

Information for Parents
on the scientific study
Identifying the Causes of Rare Diseases
using Genome-Wide Sequencing

Dear Parents!

Thank you for taking the time to read this information!

We invite you and particularly your child to participate in a scientific study on rare diseases. In the course of inpatient care or outpatient presentation, data about your child's health will be collected (hereinafter referred to as "patient data"). In addition, biosamples (body fluids or tissue) may be collected during a blood sampling or during a surgical procedure. Information on the health status of parents and other family members can also be important for understanding diseases. This data is also referred to as "patient data" in the following, even if you as parents or relatives are not yet patients of the University Hospital.

Klinikum rechts der Isar
Public Law Institution

Institute of Human Genetics

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„Patient data“

Patient data is all information about you that is collected on the occasion of examination and treatment or that has already been collected earlier. Examples of patient data are: data from doctor's letters, your entire medical history, the results and findings from current and previous medical examinations carried out on you (such as ultrasound examinations, EMG, X-ray or nuclear spin/magnetic resonance imaging examinations). Patient data also includes the results of current and previous laboratory tests of blood, urine, nerve fluid or tissue samples, including tests of your genetic material (for genetic diseases or predispositions) or the genetic material of tumours (for genetic changes present in cancer cells).

Medical research is necessary to continuously improve the early detection, treatment and prevention of (genetic) diseases. The knowledge we gain from your patient data and biosamples can contribute a great deal to this.

For this reason, we ask our patients and therefore also you and particularly your child for your willingness to provide us with certain patient data and biosamples within the framework of this study and for other medical research purposes.

If you and your child give your consent, the patient data of your child will be stored in a specially protected database of the Klinikum rechts der Isar of the Technical University of Munich. The quality-controlled long-term storage of the biosamples donated is performed in the centralised bio- and databank of the Klinikum rechts der Isar.

Your consent to the use of your child's patient data and biosamples for medical research is voluntary. If you do not want your child to participate in our study, if your child refuses to participate, or if you or your child wish to withdraw consent later, neither your child nor you will be disadvantaged in any way.

If you do not fully agree with the type and duration of the use of your child's patient data and biosamples described below, or if your queries have not been answered satisfactorily, you should not give your consent.

Within the framework of this research project, we adhere to the requirements of the Genetic Diagnostics Act (GenDG).

In the following, we inform you about the objectives of this research project, the procedures and the measures to protect your child's personal data and biosamples, so that you can make an informed decision.

Rare Diseases

A disease is considered rare if it affects **no more than 5 in 10,000** people. Most rare diseases are hereditary, so they often manifest at birth or in early childhood. However, some of these diseases only manifest in later childhood or adulthood.

Rare disease-causing changes (so-called genetic variants, formerly mutations) have already been found in many different hereditary dispositions (genes). However, many disease-causing genes are still unknown. The severity, course, and treatment of a rare disease often depend on which gene is affected or which genetic variant is present. In order to create a better basis for future treatment options, it is necessary to learn more about the genetic (i.e. hereditary) causes of rare diseases.

The investigation of genetic changes connected to the specific disease patterns is fundamental for new approaches for diagnostics and treatment. We would like to investigate either the entire genetic material (the genome) or all protein-coding regions (the exome) of patients and their relatives or families, in which the cause of disease has not yet been identified in the investigations carried out to date. In the future, our scientific study should provide the foundation for new diagnostic methods for patients with rare diseases.

Aim of the Study

The aim of our project is to find out which hereditary (or genetic) changes lead to certain rare diseases. Your child's patient data and biosamples will only be made available for medical research; financial interests will not be pursued. The sole purpose of medical research is to improve the detection, treatment, and prevention of diseases.

Study Procedure

In order to systematically investigate the changes in the genetic material (or the genes), we ask adults and children who have a rare disease, as well as their possibly unaffected relatives/family members, to donate blood samples for medical research. The interpretation of genetic changes is improved if the parents and/or other relatives of the affected child are also examined.

The aim of the research project is to examine the entire genetic material (the genome) or its protein-coding regions (the exome) of all biosample donors - i.e. children and adults - for disease-causing changes that could be associated with the respective rare disease. The significance of changes in the genetic material can then be confirmed by examining other biosamples provided, such as messenger molecules of the genetic material (the so-called ribonucleic acids, RNA), proteins or metabolic products, which can be isolated from blood, but also from tissues.

In order to assess whether a change found in the genetic material causes the disease or not, it is usually necessary to examine the genetic material of the parents of affected individuals and the genetic material of other family members. Therefore, we also address you as parents, and we ask you to also refer your family members to our study. You and other family members will then be informed in the same manner and can participate in our study even without being affected by a rare disease personally. This also means that the data collected will additionally be valuable as comparative data for research into rare diseases in other people and will be used for this purpose.

What are we asking you?

- Children, adolescents, and adult patients as well as relatives will be informed verbally and in writing by the treating physicians at the hospital in a manner appropriate to their age. After sufficient time for reflection, we ask you for your written consent for your child's participation in our study "Identifying the causes of rare diseases using genome-wide sequencing".
- Based on your child's patient data (see also box on p.1), the current state of health is described as accurately as possible. Selected patient data of your child will be entered in **encrypted form** into our study database at Klinikum rechts der Isar. Encrypted means that neither the name nor the initials nor the date of birth are used for encryption, but only a **letter-number code**, the so-called pseudonym (see also under "[Who has access to your data and biosamples and how are they protected?](#)").
- Blood will be taken from all study participants in order to examine the hereditary substance (genetic analysis) and - depending on the clinical picture - also to carry out further laboratory tests. Depending on which disease or altered hereditary disposition is suspected in your child, we may ask you for the following additional biosamples for better examination. Your attending physician will discuss with you any additional biosamples that may be required:
 - Fingernail sample
 - Urine sample (spontaneous urine)
 - 24-hour urine sample
 - Saliva
 - Skin biopsy (tissue sample from the skin only in children and adolescents of whom a skin sample is taken anyway as part of the medical diagnosis or treatment, no additional sample is taken)
 - Muscle tissue (only if a muscle sample is taken anyway as part of the medical diagnosis or treatment, no additional sample is taken)

- Cerebrospinal/nerve fluid (in children and adolescents only as an additional sample up to a maximum of 5 ml during a routine puncture that is being performed anyway)
- In addition, we ask you to allow us to use biosamples such as small tissue parts and/or body fluids that have already been taken from your child for diagnosis or therapy and are no longer needed (residual materials) for our study. These may be blood, saliva, nerve fluid or tissue taken during an operation or biopsy.
- The same rules and principles as described above apply to the handling of your child's biosamples, their pseudonymisation (encryption) and the analysis results obtained from the biosamples as have already been described above for your child's patient data.

Risks

Identification of the person of your child: Whenever data is collected, stored and transmitted in the context of research projects using patient data, there is a potential risk of traceability to the person by obtaining of additional information, e.g. from the internet (public databases) or social networks (e.g. Facebook). The risk of traceability is generally increased in the case of genetic data. The genetic information of a person can usually be linked unambiguously to this person, i.e. also to your child. This is especially the case if you or your child publish information by yourself on your hereditary constitution (i.e. genetic data) and other health data, e.g. for genealogical research via the internet.

Blood sampling: The risks for affected children are usually very low and do **not** increase the usual risks of a routine blood withdrawal. The additional blood volume for the analysis of the genetic material is only a few millilitres (less than a teaspoon). Depending on the disease or altered genetic changes we suspect in your child, further blood samples may be needed for more detailed laboratory tests. However, the total amount of blood taken will not exceed 25 ml (about two tablespoons). The physicians performing the collection will ensure that **this collection does not cause any additional health risk to your child.**

The usual risks of blood sampling include slight pain at the puncture site and the possibility of a bruise (haematoma) around the puncture site, which may be visible for a few days. In extremely rare cases, a blood clot (thrombosis), localised inflammation and/or blood poisoning may also occur. Even more rarely, permanent damage to nerves can occur with subsequent sensory disturbances or even paralysis.

Risks associated with obtaining other biosamples that may be required:

Urine sample/saliva sample: The donation of a urine sample or a saliva sample is not associated with any additional risks for your child.

Tissue sample: The procedure is performed under local anaesthesia *only in the context of treatment* if the collection of a tissue sample (skin, muscle) **is planned anyway**. The skin can be punched out with a hole punch (punch biopsy). Larger tissue samples are taken through a spindle-shaped incision with a scalpel. *The risks involved are explained separately before the skin biopsy necessary for treatment or diagnosis.* As a rule, taking small skin samples is free of complications. However, despite all the care taken, complications can occur, e.g. a bruise (a haematoma) can appear around the incision site. In rare cases, there may also be soft tissue damage and nerve damage in the collection area, localised inflammation and/or blood poisoning. Permanent damage to nerves with subsequent sensory disturbance or even paralysis is even rarer.

Nerve fluid: Spinal fluid (liquor, cerebrospinal fluid) can only be taken as an additional sample of a maximum of 5 ml during a puncture that **is planned anyway** as part of the medical treatment/diagnosis. *The associated risks will be explained separately within the framework of the routine puncture necessary for treatment or diagnosis.* The physicians performing the collection will

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ensure that the collection of additional nerve fluid **is not associated with any additional health risk for your child.**

Who receives ownership of your biosamples?

With your consent to the collection, storage and scientific use of your child's biosamples, you simultaneously transfer the ownership including all rights of use to the Klinikum rechts der Isar of the Technical University of Munich.

What are the benefits and consequences of participating in the study for your child?

By providing the patient data of your child, you help to improve research on rare diseases and contribute to better help of people with symptoms similar to your child's in the future.

Personally, you and your child can usually expect no immediate benefit or advantage in clarifying the current complaints or the disease of your child.

However, in individual cases it is possible that we will find indications of the possible genetic cause of your child's disease and would like to inform you about this. In the consent form you have the choice of allowing or denying such communications to you and your child.

Since our study examines the entire genetic material (or genome) or larger sections of it, there is also the possibility of discovering so-called additional findings about which we can inform you. This means, for example, changes in the genetic material that could potentially be of medical importance for you and your child or its descendants (e.g. an increased risk of cancer), but which are **not related to** the rare disease. The evaluation of research results could also lead to the strong suspicion of a serious, possibly previously unrecognised disease, which could be treated or the outbreak of which could be prevented. These results will only be communicated to you and your child if you indicate in the consent form that we may contact you in this case.

Please note that the health information you receive through such feedback is not sufficient on its own, but usually requires further diagnostics by the treating physicians of your child.

We would also like to point out that you may suffer disadvantages as a result of these test results, which are confirmed in further diagnostics (e.g. before taking out a life insurance policy). Since information from the genetic material of your child is also used for our scientific study, this may relate to your and your child's hereditary (or genetic) predisposition to certain diseases. Information from your and your child's genetic background can also have an impact on other family members and their future family planning. You can change your decision for or against a feedback of study results at any time by informing us.

Who has access to your data and biosamples and how are they protected?

Access, use and protection in this study

The data collected and biosamples obtained in this scientific study will only be shared and analysed in a pseudonymised (i.e. encrypted) form. All patient data can only be linked to your person by the members of your personal treatment and diagnostic team. Furthermore, the patient data and biosamples of your child will only be shared with others if you have given your permission. The patient data and biosamples of your child are used exclusively for medical-scientific purposes; they will not be sold!

The genetic material is isolated from the blood sample of your child either directly at your care centre or centrally in the molecular genetics laboratory of the Institute of Human Genetics at the Klinikum rechts der Isar of the Technical University of Munich. In addition, all biosamples that are not immediately analysed are stored in the biobank of the Institute of Human Genetics at the Klinikum

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rechts der Isar in a quality controlled manner. The genetic analyses (sequencing) and biochemical examinations are carried out at the Institute of Human Genetics of the Klinikum rechts der Isar and, within the framework of a cooperation, in a genetic research laboratory at the Helmholtz Zentrum München.

The data obtained from the study participants is stored and analysed on a secure local database on the server of the Klinikum rechts der Isar at Helmholtz Zentrum München and at the Klinikum rechts der Isar. In addition to the genetic analysis data, a small amount of patient data (e.g. the sex and age of the study participant, the presumed mode of inheritance and specifically selected individual additional study data) is also stored in the corresponding database. The complete patient data and diagnostic findings of your child, as well as details on the manifestation and severity of the disease, which are documented with a maximum of 20 standardised terms, remain in the database at the Klinikum rechts der Isar of the Technical University of Munich.

The patient data and biosamples of your child shall be stored and used from the time of your consent until your child reaches the age of adulthood, unless you or your child withdraw the consent earlier.

When your child reaches the age of 18 years, he/she must be contacted first (if necessary with your help) in order to be informed about the study participation as a person of full age and to give a declaration of consent for the further use of his/her patient data and possibly still available biosamples on his/her own responsibility. If your child is not capable of giving consent when he or she reaches the age of adulthood, consent can only be given by a guardian appointed by the guardianship court.

If your child cannot be reached for his or her own consent when he or she reaches the age of 18 years, the period of use agreed here will expire. After expiry of the period of use (attainment of the age of 18 plus one year), your child's biosamples will be destroyed and his or her patient data will be deleted. If deletion of your child's patient data is not possible or not possible with reasonable technical effort, they will be anonymized by deleting the identification code assigned to them.

Sharing of data and biosamples beyond this study

In addition, by checking the corresponding box in the consent form, you can decide whether the pseudonymised patient data, analysis data and biosamples of your child may also be shared with other scientists and centres for rare diseases inside and potentially also outside the European Union (EU) for scientific purposes. It should be noted that transfer to recipients in countries outside the EU is only permitted if one of the following conditions is fulfilled:

- The European Commission has ascertained **an adequate level of data protection** in the respective country, **or** (if this has not been done)

The Klinikum rechts der Isar signs contractual data protection agreements with its research partners that have been decided or approved by the European Commission or the competent supervisory authority. In this case, you can obtain a copy of these data protection clauses from your local study management.

Irrespective of your choice, you are of course permitted at any time to ask the study personnel which laboratories and researchers may have been involved in further scientific investigations.

Medical confidentiality and the applicable data protection regulations must be strictly respected by these external laboratories and researchers. In addition, only pseudonymised data and biosamples are shared and analysed. Parts of names, initials or dates of birth will not be used for pseudonymisation, but only **a number-letter code** (as described above).

A direct assignment of data or biosamples to your child is usually only possible if the assignment key between coding and person is known. The assignment key used for this project is only known to your supervising physician and the local study management of the project "Identifying the causes of rare

diseases using genome-wide sequencing". **Third parties do not have access to original documents or medical files of your child.**

The publication of scientific results also takes place exclusively in a way that does not allow any information to be traced back to you personally; furthermore, the publication of the complete genetic information (the genome) is excluded unless you have given your written consent. However, it is possible to include the entire genome or certain sections of it in specially protected databases that are inaccessible to the general public if you have given your consent. One such database is the German Human Genome Phenome Archive (ghga.dkfz.de).

Recontacting and communicating of results

We may like to contact you and your child again for the following reasons: First, we may want to obtain more information about your child's condition or ask for additional biosamples. Second, we may want to inform you of study results that could be of medical relevance to the rare disease of your child. This also refers to possible additional findings (see further above under "[What are the benefits and consequences of participating in the study for your child](#)"). If you agree to be recontacted, you should check the appropriate box in the consent form. You can revise your decision for or against recontacting at any time by notifying us.

All study and research results that we share with you in the context of a new consultation are only preliminary and do not represent valid genetic findings. In coordination with you, the caring doctors of your child can arrange for a renewed quality-checked human genetic analysis on the basis of the German Genetic Diagnostics Act (GenDG). We will be happy to help you arrange this.

How long is your consent valid?

Your consent to the obtainment of patient data and to the collection of biosamples of your child is valid for a **period of five years** from the date you signed your declaration of consent - unless you withdraw it to a previous date (see below). This means that - with prior notice - patient data and, if necessary, biosamples may be obtained from your child again in the next five years without needing to sign a new consent form at the Klinikum rechts der Isar of the Technical University of Munich.

Should your child visit the Klinikum rechts der Isar of the Technical University of Munich again after five years, we will possibly ask you for your consent again.

However, the utilisation of your child's patient data collected and the biosamples obtained from the time of your consent will remain permissible for beyond the period of five years. The data generated will improve medical patient care. In this sense, no end of the study can be defined and the data will continue to be used for this purpose.

What does your right of withdrawal mean?

Your consent is voluntary!

You can withdraw your consent to the further collection and scientific use of your child's patient data and biosamples at any time without providing reasons and without any disadvantage for you or your child. A withdrawal always refers only to the future use of patient data and biosamples. Information from analyses that have already been carried out or studies that have already been published cannot be subsequently removed.

In the case of a withdrawal, the biosamples provided for medical research will be destroyed and the patient data of your child stored according to this consent will be deleted. If deletion is not possible or not possible with acceptable technical effort, your child's data will be anonymised by deleting the

identification code assigned to the data. However, the anonymisation of the patient data can never completely exclude a later assignment of - in particular genetic - information to your child via other sources.

For a withdrawal, please contact the treating physician of your child:

name: _____ phone: _____

or contact the study office of the Klinikum rechts der Isar of the Technical University of Munich, tel: +49 89-4140-6381.

Further information on data protection

The legal basis for processing the above-mentioned personal patient data is your informed consent (Art. 6 para. 1a and Art. 9 para. 2a of the General Data Protection Regulation [DSGVO]). Data storage is subject to the requirements of the applicable data protection laws. The international guidelines for Good Clinical Practice (GCP) are fully respected in our study.

You and your child have the right to withdraw your consent. In this case, the personal data of your child will be deleted. If deletion is not possible or not possible with acceptable technical effort, the personal data of your child will be anonymised by deleting the identification code assigned to it. This does not concern the lawfulness of the processing of these data until the time of your withdrawal.

You and your child can request information from the Klinikum rechts der Isar of the Technical University of Munich about the data stored of you within the scope of the legal requirements; if incorrect personal data is processed, you and your child have the right to request correction. You can also request the deletion of personal data or the restriction of processing or data transfer.

If you have any questions about the progress of the study and the processing of your data, you are welcome to contact the study management at the Institute of Human Genetics (contact via: sekretariat.ihg@mri.tum.de, phone: +49 89 4140 6381).

The data controller within the meaning of the GDPR is **Klinikum rechts der Isar der Technischen Universität München**, Anstalt des öffentlichen Rechts, Ismaninger Straße 22, 81675 München, Tel.: +49 89-4140-0 or e-mail: vorstand@mri.tum.de. The Klinikum rechts der Isar of the Technical University of Munich has appointed a data protection officer, whom you can contact with any concerns about your patient data or with a report about data protection irregularities. The contact details are as following: **Klinikum rechts der Isar der Technischen Universität München, Stabsstelle Datenschutz, Ismaninger Straße 22, 81675 München, phone: +49 89-4140-0 or E-Mail: datenschutz@mri.tum.de.**

You and your child also have a right of complaint with any data protection supervisory authority. You can find a list of the supervisory authorities in Germany at:

https://www.bfdi.bund.de/DE/Infothek/Anschriften_Links/anschriften_links-node.html

The data supervisory authority responsible for the Klinikum rechts der Isar of the Technical University of Munich is:

Der Bayerische Landesbeauftragte für den Datenschutz,
Postfach 22 12 19, 80502 München, E-Mail: poststelle@datenschutz-bayern.de

If you have any questions about the research project or what it means for you and your child, please do not hesitate to contact us at any time.