Information about participation in clinical, immunological and molecular genetic research

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Dear Ladies and Gentlemen, Dear Parents /Guardians,

You or a relative are currently under medical examination or treatment for a suspected or known disease of the immune system, or you are considering donating biomaterials for research purposes. In order to examine how the immune system of patients with an immune defect presents we compare their samples with samples from immunologically healthy controls (e.g. family members) or persons with a different disease.

The mission of the immune system is to defend against pathogenic germs, i.e. infectious agents. However, clinical experience shows that the immune system does not perform this task with equal efficiency in every human being; some people are more prone to infection, i.e. they have more and / or more severe infections than others. The causes for this are complex and among other things, the genetic endowment of each individual can play a major role. There are many open questions in this context which are therefore subject of medical research and are also addressed by our research groups.

Goals of our research projects

With our current research projects we pursue the following goals:

1. To characterize disturbances of the immune system, which lead to an increased susceptibility to infection or to a malfunction of the immune system.
2. To gain a better understanding of the function of the immune system through the identified disorders of the immune system.
3. To find changes in the genetic material that may be the underlying cause for these disorders.
4. To be able to make more accurate and earlier predictions about who is at increased risk of developing a genetic disorder of the immune system or of passing on such disease to its offspring (improved genetic diagnosis).
5. To gain insights into hitherto unknown defects of the immune system.
6. To lay the foundations for improved treatment of diseases of the immune system.
7. To better understand autoimmune diseases or cancers that may be associated with genetic defects of the immune system.

Such research is only possible if biomaterials such as blood or tissue are available. These biomaterials are then used for scientific investigations.

With this in mind, we ask for your general willingness to support this research by providing blood and / or other specimens as further described below. Details will be explained to you in case you are interested in participating. We point out the following in advance:

1. Participation is voluntary.
2. It may be that you have no personal benefit from participating, but that the knowledge gained may benefit other people in the future.
3. You can withdraw from participation at any time.
4. If you are undergoing treatment as a patient, you are expressly assured that treatment of your condition will in no way depend on your willingness to participate in our research project or not.

Procedure and possible scope of your participation

Sample collection

If you decide to participate, a single time blood sample of approx. 9 ml up to a maximum of 45 ml (for underage individuals only as far as international standards permit) will be taken. If possible, this will be done within the scope of a medically necessary blood drawing, to avoid additional stinging caused by the study. To carry out certain investigations, which are not intended for each subject, the maximum amount of blood from full-aged study participants - at the discretion of the treating physician – may be up to 80 ml (for comparison: during a usual blood donation, 500 ml of blood are taken at once). The collection of a few drops of capillary blood from e.g. the fingertip could also be done for certain issues. From the blood, certain constituents, e.g. cells, the serum and the antibodies contained therein will be isolated for scientific studies, analyzed and, if necessary, frozen (item 1, informed consent). In our scientific analyzes, we examine e.g. the incidence and frequency of certain cells, their function and their cellular constituents (such as proteins). For some questions, we also use your cells to create permanent cell cultures. This helps us to carry out our scientific investigations with little sample material.

If you approved for genetic analysis, the DNA is purified to examine the genome. In the context of these genetic studies, individual genes, which among others play an important role in the immune system, are analyzed (item 2, informed consent). If appropriate, analyzes are also carried out on the whole genome. In individual subprojects, this will include also epigenetic analyses. Epigenetics is a response to environmental stimuli that also affects genetic information (for example, by altering the activity of certain genes) without altering the DNA sequence (item 3, informed consent).

In addition, depending on the concrete research project, we will sometimes ask for further samples, such as saliva, stool or other body fluids that are not taken invasively.

In case of a medically necessary surgical removal of tissue / organs (such as lymph nodes, tonsils, spleen) we would, with your consent, investigate material that is not needed for diagnostic purposes (so-called residual material), in the context of above mentioned goals (item 4, informed consent).
If biopsies are taken as part of your treatment, we will ask where appropriate for skin, bone marrow, lung, bowel, mucosa or other samples for scientific investigation (item 5, informed consent). This may mean that through additional measures slightly more material will be collected for our research purposes than is needed for your treatment..
You will receive a separate information and consent form prior to each intervention. Here, we only ask for your general willingness to provide us with these samples for scientific purposes. Solely study-related additional invasive measures are not carried out on minors.

The above-mentioned scientific analyses will be performed on all kinds of samples.

If you have given us your consent, we may contact you again later, to request another sample to conduct additional analyses or to obtain further information. For some studies, we may ask you to complete questionnaires; their evaluation can help us to better classify our scientific findings (item 6, informed consent).

Pseudonymization

The encoded (for example by patient identification number of the University of Freiburg) sample is sent to the research laboratory of the Center for Chronic Immunodeficiency (CCI) at the University Hospital Freiburg and there receives a new identification number for pseudonymization (first peudonymization step). This is a randomly-generated six-digit code. All other data (such as clinical data, laboratory data, if necessary data from questionnaires), which are also necessary for this research purpose, are available to the researcher only in pseudonymised form (with the respective identification number). An allocation of the research data to a specific person is therefore not possible for the researcher. Only the supervising medical staff and individual employees of the respective research project who are responsible for the project can assign the code to the affected person himself. The latter is e.g. necessary, to inform the subjects about the results of our research or to be able to assign subsequent supplementary examinations, if desired. The allocation is stored in a protected database with password secured access.

Our research project is geared to run over a longer period of time. If you are interested, we will gladly explain the results of our research and answer your questions. For this purpose, please send an e-mail to the study director Prof. Bodo Grimbacher or Prof. Klaus Warnatz.

Samples, research data and information (eg clinical data, laboratory data, questionnaires, if applicable) will be additionally pseudonymised in a second step (double-pseudonymised) before transferring to cooperating research institutes (item 9/10, informed consent).

The results of this research project as well as possibly the clinical and laboratory data and evaluated questionnaires can be presented and published in lectures, medical journals, scientific papers or at congresses. In addition, raw data generated in pseudonymised form can also be published in databases. In case of publication of these results/data, they will be additionally pseudonymised (triple-pseudonymised). By your signature in the declaration of consent you agree with the publication of the results/data.

Benefit

The above described examinations are intended to expand our knowledge of the functioning of the immune system. Occasionally, so-called incidental findings occur in scientific investigations, i.e. medical results that were not expected at first. If you wish to be informed about these incidental findings, you can vote Yes in the consent form (item 8) otherwise you will not be notified of these incidental findings.

If you or your child suffers from an immune deficiency, you should not assume that the gain in knowledge will directly benefit you, your child, or any other family member. However, the following could be of interest to you:
- The possible information that a specific change in the genetic material is the reason that you or your child have an immune deficiency.
- If a specific cause of your health disorder is found, it could be used to develop new and better treatment options for future patients with the same or a similar disease.

If you participate in the research project as an immune-healthy person, the following could be important to you:
- The investigation may detect a normal function of your immune system.
- Your participation may possibly provide information about personal health risks that you may use for your personal life-planning, but that may also for example have to be disclosed to an insurance company.

No compensation will be made for donated biomaterials (e.g., blood, tissue samples). Should a commercial benefit be obtained from our research, you will not be involved. With your consent, you waive the economic exploitation rights (in particular patents) on the samples obtained from you, the data generated from them, and the copyrights of the research results.

Risks and possible consequences of the investigation

The examination of your immune system poses no direct risks. However, reddening, swelling, pain or inflammation of the puncture site may occur as part of blood sampling and biopsies. If you have consented to the genetic testing, the genetic code (DNA) will be examined from you and, if applicable, your relatives during this study. You should be aware that knowing the genetic origin of a disease could have consequences for your future life. In a family examination, information about parenting becomes apparent. In doing so, aspects of adoption and paternity can be touched. It is our policy not to share such information with you unless you request it or when there are direct medical or reproductive consequences for you or your family.

Storage and use of sample material and research data

The samples or the remaining sample material and/or components derived therefrom and/or permanent cell cultures and tissue samples are kept for an indefinite period, also in the interest of the patients. They can be used in the future for specific scientific investigations relevant to the field of immunodeficiency, if for example new or improved methods or techniques are available,

However, you can withdraw your consent at any time and request that these samples be destroyed. The same applies to cells isolated from the samples, derived materials such as RNA, proteins or possibly even genetic material (DNA), permanent cell cultures and preserved tissue samples.

The research data and, in this context also information (such as clinical data, laboratory data and questionnaires) will also be kept for an indefinite period of time unless you withdraw your consent.
It is also intended to use the samples and information obtained, if applicable, for joint cooperative research projects in Germany and abroad with German and foreign research partners, such as state and private institutes, research centers or pharmaceutical companies, also possibly for commercial purposes. For this purpose, the samples - and possibly also information about the samples/subjects (such as clinical data, laboratory data, questionnaires) are made available to these research partners in double pseudonymised from, only (item 9/10, informed consent).

There is also the possibility that in the aforementioned research projects no longer required sample material and derived components, permanent cell cultures and tissue samples are transferred to and stored in the CCI Biobank of the University Hospital Freiburg. From there, it may be made available to other researchers in Germany and abroad. If you are interested, you will be informed about this more precisely and your agreement would be documented separately.

Confidentiality

In the event that the results of these research examinations (including clinical data, laboratory data, questionnaires) are passed on to third parties such as academic colleagues or pharmaceutical companies and/or are published in medical journals, at congresses or in any other form, we explicitly assure that the participants in the investigations cannot be identified by third parties.
We will **not** share information about you or your family with insurance companies or employers.

Reaching the age of majority

Minors who qualify as participants in any of the research projects addressed here are represented by their guardians. From the age of 14, their personal consent to participate is also required. Upon reaching the age of majority, these persons will again be informed personally about our research projects and the willingness to participate further will be queried again by means of patient information and informed consent.

Problems or questions

If you encounter any problems or questions concerning the research investigation, your rights as a participant or in connection with a study-related injury, you can contact the principal investigators Prof. Bodo Grimbacher or Prof. Klaus Warnatz. In their role as study directors, they are also responsible for data processing.

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Withdrawal of consent

You may withdraw your consent to the future use of your (or your child's) biomaterials and data at any time, without stating reasons, and without adverse consequences for you or your child. However, the legality of the use of the samples and data until the revocation remains unaffected. In case of withdrawal, the biomaterials are destroyed and the data is deleted. However, data from already completed analyzes cannot be removed.
To withdraw from the study, please direct your revocation of consent by e-mail or by post to one of the above-mentioned addresses of the study directors Prof. Bodo Grimbacher or Prof. Klaus Warnatz.

Privacy information

The data processing is carried out for the purpose of the mentioned research projects on clinical, immunological and molecular genetic issues. The legal basis of the data processing is the consent expressly granted by you with your signature in the declaration of consent.

If data are passed on to third parties within the scope of our research activities, we point out that the

data transfer occurs also to countries with different levels of data protection (EU countries where the GDPR applies, countries outside the EU, for which an EU-Commission adequacy decision or appropriate/adequate guarantees exist, as well as countries for which no such adequacy decision or appropriate/adequate guarantees exist) and therefore may be associated with certain data protection risks. Insofar as personal data (even if they are pseudonymised) are transmitted to bodies outside the scope of the EU GDPR, it cannot be ruled out that the same sensitivity to privacy issues exists as in Europe, even if recipients are personally familiar with confidentiality requirements. Furthermore, it cannot be ruled out that, in the case of infringements, the enforceability of participants' data protection rights would be more difficult than in Europe, and that local authorities might be able to claim access rights to data transmitted that would not exist in Europe.

For general questions about privacy please contact the privacy officer.

Medical Center University of Freiburg
Datenschutzbeauftragter
Breisacherstraße 153

79110 Freiburg
Germany
E-Mail: datenschutz@uniklinik-freiburg.de

For any specific questions about data protection of this research project please contact the privacy officer of the Center for Chronic Immunodeficiency (CCI).
E-Mail: cci-datenschutz@uniklinik-freiburg.de

Right to information, data correction and data deletion

You have the right to obtain information and a free copy of the data collected about you (Art. 15 EU-GDPR). Furthermore, you can ask for a correction in the event of an error (Art. 16 EU-GDPR) or, under the conditions specified in Art. 17 EU- GDPR, demand the deletion of the data collected about you. To exercise these rights please contact one of the above mentioned study directors.

Right of complaint concerning data protection

We would also like to point out your right of appeal to the data protection supervisory authority of the state of Baden-Württemberg, Germany, if you believe that the processing of your personal data/your child's personal data violates data protection rights (Art. 77 EU-GDPR).

Landesbeauftragte für den Datenschutz
und die Informationsfreiheit
Königsstrasse 10 a
70173 Stuttgart
Germany

Declaration of consent for participation in clinical, immunological and molecular genetic research studies:

Patient adhesive / test person

We will provide you with a copy of the information and consent form for your personal records.

1) I agree with the scientific analysis (without genetic analysis) of my samples or the samples of my child.

☐ Yes ☐ No

2) I agree with the targeted investigation of individual genes.

☐ Yes ☐ No

3) I agree with the genetic analysis of the whole genome (including epigenetic analyses).

☐ Yes ☐ No

4) *Applicable to patients only:* I agree with the scientific investigation of residual materials that may be left over from medically necessary interventions.

☐ Yes ☐ No

5) *Applicable to patients only:* I agree in principle with obtaining biopsies for research purposes in the context of medical interventions that are part of my treatment,. You will be informed separately about each detail before each intervention and asked for your consent.

☐ Yes ☐ No

6) I authorize the study director or an employee assigned by the study director to contact me (e.g. for the purpose of further information or other biomaterials).

☐ Yes ☐ No

7) I would like to be notified about health-related outcomes that are being collected about me or my child as part of the investigation of the immune system.

☐ Yes ☐ No

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8) I would like to be notified about any incidental findings that may be detected in the course of my or my child's investigations.

☐ Yes ☐ No

9) I agree with the transfer of **double-pseudonymised** samples, research data and information (eg clinical data, laboratory data, questionnaires, if applicable) to **cooperating research institutes** (public and private institutes and research centers, not pharmaceutical companies) in Germany and abroad for joint research purposes.

☐ Yes ☐ No

10) I agree with the transfer of **double-pseudonymised** samples, research data and information (e.g., clinical data, laboratory data, questionnaires, if applicable) to **cooperating pharmaceutical companies** in Germany and abroad for joint research purposes.

☐ Yes ☐ No

Please complete the relevant paragraph (A or B):

A Declaration of consent for adults	**B Declaration of consent for guardians of minor patients or legitimate adult representatives**
I have read the explanations for these research studies and have received the information sheets for the individual studies. I have been given the opportunity to ask questions and these have been answered satisfactorily. I agree to participate in these research examinations. I agree with the publication of pseudonymised research data and information (e.g., clinical data, laboratory data, questionnaires, if applicable). ---------- (Date and signature of the participant)	I have read the explanations for these research studies and have received the information sheets for the individual studies. I have been given the opportunity to ask questions and these have been answered satisfactorily. I agree that my child/the person entrusted to me may take part in these research examinations. I agree with the publication of pseudonymised research data and information (e.g., clinical data, laboratory data, questionnaires, if applicable) of my child/the person entrusted to me. ---------- (Date and signature of all guardians/persons authorized to represent) ---------- (Date and signature of the participant from the age of 14. Once the age of majority within this research project is reached, a new informed consent will be given.)

I informed the participant and answered all questions accordingly:

(Date and consenting doctor's signature)