding of the processes associated with disease development and improvement in diagnosis and care. Other patients with a cancer predisposition syndrome not participating in this research may benefit from our findings because our research aims at improving the care of all affected patients. Through the collection of biospecimen from individuals with a cancer predisposition syndrome, cancer research in general is advanced. There may be benefit for patients with cancer even in the absence of a cancer predisposition syndrome. We know that mechanism playing a role in individuals with a cancer predisposition syndrome may be relevant for cancer patients in general. In theory, it is possible that our research contributes to improve therapy and prognosis of cancer patients.

**Risks and Disadvantages of participation:**
We would like to collect approximately 45ml blood every 6 months. If possible, these blood draws should be taken as a part of your child's routine medical care. Apart from the complications that may arise with a blood collection, there are no other physical risks for your child.

Every ascertainment, storage, transfer of data is associated with the risk of breaching the confidentiality of the data (e.g. risk of identifying your person/information), which may be especially relevant for genetic information. It is impossible to exclude this type of risk entirely. This risk increases with the amount of connected data, especially if you are publishing genetic information in the internet on your own. Please see below regarding data and material security.

**Purpose of collecting biospecimen:**
The biomaterials are first prepared and stored at the Clinic for Paediatric Haematology and Oncology at Hannover Medical School, then transferred to Hopp Children's Tumor Centre in Heidelberg, where the analysis concerning tumor-DNA is conducted. The biospecimen will be stored for an unlimited time for research purposes.

**Protection of your biospecimen and data:**
The blood samples will be taken to the biobank of the Hanover Medical School and the biobank of the University of Heidelberg where they will be stored until the end of the research project. Clinical data will be stored on a server of Medical School Hannover. The initials of the first name and surname, the quarter and year of birth, and the sex are recorded. Full names or dates of birth are not stored. However, through the link to the CPS register, it may be possible for the registry team to identify your child. However, personal data can only be viewed by the collecting physician and the registry team. Your child's personal data will not be disclosed to third. All identifying information (name, date of birth, address, etc.) will be replaced by an identification code (pseudonymized).
Only after this process, biospecimen and data will be made available for research. Transfer of identifying information to researchers or others such as insurances und employers does not occur.

The encoded biomaterials and medical data can be transferred to universities, research institutes and researching companies, possibly also abroad, for more precisely defined medical research purposes

according to previously defined criteria. It is possible that our registry data will be connected to your child's data in other databases, in accordance with the law. When data is transferred abroad, it may not be possible to maintain the same high level of data protection as in Germany. Biomaterials and data issued to researchers may only be used for the predetermined research purpose and may not be passed on by the recipient for other purposes. Remaining material will be returned to the Hannover Unified Biobank or destroyed.
The prerequisite for the use of biomaterials and data for a concrete medical research project is, in principle, that the research project has been evaluated and approved by an ethics committee.
Publications are written in an anonymized fashion to prohibit identification of individual participants. This implies the situation, if data is entered into scientific online databases. A publication of your child's entire genetic information (genome) is impossible without your explicit written permission.

**Financial benefits to you or the biobank:**
You will not be paid for allowing us to collect and store your child's biospecimen and data. You will not receive financial or other compensation, should findings resulting from the research on your child's biospecimen become commercially valuable. With the transfer of the biomaterials to the biobank of Hannover Medical School or biobank of University of Heidelberg, they become the property of the CPS-R01 Registry of the German Society of Pediatric Oncology and Hematology. The biobank will only use the biospecimen for research purposes. You authorize the registry to use your child's data for research purposes. Your child's specimen and data will not be sold. However, the biobank can ask researchers for an expense allowance for providing specimen to collaborating researchers.

**Other Questions and Concerns**

**Is it possible that you will be contacted regarding the registry?**
On a regular basis, results from your child's medical visits are being forwarded to the registry team. In case of missing data, it could be useful that you are contacted at a later time point in order to request additional information or specimen. Also, this contact could occur to request your permission for connecting your child's data with other databases or in order to give feedback to you or your child's physician on findings that may be relevant to your child's health. You will not be contacted through the registry team directly but through your child's physician or the health care institution that cares for your child.

In case you do not wish to be contacted, please check the box containing "no" on the informed consent.

**What is your right of withdrawal from the registry?**
Any time and without justification and disadvantages you may withdraw your consent that allows us to use your child's biospecimen and data. In case you withdraw your consent, you may decide whether your child's specimen should be destroyed or be anonymized. In the latter situation, we delete the identification code that allows us to connect a specimen to your child. One has to keep in mind that such an anonymization process cannot entirely exclude the small chance that a specimen can be tracked back to your child. Deletion of data may be limited technically feasibility, however. You can also decide whether your child's already collected data should be deleted or may be further used in anonymized form. Data can only be deleted under the conditions of Art. 17 DSGVO. As soon as the purchase of the biomaterials and other data relating to your child's person has been deleted (anonymization), destruction is no longer possible. In addition, data from analyses already carried out can no longer be removed.
In case you would like to withdraw your consent, please contact:

Christian P. Kratz, MD, Director
Pediatric Hematology and Oncology
Hannover Medical School
Carl-Neuberg-Str. 1
30625 Hannover
Germany
Phone: +49 (0)511 532 6711
Fax: +49 (0)511 532 9120
Email: kratz.christian@mh-hannover.de

**Is your participation voluntary?**
Your child's participation in this registry is voluntary. In case you prefer not to participate, your child will experience no disadvantage.

**Where can I get additional information?**
Should you have additional questions, please contact your child's physician prior to giving your consent. You can also contact Prof. Kratz or Prof. Pfister. Information regarding findings can be found on www.krebs-praedisposition.de.

We are happy to address your questions.

Sincerely

Christian Kratz, MD Stefan Pfister, MD

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Im Neuenheimer Feld 580, 69120 Heidelberg

**Informed consent for parents/guardians**

Liquid Biopsy

As a part of Cancer-Predisposition–Syndrome-R01

_____ _____
Patient (Last Name, First Name) Date of Birth (dd/mm/yy)

_____
Treating Hospital

I have read the information sheet and have had the opportunity to ask questions. My questions were answered comprehensively and comprehensibly. I know that my child's participation is voluntary and that I can retract my consent anytime without justification and without disadvantages. I had enough time to consider my decision to my child's participation and make my own decision.

I give my informed consent that my child's biospecimen as well as medical information as described in the information sheet are sent to the CPS-R01 to be used for medical research purposes, especially for the Liquid Biopsy project.
I also give my consent that the specific scientific projects, for which the biospecimen and medical information will be used are without restriction.

I transfer ownership of my child's biospecimen to Medical School Hannover.

I approve that I may be contacted at a later point in time for the following reasons, please check the boxes with "yes" or "no":

- For the collection of additional medical information/biospecimen □ yes □ no
- If further consent is necessary for the use of your child's medical information □ yes □ no

- If our research identifies actionable findings that may be relevant to your child's health □ yes □ no

This contact will occur through the institution that collected my biospecimen and data **or** by the following physician (please give this information to the physician if the latter is preferred):

Physician's name and address: _____

**Data Protection Statement**

**I approve that the registry team conducts the following actions (also described in the information sheet):**

**- Collects and stores the initials of my child's first and last name as well as the quarter and year of birth**

**- Collects and stores identifying materials and information related to my child's health**

**- After the collection, the biospecimen and data will be coded to de-identify the data to be used for medical research purposes**

**- Coded non-identifying information will be used for scientific publications and online databases**

**My child's biospecimen and data may be used for medical research purposes for an unlimited time period. In a non-identifiable manner, biospecimen and data may be transferred to universities, research institutes/companies for the purpose of medical research. This may include international research projects.**

**I was informed that I may withdraw my consent to my child's participation in the registry anytime without justification. In case of withdrawal, I may request that any remaining biospecimen and data be destroyed, deleted or anonymized.**

**Please note: If an analysis has been completed, the data cannot be removed.**

I have the right to be informed about the stored personal data concerning my child (Art. 15 DS-GVO). If I discover that incorrect personal data of me are being processed, I can demand correction (Art. 16 DS-GVO).

I have the right to demand the deletion of personal data if certain reasons for deletion exist. This is the case, for example, if the personal data are no longer necessary for the purpose for which they were originally collected or processed, or if I revoke my consent and there is no other legal basis for the processing (Art. 17 DS-GVO). Furthermore, I have the right to limit the processing of my child's personal data (Art. 18 DS-GVO), to data transferability (Art. 20 DS-GVO) and a general right of objection (Art. 21 DS-GVO).

Data controller: Christian Kratz, MD
Pediatric Hematology and Oncology, OE 6780
Carl-Neuberg-Straße 1
30625 Hannover
Germany

If I have any questions or if I have the opinion that the processing of my child's personal data is not lawful, I have the option of contacting the MHH data protection officer:

Datenschutzbeauftragte der MHH
OE 0007
Carl-Neuberg-Straße 1
30625 Hannover
Germany

I have the right to complain at the supervisory authority if I believe that the processing of my child's personal data is not lawful.
The address of the supervisory authority responsible for the MHH is:

Die Landesbeauftragte für den Datenschutz Niedersachsen
Prinzenstraße 5
30159 Hannover
Germany

I am aware that the data protection regulations set out in the information letter also applies.

I have received a copy of the information sheet and the signed informed consent. The original is kept in the patient's medical record.

In addition, I was orally informed about the study.

**CONFIRMATION OF PARENTS/GUARDIANS**

_____
Name of patient

_____ _____
Place, date Signature of parents/guardians

**CONFIRMATION FROM THE ATTENDING PHYSICIAN**

I have discussed the Liquid biopsy project as a part of CPS-R01 and the accompanying research including the patient information and the declaration of consent with the custodians. All questions were answered comprehensively. I have explained to the parents/guardians that participation is voluntary.

_____
Name of physician

_____ _____
Place, date Signature of physician